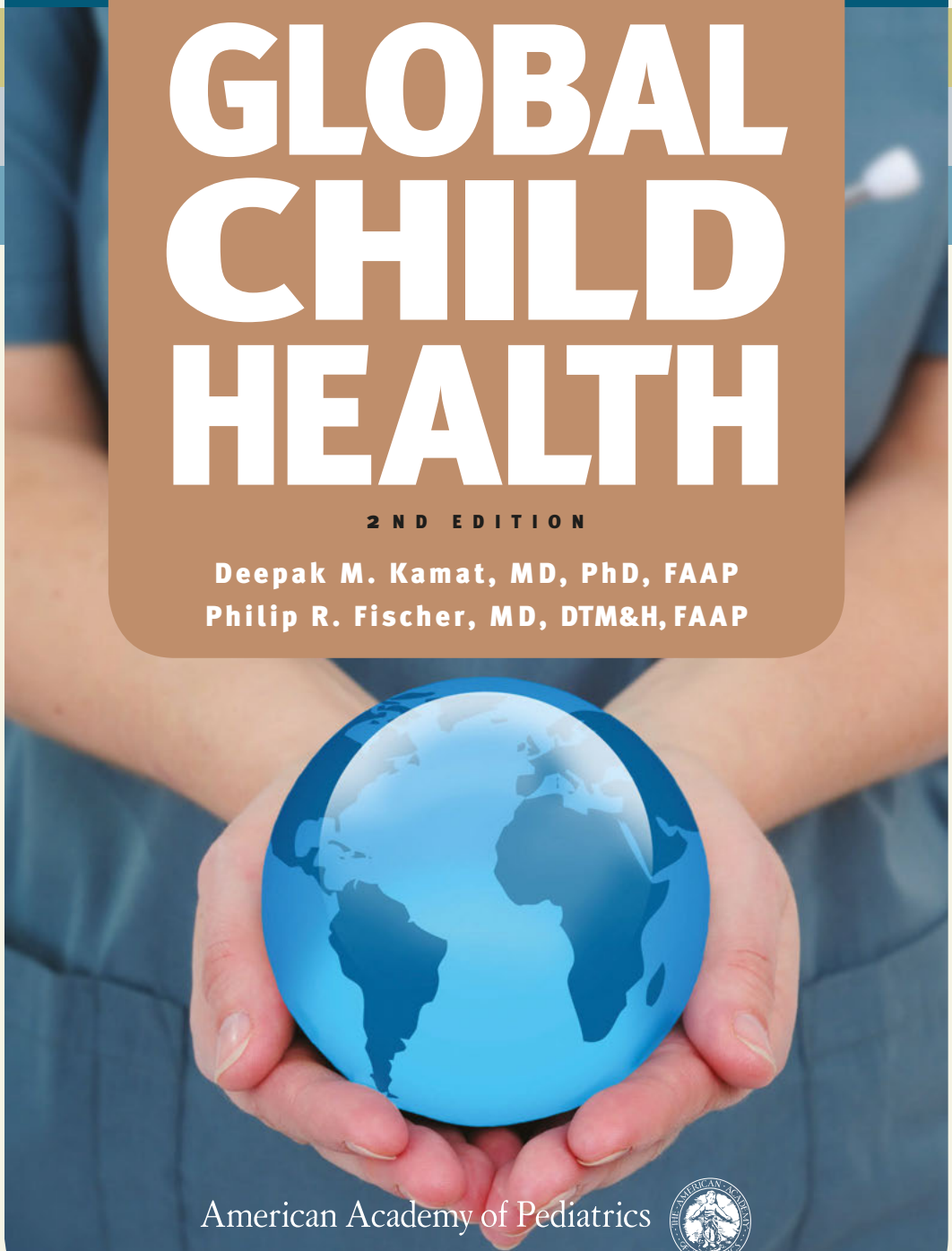
AMERICAN ACADEMY OF PEDIATRICS

TEXTBOOK OF GLOBAL CHILD HEALTH

2ND EDITION

Deepak M. Kamat, MD, PhD, FAAP
Philip R. Fischer, MD, DTM&H, FAAP



American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

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PREFACE

Globally, the health of children is improving. Child mortality rates are dropping. Functional measures of health are improving.

At the same time, professional interest in global child health continues to increase. A large number of US trainees and practitioners have been or desire to be engaged in international health efforts.

The world is moving from Millennium Development Goals to Sustainable Development Goals. Efforts are growing to help children not only survive but thrive.

This second edition of the American Academy of Pediatrics (AAP) *Textbook of Global Child Health* is pleased to contribute toward international efforts to improve the lives of the next generation. Even since the release of the first edition 4 years ago, progress has been made. This new edition should help prepare and support child health professionals as they join international efforts on behalf of children.

A large multinational team of authors has joined together to produce this updated, improved, and expanded resource. The first section still provides foundational understanding of societal factors related to health and disease. The second section promotes appropriate care of children traveling internationally. The third section has new chapters to better cover the breadth and depth of the clinical management of children in resource-limited areas. Images and user-friendly formatting changes help make this book useful while readers are preparing to see children as well as at the point of care when seeing ill children—whether using print or digital formats. The textbook is designed to be a stand-alone resource but also complements the material included in the AAP *Working in International Child Health* (2008), *Global Child Health Advocacy: On the Front Lines* (2014), and *Atlas of Pediatrics in the Tropics and Resource-Limited Settings*, 2nd Edition (2016).

We appreciate the input of readers who helped in the preparation of this second edition of the textbook. We heard how this book encouraged and empowered child health professionals, and you told us of children whose lives were saved through the use of this book. Please stay in touch! Let us know how the book is useful to you, and please give us ideas on how we can provide further help. We join together in this published effort to improve the health of the world's children.

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SECTION 1

Understanding Principles of Global Child Health

CHAPTER

1

The Reality of Child Mortality

A. Barbara Oettgen, MD, MPH, FAAP
Ambika Mathur, PhD
David A. Sleet, PhD, FAAHB

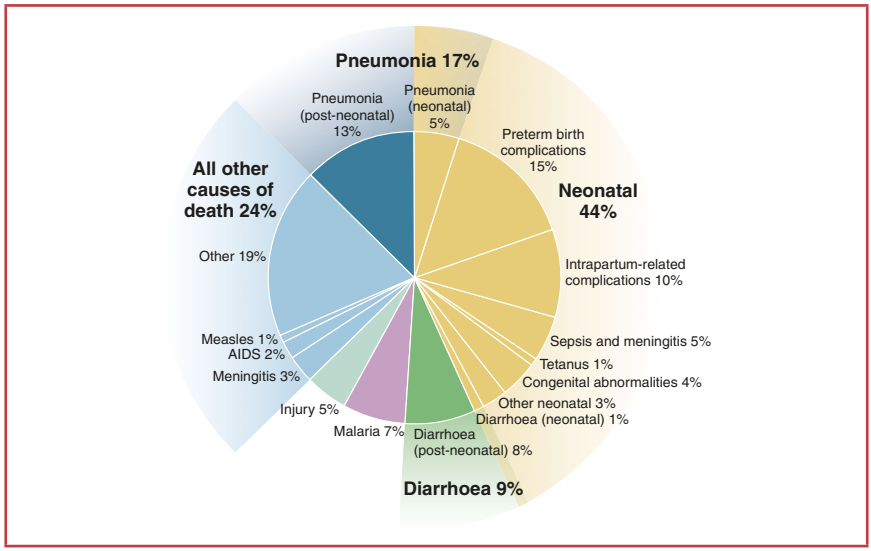
"We have an opportunity to focus global attention on what should be obvious: every mother, and every child, counts. They count because we value every human life. The evidence is clear that healthy mothers and children are the bedrock of healthy and prosperous communities and nations."

— Dr LEE Jong-wook, former World Health Organization Director-General

CURRENT STATUS OF CHILD MORTALITY

Global child mortality has significantly decreased in the last 20 years from 12.6 million deaths per year in children younger than 5 years in 1990 to 6.6 million deaths per year in 2012. The younger-than-5 mortality rate has decreased by 47% since 1990 from 90 deaths per 1,000 live births to 48, and the decline rate is accelerating.[1] Of the 61 countries with the highest mortality, 25 decreased their child mortality rate by more than two-thirds, including successes in Bangladesh (72%), Malawi (71%), and Nepal (71%). Despite these great strides, 18,000 children die every day—the majority from preventable causes.[1] Deaths are increasingly concentrated in neonates (now 40% of all child deaths), as global public health efforts have resulted in declines in the mortality rate among older infants and children. Figure 1-1 shows the primary causes of global child mortality, including neonatal causes, pneumonia,

Figure 1-1. Global Distribution of Deaths Among Children Younger Than 5 Years, by Cause, 2012



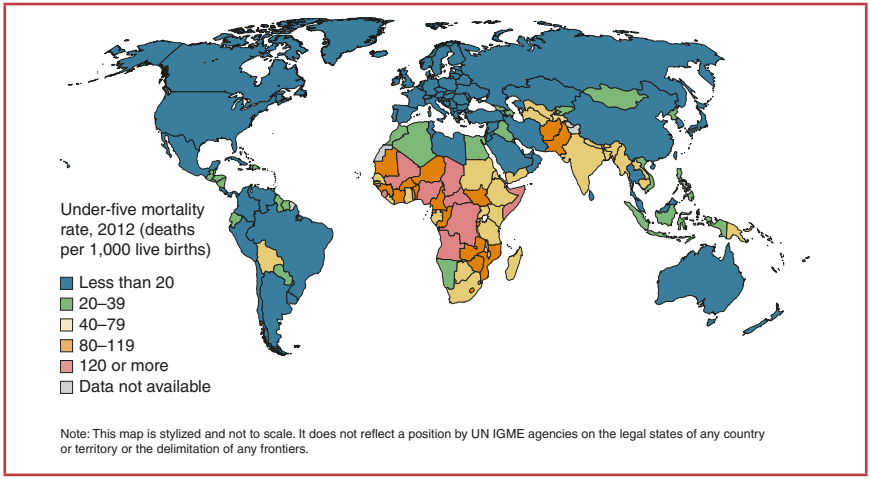
From United Nations Children's Fund. *Committing to Child Survival: A Promise Renewed. Progress Report 2013.* New York, NY: United Nations Children's Fund; 2013. http://www.unicef.org/publications/index_70354.html. Accessed May 29, 2015.

diarrhea, and malaria. The past 5 years have seen significant declines in measles and HIV. Globally, pneumonia is the number one cause of child death.

However, global statistics fail to describe the great inequality of childhood mortality rates from country to country. While child mortality has declined in all regions of the world, the rate of decline is much slower in sub-Saharan Africa and South Asia, and it is in these regions that the greatest burden of child mortality is increasingly concentrated (Figure 1-2). Sub-Saharan Africa continues to have the highest mortality rate (98 per 1,000 live births), which is double that of other developing regions and 16 times more than developed countries.[1] Child death is also disproportionately seen in rural areas among children whose mothers are not educated and those living in poverty and war-torn regions.[1]

There is also regional variation in childhood death patterns. Malaria is the primary killer of children younger than 5 years in Sub-Saharan Africa; while infectious diseases account for 64% of deaths globally, they are responsible for 81% of the deaths in Africa. More than half of deaths caused by infections can be ascribed to 5 pathogens: *Plasmodium falciparum, Streptococcus pneumoniae,* rotavirus, measles, and *Haemophilus influenzae* type b (Hib).[2]

Figure 1-2. Children in Sub-Saharan Africa and Southern Asia Face a Higher Risk of Dying Before Their Fifth Birthday



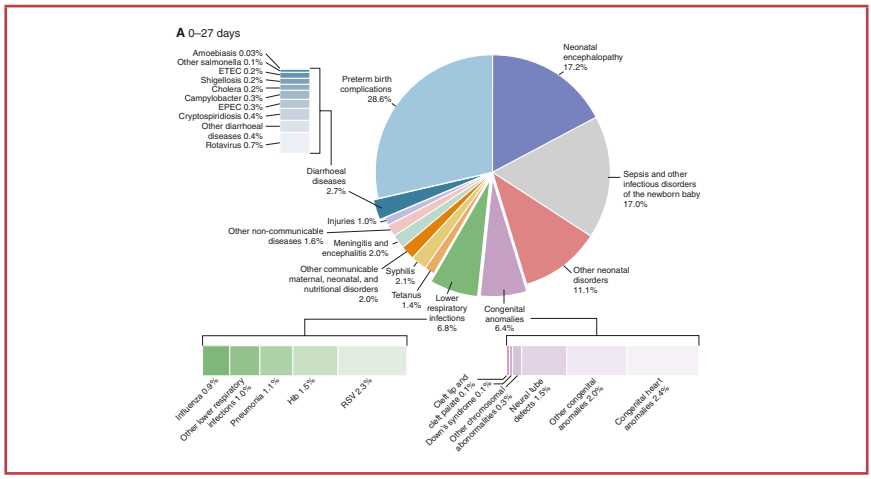
From United Nations Children's Fund. *Levels & Trends in Child Mortality: Report 2013. Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation.* http://www.childinfo.org/files/Child_Mortality_Report_2013.pdf. Accessed May 29, 2015.

Malnutrition contributes to more than one-third of deaths in this age group, while war, poverty, lack of education, and indirect effects of the HIV epidemic have also contributed significantly to child mortality across the globe.[3,4] Undoubtedly, great progress has been made, but the current status of child health remains morally and ethically unacceptable.

GLOBAL BURDEN OF DISEASE 2010

Statistics of global health for people of all ages have been examined independently by the Global Burden of Disease Study 2010, funded by the Bill & Melinda Gates Foundation. This comprehensive data summary includes 235 causes of morbidity and mortality for people of all ages and looks at causes of death and trends in morbidity and mortality from 1990 to 2010.[5] The overall global trend across all ages is a movement away from maternal, neonatal, nutritional, and communicable causes of death to noncommunicable causes, such as ischemic heart disease, stroke, lung cancer, and injury. This trend is driven by population growth and aging. Deaths related to diabetes doubled, and the number of deaths from road traffic crashes rose by 46%. Yet the picture can look quite different regionally. Specifically, communicable diseases and maternal, neonatal, and nutritional causes of mortality account for 76% of deaths in sub-Saharan Africa. Figures 1-3a,b,c show the primary

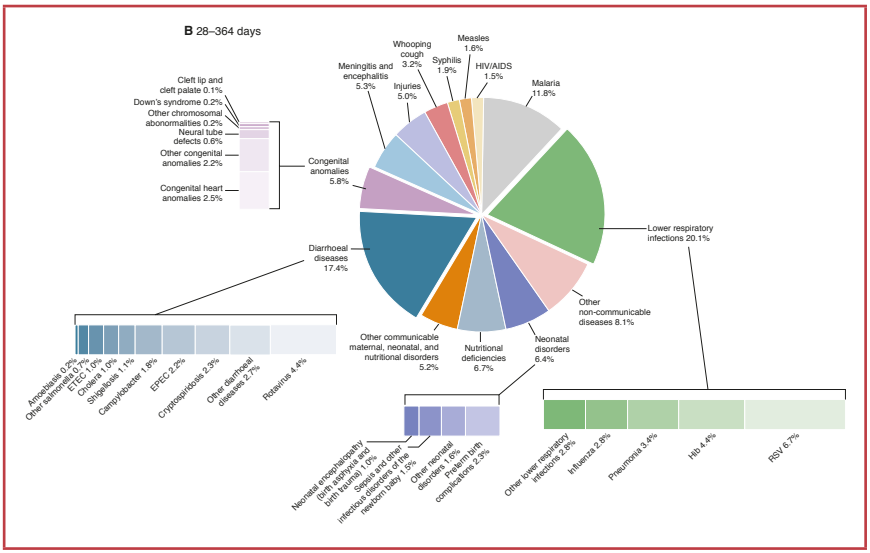
Figure 1-3a. Global Burden of Disease Study—Neonates (0–27 Days)



Abbreviations: EPEC, enteropathogenic *Escherichia coli;* ETEC, enterotoxigenic *Escherichia coli;* Hib, *Haemophilus influenzae* type b; RSV, respiratory syncytial virus. **A**, 2,840,157 total deaths.

From Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095–2128. Copyright 2012, with permission from Elsevier.

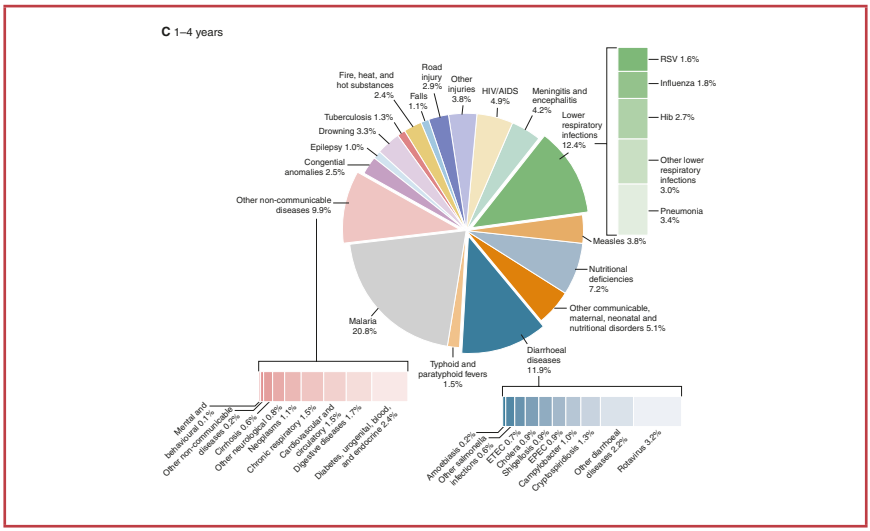
Figure 1-3b. Global Burden of Disease Study—Infants (<1 Year)



Abbreviations: EPEC, enteropathogenic *Escherichia coli;* ETEC, enterotoxigenic *Escherichia coli;* Hib, *Haemophilus influenzae* type b; RSV, respiratory syncytial virus. **B**, 2,031,474 total deaths.

From Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095–2128. Copyright 2012, with permission from Elsevier.

Figure 1-3c. Global Burden of Disease Study—Children (1–4 Years)



Abbreviations: EPEC, enteropathogenic *Escherichia coli;* ETEC, enterotoxigenic *Escherichia coli;* Hib, *Haemophilus influenzae* type b; RSV, respiratory syncytial virus. **C,** 1,969,567 total deaths.

From Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095–2128. Copyright 2012, with permission from Elsevier.

causes of death (both sexes combined) for neonates, infants younger than 1 year, and children 1 to 4 years of age.

MILLENNIUM DEVELOPMENT GOALS FOR 2015

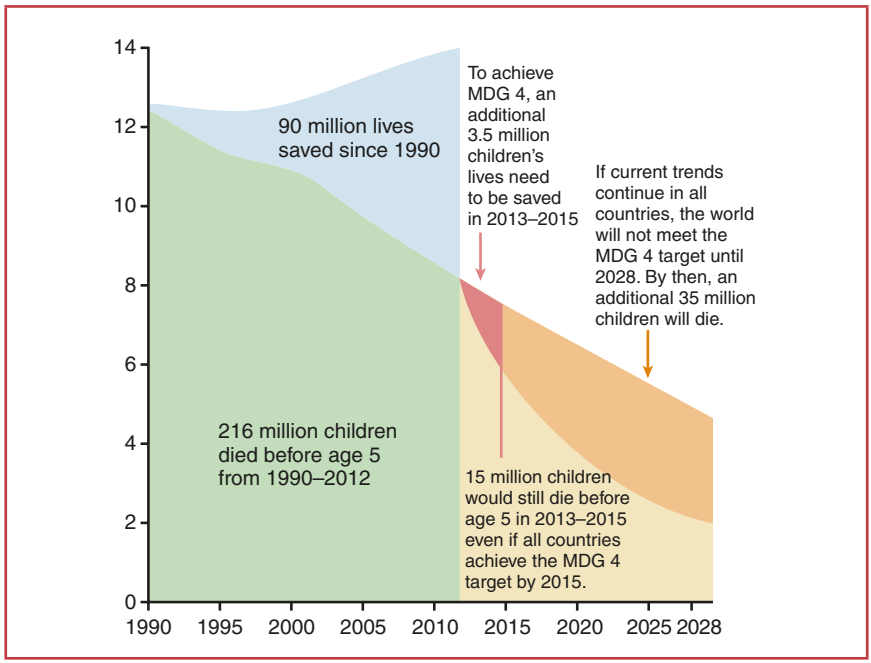
In 2000, 189 governments and at least 23 international organizations convened at the UN Millennium Summit to adopt a uniform worldwide set of 8 goals—Millennium Development Goals (MDGs)—to promote continued progress toward improving global public health. Several of these goals pertain to child health. Millennium Development Goal 4 sets the goal to decrease the mortality of children younger than 5 years to 5 million per year by 2015. Essentially, successful implementation of MDG 4 will decrease deaths by two-thirds of the levels seen in 1990 (13 million).

Other MDGs will indirectly improve child mortality rates. For example, MDG 5 is aimed at reducing maternal mortality by three-fourths (which will affect neonatal mortality), and MDG 6 strives to reverse the spread of HIV/AIDS and malaria.[6] While injury prevention was not part of the original MDG, Anupama Rao Singh, regional director of United Nations Children's Fund (UNICEF) East Asia and Pacific, points out, "If

we are ultimately going to meet the Millennium Development Goal to reduce child mortality, it is imperative that we take action to address the causes of childhood injury."[7]

The MDGs are a valuable benchmark intended to move the world forward. Despite the overall decline in child mortality, only 23 of the 75 Countdown countries are on track to achieve MDG 4. These 75 Countdown countries carry 95% of the burden of maternal, newborn, and child death. Their progress is monitored as the world "counts down" to 2015. The current rate of decline needs to accelerate if we are to achieve the 2015 goal (Figure 1-4).[4]

Figure 1-4. Younger-Than-5-Years Mortality Rate, 1990–2012, and Projected Rate, 2013–2028 (rate of decline and required rate of decline for Millennium Development Goal 4)



From United Nations Children's Fund. *Committing to Child Survival: A Promise Renewed. Progress Report 2013*. New York, NY: United Nations Children's Fund; 2013. http://www.unicef.org/publications/index_70354.html. Accessed May 29, 2015.

THE EVOLUTION OF GLOBAL CHILD HEALTH

From 1960 to 1999, there was already significant success in global child health—a 50% reduction in child mortality attributable to a variety of public health approaches.[8] Mass immunization campaigns conducted in the 1950s through 1970s resulted in smallpox eradication and reductions in other vaccine-preventable diseases. The Expanded Program on Immunization (EPI), established in 1974, allowed for continued strides in improving worldwide vaccination status among children, from a baseline of 5% (3 doses of diphtheria, pertussis, tetanus [DPT3] vaccine) in 1974 to a current rate of 83% (2012).[9] The UNICEF growth monitoring for undernutrition, oral rehydration, breastfeeding, and immunization program, instituted in 1982, expanded the focus of public health programs from solely immunizations to include other important interventions. There began a growing awareness and interest in improving primary care infrastructure to better disseminate a greater number of interventions that positively affect child health.[10]

The Integrated Management of Childhood Illness (IMCI) program was created in the mid-1990s.[10] In this program, local-level caseworkers were identified in rural and urban communities and trained to provide health education and support to families for a variety of maternal and childhood diseases and conditions. The IMCI program was initially created as a facility-based program using case management with a defined set of evidence-based guidelines for sick children. It was eventually expanded to include interventions that could be performed in the household, in the community, or by referral. Such a change required improving case management and health systems, as well as family and community services, including health education in growth promotion and development, disease prevention, care, and compliance with the advice of health workers.

Adoption of all IMCI program aspects (ie, facility-based services, case management, and family and community health services) is not complete, even in countries with the most effective implementation. While these countries have well-trained community health workers, changes in their health systems and family health practices have been slow. Evaluators note that one of the significant problems associated with IMCI implementation is high staff turnover, which makes it difficult to achieve a sustained effect. The staffing problem is a greater issue among facility-based staff (who could be moved from the area) than with staff who are local community women, demonstrating that it may be preferential to increase participation of local workers. Future success of the IMCI program requires that regions work from the top down

(strengthening the health service system) and also from the bottom up (mobilizing the community to use those services).[10]

MAJOR CAUSES OF CHILD MORTALITY

Further reducing child mortality requires improving primary care infrastructure across a continuum for women, newborns, and children, allowing for the successful dissemination of interventions known to be effective for the major causes of maternal, newborn, and child mortality. The following recurrent themes emerge in the description of progress addressing the major causes of child mortality:

1. A need to strengthen and improve community-based services for a greater effect on diseases (ie, pneumonia, diarrhea, malaria)
2. A need to address the inequities of how effective interventions are being disseminated among people of different socioeconomic statuses and urban versus rural

Pneumonia

Pneumonia is associated with 18% or 1.2 million childhood deaths every year, a number greater than deaths from malaria and diarrhea combined and the number one cause of death in children younger than 5 years globally.[11] Morbidity from pneumonia is estimated at 156 million cases annually.[12] Ninety percent of pneumonia deaths occur in South Asia and sub-Saharan Africa.[11] The pathogens *S pneumoniae,* Hib, respiratory syncytial virus, and influenza cause the majority (estimated at 55%) of pneumonia deaths, while household air pollution and overcrowding are environmental contributors.[13] It is estimated that 3 billion people use solid fuel for cooking (wood, crop waste, coal), contributing to indoor pollution (Figure 1-5).[14]

Together, pneumonia and diarrhea account for almost 30% of deaths in children younger than 5 years; several of the most effective interventions to combat these diseases overlap, including improved nutrition, breastfeeding, and zinc therapy. In April 2013, the World Health Organization (WHO), UNICEF, and Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the Global Action Plan for Pneumonia and Diarrhoea (GAPPD). It is a framework for governments to plan and implement effective interventions for prevention and control of both diseases; this is one of the biggest opportunities in global health. Scaling up these activities could prevent 95% of diarrhea deaths and 67% of pneumonia deaths by 2025.[12]

The current global health approach to decreasing deaths from pneumonia involves prevention and early detection with prompt treatment.[14]

Figure 1-5. Indoor Air Pollution (picture of child exposed to indoor smoke)

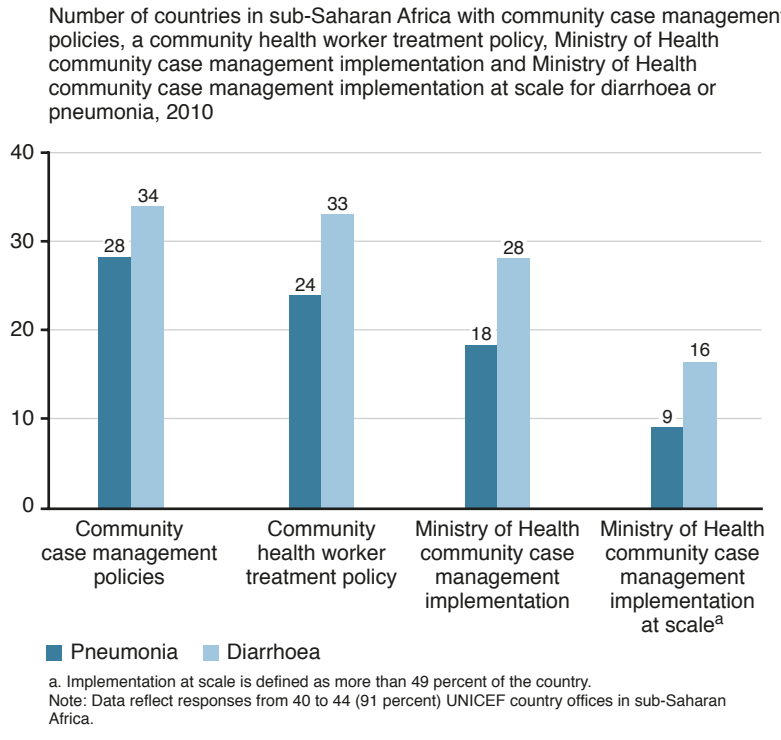
Uganda 2006: A young child sits over a cooking fire inside his family's hut in the Awer IDP camp in northern Uganda's conflict-affected district of Gulu. (22 08 2006)

From United Nations Children's Fund. *Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children*. New York, NY: United Nations Children's Fund; 2012:19. http://www.childinfo.org/files/Pneumonia_Diarrhoea_2012.pdf. Published June 2012. Accessed May 29, 2015. © UNICEF/UGDA01253/Hyun.

Early Detection and Treatment

It is essential to educate and encourage families to seek care early in the course of respiratory illness; the IMCI program is an ideal conduit for education and treatment. First, families can be taught to observe respiratory rates and chest wall appearance (eg, in-drawing). The IMCI program workers can also look at these physical signs, refer severe cases, and treat non-severe cases with selective antibiotics.[11] Statistics show that worldwide, too few people know to access care when their child is ill with respiratory symptoms. Only 60% of caregivers worldwide seek care, with little progress over the last decade (54% sought care in 2000).[14] This number is even lower in sub-Saharan Africa (49%).[10] Only one-third of those needing antibiotics are getting them.[14] The case management approach also suffers due to a lack of caregivers, inadequate training and program coordination, and trouble with the supply chain for items such as antibiotics.[15] While most countries agree that case management is important, the number of countries who implemented the policy to scale, reaching all children, is few (Figure 1-6); thus, more work must be done to expand the reaches of the IMCI program.

Figure 1-6. Community Case Management Policy



From United Nations Children's Fund. *Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children*. New York, NY: United Nations Children's Fund; 2012:25. http://www.childinfo.org/files/Pneumonia_Diarrhoea_2012.pdf. Published June 2012. Accessed May 29, 2015.

Prevention

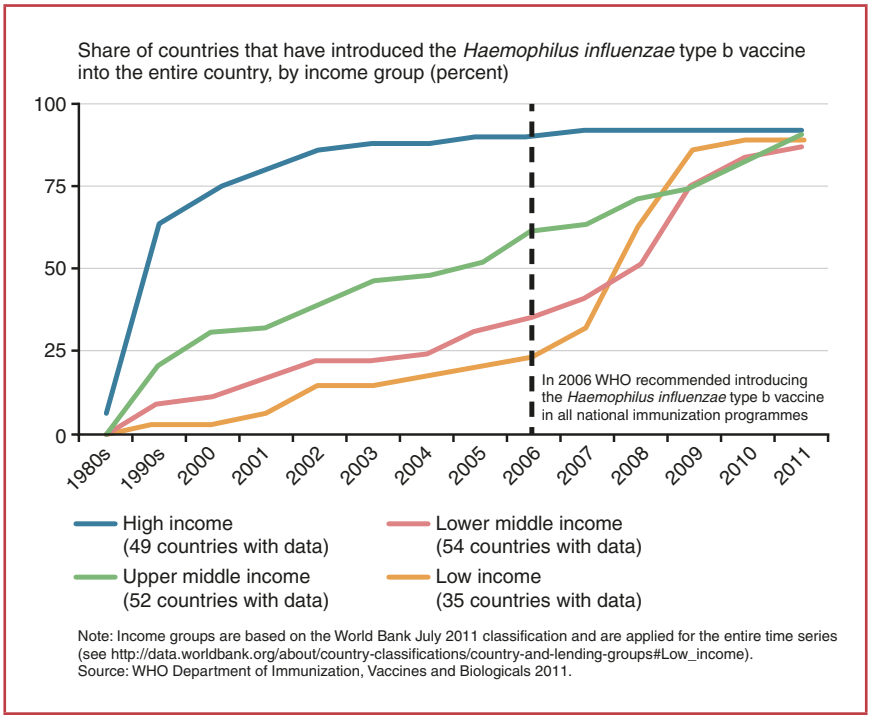
Not only can IMCI workers instigate prompt treatment, they can also encourage breastfeeding, improved nutrition (including increased zinc intake), and hand washing.[10] Human milk can provide antibodies as well as have a positive economic and social effect on families. All-cause mortality increased 566% in infants 6 to 11 months and 223% in children 12 to 23 months who were not breastfed.[16]

Expanded use of Hib, pneumococcal, pertussis, measles, and influenza vaccines is also an important approach to decreasing childhood pneumonia.[17,18] *H influenzae* type b vaccination is very effective in Kenya, where the incidence of the disease decreased to 12% of its baseline level in children younger than 5 years over the first 3 years it

was distributed.[19] For years, access to Hib vaccine demonstrated a rich/poor gap between countries. Thankfully, that gap is closing, owing to an increase in funding as well as global and national leadership. In 2000, Gavi, the Vaccine Alliance, began financially supporting Hib vaccination in 72 of the poorest countries. Countries apply for Gavi funding based on a financial plan, vaccine introduction plan, and 5-year national vaccine strategy. Initially, uptake of Hib vaccine was very slow. When the Hib Initiative was launched in 2005 to accelerate introduction of the Hib vaccine, there was a sharp increase in the number of eligible countries using the vaccine (Figure 1-7).[14] Eighty-five percent to 90% of all-income countries introduced the Hib vaccine by the end of 2011.

Since 2007, WHO has recommended global use of pneumococcal vaccine, especially because pneumococcus is the leading cause of pneumonia globally. It is estimated that 500,000 child deaths could be averted annually with the use of pneumococcal vaccine.[20] While the uptake

Figure 1-7. Closing the Rich/Poor Gap in the Introduction of *Haemophilus influenzae* Type b Vaccine in Recent Years



Note: Income groups are based on the World Bank July 2011 classification and are applied for the entire time series (see http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Low_income).
Source: WHO Department of Immunization, Vaccines and Biologicals 2011.

From United Nations Children's Fund. *Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children*. New York, NY: United Nations Children's Fund; 2012. http://www.childinfo.org/files/Pneumonia_Diarrhoea_2012.pdf. Published June 2012. Accessed May 29, 2015.

of pneumococcal vaccine globally is slowly rising, there are significant numbers of unimmunized children and a large gap in access between the rich and the poor.[14] Hopefully, with initiatives (ie, advance market commitment) intended to lower vaccine prices and increase distribution, the financing and organizational mechanisms that improved Hib vaccine uptake will also lead to expanded coverage of pneumococcal vaccine.[12]

Diarrhea

Diarrhea is responsible for 11% (750,000) of child deaths annually worldwide.[21,22] Fortunately, significant strides have been made in diarrhea control over the last 15 years. Rotavirus, enteropathogenic *Escherichia coli,* calicivirus, and enterotoxigenic *E coli* cause more than 50% of severe diarrhea episodes (ie, those most likely to result in death).[23] It is estimated that rotavirus causes 38% of diarrheal deaths.[23] Diarrheal control and decreases in mortality are achieved through prevention and also adequate treatment during the illness. One of the leading success stories in public health is the use of oral rehydration therapy (ORT) as a key element in fighting diarrhea. Oral rehydration therapy is associated with a 69% decrease in mortality.[16] Deaths caused by diarrhea decreased by more than two-thirds since 1980; diarrhea is no longer the number one cause of death.[22]

The GAPPD goal is to decrease mortality from diarrhea to fewer than 1 per 1,000 live births and have 90% case management coverage by 2025.[12,24] Treatment includes ORT, continued feeding (especially human milk for young children), and zinc.[21,22] Prevention includes safe water supply, feces disposal (MDG 7), hand washing, immunization (for rotavirus and measles, specifically), and improved nutrition (including adequate vitamin A). Stunting, a chronic marker of malnutrition, occurs when there are repeated diarrhea episodes, setting up a vicious cycle of undernutrition and infection that needs to be broken.[14]

Oral rehydration solution (ORS) is the mainstay of ORT. Oral rehydration solutions evolved over time and now are composed of a lower salt concentration than previously recommended in the 1980s and 1990s. Homemade rehydration solutions are loosely encouraged in regions where ORS is not available. Zinc has become an important adjunct to diarrhea control. It is estimated that 17% of the world's population is zinc deficient.[16] While ORS acts to rehydrate, zinc decreases the amount of diarrhea and length of illness.[24] In addition to ORS and zinc, families are encouraged to continue feeding and increase fluids in general.[24] Unfortunately, treatment use slowed after an initial dramatic rise in the uptake of rehydration recommendations in the early 1990s.[24] Overall, only about 34% of children with diarrhea receive low-osmolar ORS and

only 5% get zinc; however, there are regional variations.[24] Treatment inequities occur depending on socioeconomic status: children are 1.5 times as likely to receive treatment in households with higher income levels. There are also urban/rural inequities: those in urban settings are more likely to receive treatment than those in rural areas (43% versus 34%).[21,22]

Prevention

Integrated Management of Childhood Illness workers promote hand washing, which is estimated to decrease the rate of diarrheal morbidity by 42%.[14] However, the poorest households do not have access to necessary soap and water.[14] Globally, the MDG to achieve safe drinking water was met (a huge success), but access in rural areas is often still poor.[14] Sanitation has also been improved but, again, less so in rural areas. Improved nutrition also helps decrease severity of diarrhea illness; exclusive breastfeeding for the first 6 months of life is encouraged and then continued breastfeeding until 2 years of age along with other solid food.

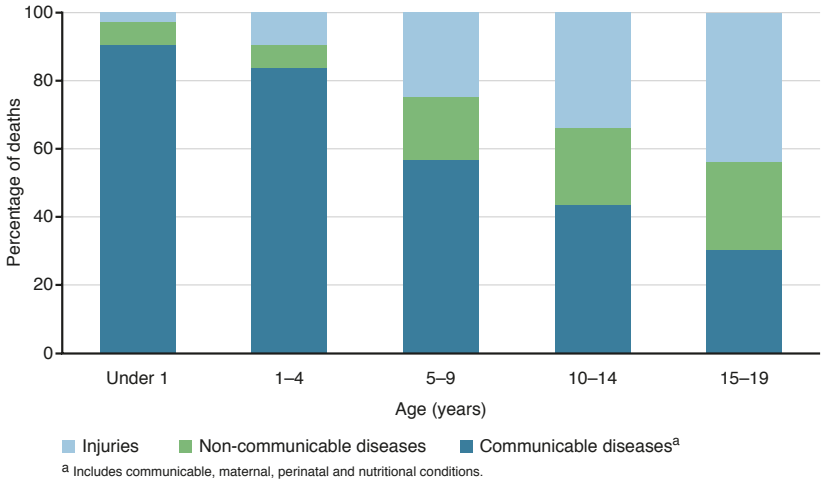
Because rotavirus infection is the leading cause of severe-acute diarrhea worldwide, an important consideration is an effective rotavirus vaccine. The WHO now recommends rotavirus vaccine worldwide, especially in South Asia and sub-Saharan Africa, where the burden of disease is the greatest. The goal for 2015 is that Gavi can provide monetary assistance to 40 of the world's poorest countries to introduce the rotavirus vaccine.[14] As of 2011, rotavirus vaccine was basically unavailable in low-income countries.[14]

To make headway with diarrhea, there must be an increase in funding, policy changes, collaboration between public and private organizations, government support, and adequate supply and uniform distribution of ORS and zinc.[24] Bangladesh is a model country for what can be done; mortality from diarrhea is at 2% (down from 20% in 1993) and almost 80% of people are receiving ORS and 33% are receiving zinc.[24]

Injury

Injury and violence are major killers of children throughout the world, responsible for approximately 950,000 deaths each year in children and adolescents younger than 18 years.[25] Unintentional injuries account for almost 90% of these cases and are the leading cause of death for children aged 10 to 19 years. Figure 1-8 demonstrates that as children age, the proportion of deaths attributable to injury, compared with communicable and noncommunicable disease, increases. The majority of these injuries are the result of road traffic collisions, drowning, burns (fire or scalds), falls, or poisoning. These 5 categories of unintentional injuries

Figure 1-8. Proportion of Deaths From Injuries, Noncommunicable Diseases, and Communicable Diseases, by Age, Among Children in the World, 2004



From World Health Organization. *World Report on Child Injury Prevention.* Geneva, Switzerland: World Health Organization; 2008. http://www.who.int/violence_injury_prevention/child/injury/world_report/en. Accessed June 10, 2015.

make up 60% of all child injury deaths. Road traffic injuries alone are the leading cause of death among 15- to 19-year-olds and the second leading cause among 10- to 14-year-olds.

Other unintentional injuries include suffocation, asphyxiation, choking, animal bites or snakebites, hypothermia, and hyperthermia. This group accounts for 23% of childhood deaths, which is a significant proportion. The rate of child injury death is 3.4 times higher in low- and middle-income countries than in high-income countries, but there are large variations in the injury-related death category. For fire-related deaths, the rate in low-income countries is close to 11 times higher than in high-income countries, drowning is 6 times higher, poison is 4 times higher, and falls are around 6 times higher.

Burden of injury is heaviest among the poor in countries with lower incomes. Overall, more than 95% of all injury-related deaths in children occur in low- and middle-income countries. Although the child injury death rate is much lower among children from developed countries, injuries are still a major cause of death, accounting for approximately 40% of all child deaths.[25]

Many children who survive death are disabled from nonfatal injuries, often with lifelong consequences. Road traffic injuries and falls rank in the top 15 causes of disability-adjusted life years lost for children 0 to 14 years of age.

Survey data from Bangladesh, China, the Philippines, Thailand, and Vietnam show that suffocation is the main cause of injury-related death in children younger than 1 year; drowning is the main cause of injury-related death in children younger than 5 years; drowning, road traffic injuries, and animal bites are the main cause of injury-related death for children between 5 and 9 years; and road traffic deaths are the most significant unintentional injury among children 10 to 17 years of age. However, there are large differences between rich and poor countries. While drowning is the leading cause of injury death among children younger than 5 years in the United States and Asia, the rate of death per 100,000 children is 30 times higher in Asia.[1,20]

In an analysis of child death rates by gender, male deaths exceed female deaths in nearly all mechanisms of injury, with the exception of fire-related burns. Excess deaths from fire-related burns among females is particularly noticeable in the Southeast Asia region and low- and middle-income countries of the Eastern Mediterranean region, where female adolescent deaths can exceed adolescent male death by up to 50%.[7] Male death rates are one-third higher than female death rates in children 5 to 9 years of age, a discrepancy that increases to 60% among children 10 to 14 years of age. Adolescents 15 to 17 years of age show an adult profile; males in this age group account for more than 86% of all injury-related deaths, particularly in high-income countries.

Prevention

Injuries are not accidents—they are not inevitable. The global community now recognizes that most child injuries are predictable and preventable.[7,10] In Organisation for Economic Co-operation and Development countries, for example, the number of injury deaths among children younger than 15 years fell by half between 1970 and 1995.[10] Preventing child injury is closely connected to other issues related to children's health, including poverty, inequality, the built environment (eg, housing stock, water access, cultural practices, quality of roads and vehicles), and personal protective behaviors (eg, seat belts, motorcycle helmets, child supervision).

Child injury prevention can be a central part of all initiatives to improve child mortality. Every child death is a loss to the country's future economy. Injury prevention will reduce costs in the health care system, improve country capacity to meet its development goals, and,

most importantly, improve the chances of children living a long, productive, and healthy life. Unless injury prevention is included in child survival programs, children will grow up subjected to injuries, and the effect of large investments in immunization, nutrition, and maternal and child health care may be lost.[1,20]

Malaria

More than 600,000 annual deaths are ascribed to malaria, of which the majority are in sub-Saharan Africa. Forty percent of all deaths occur in just 2 countries: the Democratic Republic of Congo and Nigeria. Children younger than 5 years comprise 91% of the malaria victims; this essentially equates to one child dying every minute from the disease.[26–28] Malaria is the number one killer of children in the sub-Saharan region, exceeding the number of children who die from pneumonia (Figure 1-9).[28] Malaria also causes significant morbidity; recurring infections can lead to chronic anemia and impaired growth and development. Perinatal infection causes low birth weight.[26–28]

From 2000, when 44 African leaders signed the Abuja Declaration to cut malaria deaths in half, to 2010, 1.1 million lives were saved and mortality rates declined by 33%.[27] Fifty countries are on track to decrease malaria incidence by 75% by 2015. Increasing attention to the fight against malaria is also reflected in increased funding, from $100 million annually in 2000 to $1.7 billion in 2010, which is attributable to such groups as the Global Fund to Fight AIDS, Tuberculosis and Malaria; World Bank Booster Program for Malaria Control in Africa; and US President's Malaria Initiative.

Malaria control has centered on prevention (vector control), early detection, and prompt treatment.[24] Prevention includes long-lasting insecticide-treated nets (LLINs) (formerly called insecticide-treated bed nets). If used regularly, LLINs decrease mortality in children by 20%.[26] Bed nets not only protect the individual using it but also those individuals in close proximity because of their insecticidal or repellent effects.[29] An innovative and highly effective approach is to combine LLIN distribution programs with other interventions such as immunization.[30,31] In 2005, LLINs were distributed as an adjunct to a polio campaign in Niger, which resulted in disseminating 2 million LLINs and increasing ownership from 6% to 70%.[32] Bed net ownership in Africa varies from 30% to 80% of households, depending on the country. Bed net ownership for children increased from less than 5% in 2000 to more than one-third in 2012.[28] It is also a goal to reach pregnant women with this preventive measure, for which success varies from less than 40% coverage to as high as 70%.[27,28] Protection is even greater when LLINs are combined

with indoor residual spraying; their combined use is promoted where funding allows.[33]

Families are encouraged to seek early care for their febrile ill-appearing child by medical workers or IMCI staff who are able to provide prompt and early treatment.[26,27] A recent Nigerian study shows some of the barriers to care seeking. Mothers frequently wait to see if the disease truly is malaria and will then use home remedies from a dealer rather than a clinic. Many also must wait for their husband's decision to seek care.[34]

The 2010 WHO recommendation calls for universal diagnostic testing when available and discontinuing empiric treatment. Malaria is now treated with artemisinin combination therapies, which are the only effective treatments due to increasing parasite resistance. These medications are expensive and quantity is limited; thus, the recommendation is to use them only if the illness is documented. Rural areas currently lag behind in access to diagnostic testing.[28]

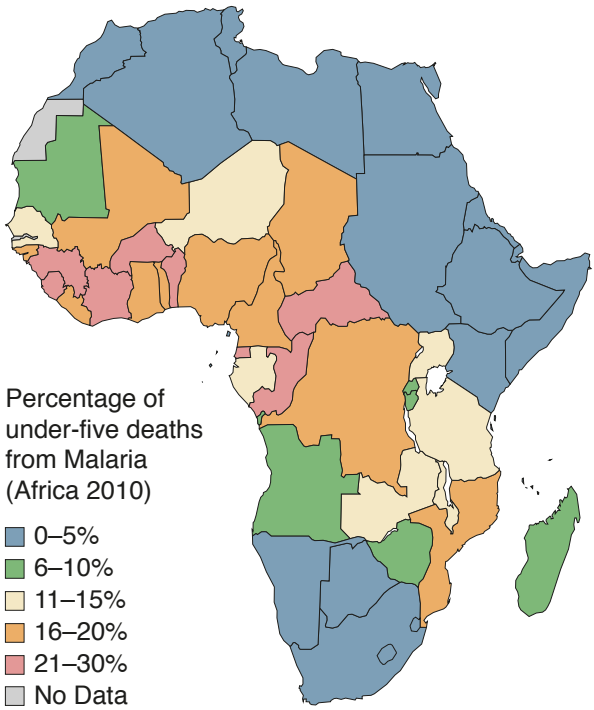
Preventive intermittent treatment during pregnancy in endemic areas (2 doses of an antimalarial drug in the second and third trimester) is another element in the fight against malaria. This treatment considerably reduced the number of women with anemia as well as the incidence of placental malarial infection and low birth weight.[35] The number of women receiving preventive intermittent treatment during pregnancy increased in the last 10 years but still ranges from 5% to 70%, depending on the country.

HIV

The HIV/AIDS epidemic directly and indirectly affects children. Children not only contract HIV, but they are adversely affected when they live with family members, especially parents or other caregivers, who are infected. These children may be left responsible for heading households and earning wages to support their family. Children lose access to education, health care, and adequate food supplies in the many communities where teachers, health care workers, and farmers are infected with HIV. It is estimated that more than 17.8 million children worldwide have lost at least one parent to HIV.[36] The HIV epidemic dealt a severe blow to child mortality progress, not only directly because of child deaths but also because of the necessity of redirecting resources to deal with HIV and its fallout. The resulting economic disruption of countries further contributed to malnutrition and poor health among the children in affected communities.

While the total number of people living with HIV increased over the last decade, the increase reflects longer life expectancy because more people are accessing treatment. The number of new cases actually

Figure 1-9. Malaria Deaths Among Children Younger Than 5 Years in Africa (as percent of younger-than-5 deaths)



From United Nations Children's Fund. *Invest in the Future: Defeat Malaria. World Malaria Day 2013*. New York, NY: United Nations Children's Fund; 2013. http://www.childinfo.org/files/Malaria_brochure_2May2013.pdf. Accessed May 29, 2015. Source of data: Child Health Epidemiology Reference Group (CHERG) 2012.

declined (incidence decreased by 33% since 2001; 2.3 million new cases in 2012), as has the number of deaths (down by 30%).[37]

Sub-Saharan Africa is still the most severely HIV-affected region. Of the 35.3 million people infected with HIV, 70% live in sub-Saharan Africa (25 million), including the majority (88%) of the 3.4 million children who are infected with HIV.[36–38]

The majority of children infected with HIV (90%) acquire the infection perinatally or through breastfeeding. Without perinatal medicines, risk of HIV transmission from mother to child is 15% to 30%; with prolonged breastfeeding, the transmission rate can be as high as 45%.[39,40]

However, UNAIDS reports significant progress. In 2012, 62% of pregnant women received antiretroviral treatment, compared with only 9% in 2004. As a result, new pediatric HIV infections declined by 35% between 2009 and 2012.[38] Four of the priority countries already achieved the goal of 90% coverage by 2015: Botswana, Ghana, Namibia, and Zambia. Botswana is an example of how political will has the power to produce change. This country put a high priority on screening programs—the president of Botswana declared that all women in antenatal clinics would be screened unless they refused; subsequently, the screening rate of women jumped to 90%.[41]

Most recently, a global plan was developed by UNAIDS in partnership with at least 25 countries, as well as international organizations. The plan focuses on the 22 countries with the greatest percentage of women with HIV in the world (90%) who are still in need of services. The "Zero-HIV" plan aims to eliminate HIV transmission to infants by 2015.[42] The plan includes preventing new HIV infections in women of reproductive age, helping women with HIV avoid unintended pregnancy, improving access to HIV testing and treatment for pregnant women, and providing HIV treatment to all infected women and children.[37] Treatment is recommended in breastfeeding women to prevent transmission to the infant, but far fewer postpartum women (49%) are receiving antiretrovirals other than at the time of delivery. The current estimate is that half of all new HIV infections in infants occur during breastfeeding.[37]

The number of infants receiving prophylaxis who were born to HIV-positive mothers remains inadequate compared with the strides being made with adults. Only 34% of HIV-infected children were receiving treatment in 2012, compared with 64% of adults.[37] One of the problems is the lack of identification of HIV-infected children early in infancy with screening programs.[37] The proportion of mothers and infants receiving newer and more effective regimens also needs improvement.

Increasing antiretroviral treatment in all people infected with HIV is one of the targets of MDG 6—reach 15 million people with HIV by 2015. Therapy can prevent people with HIV from dying from AIDS or tuberculosis and prevent transmission of those diseases. Since 1995, 6.6 million deaths have been averted and life expectancy has increased by more than 10 years in some regions.[37] At the end of 2012, 9.7 million people were accessing treatment; globally, treatment has tripled since 2005. But access is uneven across countries. New WHO treatment guidelines (2013) recommend expanding antiretroviral use; however, the 9.7 million people receiving treatment still only represent 34% of those who are eligible.[37]

While HIV infection in newborns and infants remains a concern, the group becoming infected at the highest rate is 15- to 24-year-olds because of their risky behaviors, including unprotected sex and drug abuse. While this age group's infection rate has decreased by 42% since 2001, there are still great hurdles to overcome. Women in this age group are 2 times more likely to be infected than men. The social, legal, and economic inequities in many parts of the world impede their ability to protect themselves from getting a disease and access education, testing, and treatment.[37] Knowledge about HIV and condom use has increased over the last 10 years. However, only 36% of men and 28% of women have a comprehensive understanding of the disease; challenges include the lack of youth-friendly HIV services, barriers to comprehensive sex education, and sexual violence toward women.[37]

The 4 priority areas for HIV/AIDS are

1. Prevent mother-to-child transmission.
2. Provide treatment to HIV-infected children.
3. Prevent infection in the 15- to 24-year-old age group.
4. Protect and support children affected by HIV.[37]

Measles

The quest to decrease measles morbidity and mortality has experienced great strides over the last 10 years. Once the cause of 8% of child deaths in the early 2000s, it is now only responsible for 1%. Success is largely due to concerted vaccination efforts, which redoubled in recent years with the Global Vaccine Action Plan (GVAP). This plan, endorsed by 194 countries in the World Health Assembly (the decision-making body of WHO), was adopted in 2012 and named the Decade of Vaccines Collaboration.[43] Its aim is to make vaccines universally accessible by 2020 and thereby avert millions of deaths.

The goals for measles control and eradication established in 2010 for 2015 were to

1. Increase routine coverage with the first dose of measles-containing vaccine for children 1 year or older to 90% or more nationally and 80% or more in each district.
2. Decrease annual measles incidence to fewer than 5 cases per million.
3. Decrease measles mortality by 95% from 2000.[44]

Between 2000 and 2012, annual incidence of measles decreased 77% worldwide (146 to 33 cases per 1 million population) and annual measles deaths declined 78% (122,000 deaths in 2012). Vaccination rates are currently at 84% worldwide, but 128 countries have 90% or greater coverage. The number of countries giving 2 doses of measles-containing

vaccine increased from 96 to 145. The dramatic increase in measles vaccination rates has averted 13.8 million deaths since 2000.[43]

Neonatal Causes

Newborn Care

While great progress has been made in reducing the mortality rate among children younger than 5 years, with rates decreasing by almost 50% since 1990, gains have been much less among neonates (defined as birth to 28 days of life). Proportionally, neonatal deaths have grown and are now 40% of younger-than-5-years deaths.[45,46] The primary causes of neonatal death remain infection (28%), preterm birth (35%), and birth complications (23%).[46]

It is essential to address neonatal causes of mortality to make overall progress with child mortality. Every year, approximately 2.8 million neonates die within the first 28 days of life. Most deaths occur at home and in poverty, especially in sub-Saharan Africa and Southeast Asia, and are the result of insufficient prenatal care and inadequate assistance at the time of delivery.[46]

Successfully decreasing neonatal mortality rates (NMRs) in low-income countries can be achieved, even without access to advanced technology. In developed countries, the biggest declines in NMR occurred before the advent of the neonatal intensive care unit (NICU). In England, the NMR fell from 30 per 1,000 live births in 1940 to 10 per 1,000 live births in 1975, mostly because of free antenatal care and improved care during labor.[47] In some regions, a concerted effort to address neonatal mortality has been fruitful. For example, there was a 50% decrease in the NMR in Latin America.[8] Indonesia, Moldova, Sri Lanka, and Vietnam also showed improvements. The NMR in Sri Lanka in 1950 was approximately 50 deaths per 1,000 live births. These numbers declined to about 10 per 1,000 live births by 1990 even though the first NICU was not established until the mid-1980s (at which time the NMR was already below 20 deaths per 1,000 live births).

The success in Sri Lanka was attributed to an investment in the primary care infrastructure, ensuring that there was an extensive network of midwives who could provide outreach antenatal care (there was almost 100% coverage in 1999).[47] The global public health community advocates low-tech and low-cost interventions along a continuum of care (Figure 1-10), realizing that a newborn's health starts prenatally. Mothers should have access to folate in pregnancy as well as tetanus immunization, treatment for HIV, and preventive treatment for malaria. Breastfeeding is recommended in the first hour of a

newborn's life, along with clean cord care and keeping the newborn warm and dry. Community caseworkers can help with education and early identification of danger signs.[46] Using these simple measures, Darmstadt et al predict that neonatal deaths could decrease by 18% to 37%.[48] Figure 1-10 shows that coverage for many of these interventions in the least-developed countries is low and that there is much room for improvement.

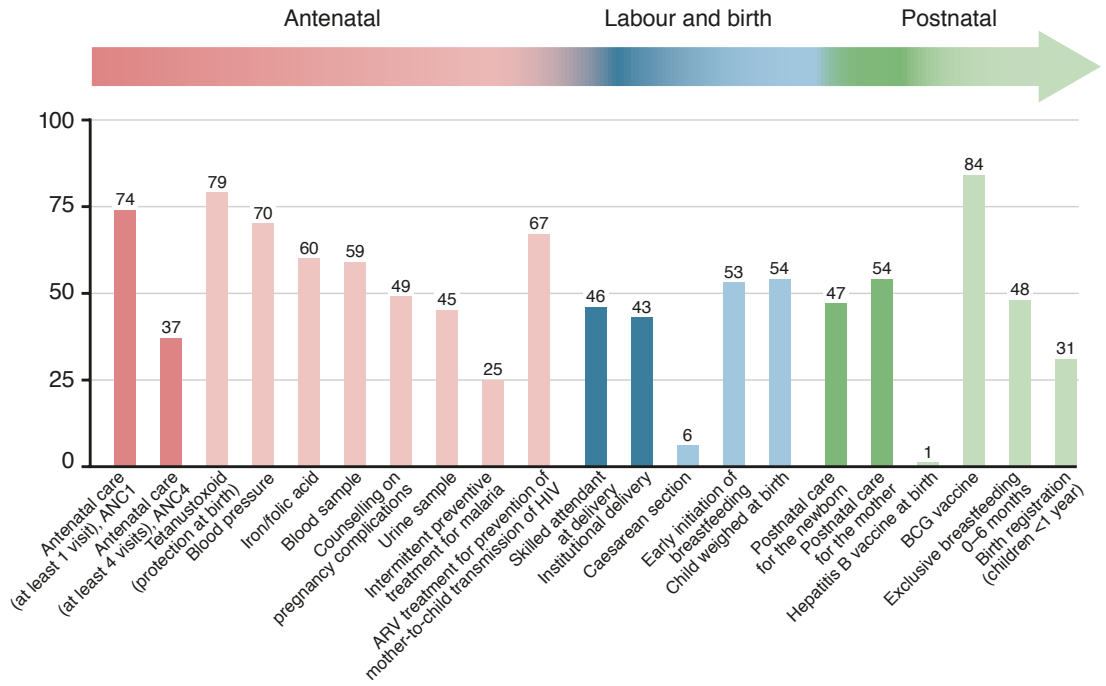
Maternal Care

Lack of improvement in neonatal mortality is clearly linked to the minimal progress in maternal mortality reduction.[49] There is an urgent need to improve women's health in pregnancy, especially nutrition. Maternal malnutrition-associated low birth weight reportedly accounts for 60% to 80% of neonatal deaths.[8] Every day, 800 females die worldwide due to complications of childbirth and pregnancy; 85% of these deaths are concentrated in sub-Saharan Africa and South Asia, and the most common cause (one-third) is hemorrhage.[50] Care for mother and baby should be provided at and immediately after delivery and should extend to baby care for at least the first few weeks following birth. To achieve the desired MDGs, significant funding must be provided for more technical interventions, such as skilled maternal care, immediate neonatal care, emergency obstetric care, and emergency neonatal care.[48] Table 1-1 shows the decrease in NMRs when skilled birth attendants are available. The risk of subsequent neonatal death is much greater if a mother dies during delivery or shortly after. A study conducted in Afghanistan showed that of live neonates born to women who died during delivery or shortly after, 74% of the neonates subsequently died.[51] Global inequalities in maternal health are also stark. The lifetime risk of maternal death in sub-Saharan Africa is 1 in 39 versus that in industrialized countries, which is 1 in 4,700.[50]

Ideally, local and federal governments, as well as global child health programs, should move forward with a seamless, integrated continuous health system for mothers to neonates to children. The past approach was to implement discrete programs; today, there is need for political will, locally and regionally, to creatively flesh out programs in communities and beyond.[52]

> *"Poor health care is a weapon of mass destruction. Poor education is a weapon of mass destruction. Discrimination is a weapon of mass destruction. Let us abolish such weapons of mass destruction here at home."*
>
> *— Dennis Kucinich*

Figure 1-10. Coverage of Key Maternal and Newborn Interventions Across the Continuum of Care (2007–2013)



From United Nations Children's Fund. *Committing to Child Survival: A Promise Renewed. Progress Report 2014*. New York, NY: United Nations Children's Fund; 2014. http://www.unicef.org/publications/index_75736.html. Accessed June 13, 2015.

Table 1-1. Attendance at Birth by Skilled Attendant and Neonatal Mortality Rate

	MORTALITY SETTING			
	NMR >45	NMR 30–45	NMR 15–29	NMR <15
Numbers of neonatal deaths (1000s) (number of countries)	1147 (18)	1759 (39)	838 (40)	254 (95)
Institutional delivery, median coverage (IQR)[a]	33% (16–49)	48% (18–78)	65% (51–91)	98% (95–99)
Skilled attendance at birth, median coverage (IQR)[a]	41% (22–44)	50% (27–77)	85% (62–96)	99% (95–100)
Traditional birth attendants present, median coverage (IQR)	20% (18–25; 7 countries)	18% (8–37; 21 countries)	9% (1–31; 16 countries)	9% (9–41; 3 countries)

Abbreviation: NMR, neonatal mortality rate.

[a] Based on World Health Organization/United Nations Children's Fund estimates for around 2000 for 192 countries.

From Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? *Lancet.* 2005;365(9462):891–900. Copyright 2005, with permission from Elsevier.

Equally important is the need to empower women. If women are not accorded better status, it will be more difficult to make progress with child health.[10] Programs to facilitate the goals of MDG 2 (universal education) and MDG 3 (gender equality and empowering women) must be promoted because enhancing a woman's ability to participate in important decision-making translates into taking better care of her children. Women must be empowered at home, in the community, and in politics to achieve these goals.[10]

Education plays a significant role in increasing empowerment. Less-educated caregivers are less likely to know when to access care appropriately. Educated women are better able to earn an income and invest in their children's health care, nutrition, and education. They are also more likely to participate in community life and advocate for improvements.[10] Educated mothers are more likely to seek health care for themselves and have a skilled birth attendant. They are more likely to delay marriage and avoid pregnancy while they are very young and thus avoid the increased risks associated with teen pregnancy.[51] In Bangladesh, it is shown that a child's chance of survival increases by 20% if the mother has a primary education and a child's chance of survival increases to

80% if the mother has a secondary education.[10] While globally, 90% of primary school-aged children are enrolled in school, as of 2011, there was still an estimated 67 million children without primary education, with big pockets of need in West and Central Africa, where only 66% of children were receiving primary education.[53]

Women face illiteracy and sociocultural practices that prevent them from leaving their homes to access health services. While enrollment in primary education is fairly evenly split globally between boys and girls (53% girls), in many countries of Africa, the proportion of girls receiving primary or secondary education is much lower than boys.[53] Often, women report that they do not make decisions about health for themselves or their children—their husbands do. This is particularly true in sub-Saharan Africa, where 75% of women in Burkina Faso, Mali, and Nigeria reported that their husbands make the decisions about their health.[10] The same husband-directed care was reported by 50% of women in Bangladesh and Nepal.[51]

Training women as community health workers has made considerable inroads in surmounting some of these barriers. There is a doorstep program in Bangladesh in which health workers are able to provide care by going to the homes of women who are not allowed to access health services outside the home.[10] Immunization rates for tetanus in women in Pakistan increased by 30% after Lady Health Workers were able to perform home visits and provide vaccines to women who were reluctant to receive them from male vaccinators.[10]

Loss of a mother to a road traffic crash, as a pedestrian, driver, or occupant, can compromise children's ability to survive and thrive. Women who seek medical care, including those who are transported by vehicle or on foot for critical medical treatment or to deliver a baby, are vulnerable to road traffic crashes and at the mercy of safe roads, safe vehicles, and safe driver behavior.

Malnutrition

The goal of MDG 1 is to reduce the proportion of people who suffer from hunger by half by 2015.[10] As of 2012, 25% of children in the world (about 162 million) were stunted due to malnutrition—a 37% decrease from 1990.[54] Malnutrition is estimated to contribute to at least one-third of all child deaths.[54] It also contributes to significant morbidity due to prenatal malnutrition (eg, iodine deficiency causing devastating neurologic problems) and postnatal malnutrition (eg, iron deficiency leading to learning problems).[10] Reduced immunity is a major consequence of malnutrition.[10]

Maternal nutrition is important for pregnancy outcome: women with short stature (possibly due to malnutrition) are at increased risk for needing assistance with delivery; such assistance is often not available, which places the mother and baby at risk. While maternal undernutrition does not seem to affect human milk composition, there may be micronutrient deficiencies.[55] If a baby is born at term with intrauterine growth restriction and a birth weight of 1,500 to 1,999 g, she is 8 times more likely to die, usually from birth asphyxia or sepsis complications. If birth weight is 2,000 to 2,499 g, the baby is 2.8 times as likely to die. Globally, prevalence of underweight births is estimated at 15%, but it is a difficult number to estimate because more than half of babies globally are not weighed at birth.[56] South Asia is a particular problem spot; it is where more than half of low birth weight babies are born—an estimated 1 in 4 births.[56] These regions also have the highest rates of stunting and wasting. Thirty six countries account for 90% of stunted children worldwide.[55] Table 1-2 shows the increased odds ratio for mortality as affected by poorer growth measurements for some of the most common causes of death. The same socioeconomic inequalities hold true for malnutrition as for other diseases; children from poor families have approximately twice the likelihood of being stunted as do children from wealthier families.

Malnutrition may not be apparent because it is not always manifested in low weight. Deficiencies in vitamin A, zinc, iron, and iodine can all contribute to a weakened immune system. Vitamin A deficiency contributes to deaths from diarrhea and measles.[55] Adding Vitamin A therapy to the treatment of children with measles decreases measles-associated pneumonia.[14] Vitamin A also causes significant morbidity secondary to xerophthalmia, resulting in corneal scarring and blindness. Xerophthalmia is the most common preventable cause of blindness in children in the developing world. The promotion of vitamin A has resulted in the successful dissemination of 2 vitamin A doses annually to more than 80% of children in the least-developed countries.[14] Zinc deficiency is related to increased risk of death from diarrhea, malaria, and pneumonia. Zinc can help decrease duration and severity of illness when given preventively and is estimated to decrease deaths in 1- to 4-year-olds by 18%.[14] Iron and iodine, while not significant factors in childhood death, do cause significant morbidity, with iron deficiency affecting cognitive development and behavior in children.[55] The Maternal and Child Undernutrition Study Group reviewed available interventions that positively affect malnutrition. Its report suggests that the following interventions could be helpful: iron and folate

Table 1-2. Odds Ratio for Mortality by Weight-for-Age, Height-for-Age, and Weight-for-Height				
	<-3 (95% CI)	-3 TO <-2 (95% CI)	-2 TO <-1 (95% CI)	MORE THAN -1
WEIGHT-FOR-AGE (Z SCORE)				
Overall*	9·7 (5·2-17·9)	2·5 (1·8-3·6)	1·8 (1·2-2·7)	1·0
Diarrhoea*	9·5 (5·5-16·5)	3·4 (2·7-4·4)	2·1 (1·6-2·7)	1·0
Pneumonia*	6·4 (3·9-10·4)	1·3 (0·9-2·0)	1·2 (0·7-1·9)	1·0
Malaria†	1·6 (1·0-2·7)	1·2 (0·5-3·5)	0·8 (0·2-3·2)	1·0
Measles‡	6·4 (4·6-9·1)	2·3 (1·7-3·2)	1·3 (1·1-1·5)	1·0
HEIGHT-FOR-AGE (Z SCORE)				
Overall*	4·1 (2·6-6·4)	1·6 (1·3-2·2)	1·2 (0·9-1·5)	1·0
Diarrhoea*	4·6 (2·7-8·1)	1·6 (1·1-2·5)	1·2 (0·9-1·7)	1·0
Pneumonia*	3·2 (1·5-6·7)	1·3 (0·9-2·1)	1 (0·6-1·6)	1·0
Malaria†	2·1 (0·9-4·9)	1·0 (0·4-2·4)	0·7 (0·5-0·9)	1·0
Measles‡	2·8 (1·4-5·8)	1·7 (0·8-3·6)	0·7 (0·5-0·9)	1·0
WEIGHT-FOR-HEIGHT (Z SCORE)				
Overall*	9·4 (5·3-16·8)	3·0 (2·0-4·5)	1·5 (1·2-1·9)	1·0
Diarrhoea*	6·3 (2·7-14·7)	2·9 (1·8-4·5)	1·2 (0·7-1·9)	1·0
Pneumonia*	8·7 (4·8-15·6)	4·2 (3·2-5·5)	1·6 (1·1-2·4)	1·0
Malaria†	2·3 (1·6-3·2)	3·0 (1·0-8·9)	0·9 (0·3-2·6)	1·0
Measles‡	6·0 (4·3-8·2)	3·7 (2·5-5·5)	1·8 (0·9-2·6)	1·0

*Ghana, Senegal, Guinea Bissau, the Philippines, India, Nepal, Bangladesh, Pakistan.

†Ghana, Senegal, and Guinea Bissau.

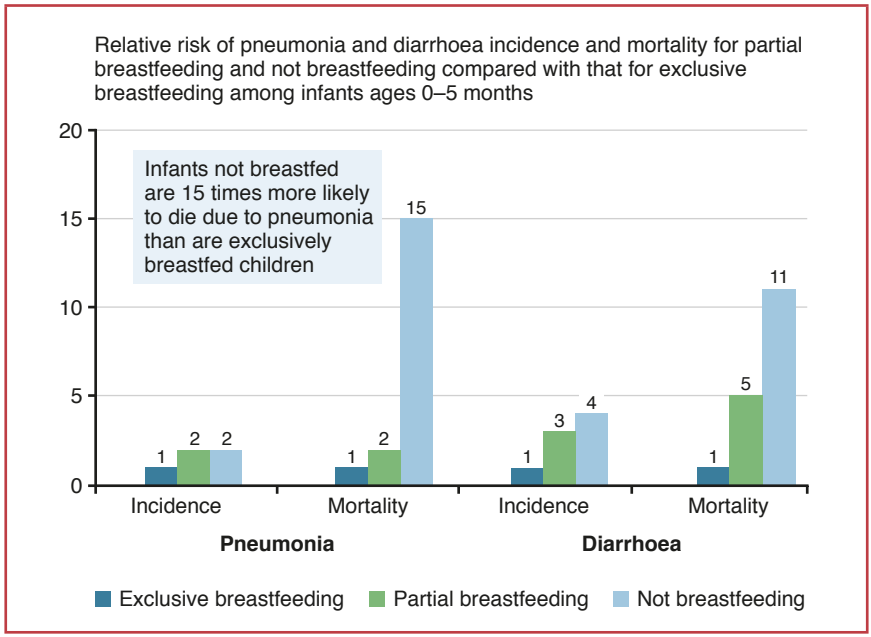
‡Nepal, Ghana, Senegal, Guinea Bissau, and the Philippines.

From Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet.* 2008;371(9608):243–260. Copyright 2008, with permission form Elsevier.

supplementation to pregnant women, vitamin A supplementation in the neonatal period and infancy, preventive zinc supplementation, and universal iodized salt. This group estimates that implementing these interventions could decrease stunting by 36% and mortality of children from birth to 3 years of age by 25%.[57]

There is continued focus on the importance of breastfeeding promotion. Figure 1-11 shows the increased risk of dying from pneumonia and diarrhea if a child is not exclusively breastfed. The recommendation for child-feeding practices is exclusive breastfeeding for the first 6 months and subsequent breastfeeding until the age of 2 years along with other food. However, only 37% of infants worldwide are exclusively breastfed for the first 6 months of life.[54] The importance of *early* breastfeeding has also been stressed: breastfeeding needs to start within the first hour of life.[54] Breastfeeding needs to be promoted with professional support by skilled health professionals and counselors, lay and peer supports, community-based counseling, and enforcement of the International Code of Marketing of Breast-milk Substitutes. This code, developed in 1981 by WHO and UNICEF, not only promotes breastfeeding but seeks to ensure that nonhuman milk formulas are not aggressively marketed, thereby ensuring that mothers around the world are given accurate information with which to make informed decisions about feeding their infants.[58]

Figure 1-11. Young Infants Who Are Not Breastfed Are at a Greater Risk of Dying Due to Pneumonia or Diarrhea



From United Nations Children Fund. *Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children*. New York, NY: United Nations Children's Fund; 2012. http://www.childinfo.org/files/Pneumonia_Diarrhoea_2012.pdf. Accessed June 10, 2015.

Immunizations

Immunizations are among the single most cost-effective public health interventions that exist. As many as 20% of all child deaths could be prevented with vaccination.[20] Significant strides in immunizing children were made over the past 40 years. Polio is almost completely eradicated, with only 223 cases left worldwide in 2012 and only 3 countries with indigenous polio transmission (Nigeria, Afghanistan, and Pakistan).[59] Starting with the EPI in 1974, coverage for DPT3 increased from 20% in 1974 to 83% in 2012.[43] However, approximately 22.6 million children were still not immunized with DPT3, particularly in India and some countries in Africa.[43] There is also a slow expansion in the number of vaccines recommended for global distribution; hepatitis B was added in 1992 and Hib vaccine in 1998.[60] In 2012, the GVAP was adopted by the World Health Assembly (194 nations); it is a plan to provide equitable access to vaccination for all around the world.[43] The GVAP has several goals, 4 of which are

- Improving immunization coverage of routine vaccines
- Encouraging introduction of new vaccines
- Working toward eradicating vaccine-preventable diseases, polio being the first
- Encouraging research in vaccine development[43]

Unfortunately, long-term funding issues remain a challenge. Programs such as Gavi help increase support for vaccines. By the end of 2012, Gavi helped 70 countries with vaccine financing.[20] Gavi has spent the last 10 years focused on adopting vaccines such as yellow fever, hepatitis B, and Hib and plans to spend the next decade assisting countries with funding for meningitis, pneumococcal, and rotavirus vaccines. By the end of 2012, the pentavalent vaccine (diphtheria, tetanus, pertussis; hepatitis B; and Hib) was being used routinely in 70 countries, pneumococcal in 24 countries, and rotavirus in 12 countries. Regions that had newly introduced pneumococcal or rotavirus vaccine were seeing a dramatic drop in hospitalizations and deaths from these diseases.[20] Obtaining funding to aid with the eventual dissemination of the human papillomavirus vaccine is also a goal.[20] The ability to achieve the Gavi plan goals has been hampered to a certain extent by challenges in vaccine supply and country readiness.[20] Security concerns have also impeded the success of immunization efforts, particularly in war-torn areas of Afghanistan and Syria and in bordering countries such as Pakistan.[59]

War

Armed conflict profoundly affects children and their health. It is estimated that 90% of deaths during a war are civilian and half of those civilian deaths are children.[61] In the last 10 years, the wars in Afghanistan, Iraq, and Syria have taken hundreds of thousands of civilian lives and millions have become refugees.[62–64] Civilian deaths are compounded because war disrupts the food supply and availability of health care, leading to malnutrition and increased risk of disease. Children are forced to become child soldiers, endure rape, and undergo unimaginable psychologic stress. Unfortunately, war affects countries in poverty. Of the 20 countries with the highest younger-than-5 mortality rates, 13 were involved in conflict or fragile situations. The annual child mortality decline rate in these countries was also low or stagnant.[1] War leads to fewer resources to improve child health and decreases the availability of health care and immunizations.[61]

Poverty

Millennium Development Goal 1 addresses poverty—eradicate extreme poverty, and cut in half the numbers of people whose income is less than $1 per day. Many diseases would not have such a stronghold if there was less poverty. Those children born in impoverished nations have a much greater risk of dying; the chance of dying before the age of 5 years is almost 90 times greater in Sierra Leone than in Sweden.[10] To have a lasting effect on child mortality, economic inequalities, exemplified by the fact that the world's 85 richest people have a combined wealth equivalent to the annual income of the poorest 3.5 billion people, must be addressed.[65]

> *"This indifference—by politicians, policy makers, donors, research funders, and civil society—is a betrayal of our collective hope for a stronger and more just society, one that values every life no matter how young or hidden from public view that life might be. It signifies an unbalanced world in which only those with money, military strength, and political leverage determine what counts and who counts. As health professionals, we should not accept this pervasive disrespect for human life."*[66]
>
> *— Richard Horton*

Funding

"If access to health care is considered a human right, who is considered human enough to have that right?"
— Paul Farmer

"Children and mothers are dying because those who have the power to prevent their deaths choose not to act."[66]
— Richard Horton

The most recent published accounting of official development assistance for maternal and child health programs globally appeared in *Lancet* in 2012.[67] Between 2003 and 2010, official development assistance more than doubled from $2.6 billion to $6.5 billion. However, funding streams were unpredictable, making it difficult at times for countries to sustain programs. Funding also needed to be better targeted to countries and programs within countries with the greatest need.[67]

The WHO recently convened a study group to investigate and develop an economic analysis of the benefits of investing in women's and children's health. Published in *Lancet,* the Global Investment Framework for Women's and Children's Health aims to go above and beyond the obvious social benefits of decreased morbidity and mortality to show the great economic benefits, particularly if the investment rate is increased over the next 20 years (2013–2035).[68] If health expenditures are increased by just US $5 per person per year until 2036 in the 74 high-burden countries (where 95% of deaths occur), there could be a return of *9 times* that value in economic and social gains. The investment would mean a US $30 billion per year increase, which is about 2% above current spending. Increased family planning services alone would result in a 47% reduction in child deaths and a 53% reduction in maternal deaths. Interventions would lead to healthier children, which translates to a healthier future workforce.[68]

THE NEXT MILLENNIUM DEVELOPMENT GOALS

The process has already begun to create new global development goals beyond 2015. Some suggested continuing with the current MDGs and just recalibrating them.[69] Table 1-3 lists alternative suggestions for future goals, given the change in landscape since 2000, including climate change concerns and economic shifts. A UN-appointed panel, the High-Level Panel of Eminent Persons, developed one list. The other list was developed by looking at the last 15 years of UN summits and conferences and distilling the major themes, which resulted in overlap with previous MDGs (at least 6) and the development of 4 new ones: Protect

Table 1-3. Comparing Millennium Development Goals and Post-2015 Development Goals With the High-Level Panel of Eminent Persons 12 Illustrative Goals

8 MDGs	10 POST-2015 DGs	12 HLP-Gs
1. Eradicate Poverty	1. Eradicate Poverty	1. End Poverty
2. Universal Primary Education	2. Universal Primary Education of Good Quality	3. Provide Quality Education and Lifelong Learning
3. Promote Gender Equality	3. Ensure Gender Equality, Women's Empowerment, Health and Well-being	2. Empower Girls and Women and Achieve Gender Equality
4. Reduce Child Mortality	4. Protect Children's Lives and Rights	4. Ensure Healthy Lives
5. Improve Maternal Health	5. Optimise the Health and Well-Being of the Ageing	
6. Combat HIV/AIDS, Malaria, and Other Diseases	6. Combat HIV/AIDS and Other Communicable Diseases	
	7. Ensure Food and Water Security	5. Ensure Food Security and Good Nutrition
		6. Achieve Universal Access to Water and Sanitation
7. Ensure Environmental Sustainability	8. Ensure Sustainable Development	7. Secure Sustainable Energy
		8. Create Jobs, Sustainable Livelihoods, and Equitable Growth
	9. Create Universal Access to Communication and Information	9. Manage Natural Resource Assets Sustainably
8. Global Partnership for Development	10. Global Partnerships in Governance and Financing for Development	10. Ensure Good Governance and Effective Institutions
		11. Ensure Stable and Peaceful Societies
		12. Create a Global Enabling Environment and Catalyse Long-term Finance

Abbreviations: DG, Development Goal; HLP-G, High-Level Panel Women and Girls; MDG, Millennium Development Goal.

From Brolan CE, Lee S, Kim D, Hill PS. Back to the future: what would the post-2015 global development goals look like if we replicated methods used to construct the Millennium Development Goals? *Global Health.* 2014;10:19. http://www.globalizationandhealth.com/content/10/1/19. Accessed July 14, 2015.

Children's Lives and Rights, Optimise the Health and Well-Being of the Ageing, Ensure Food and Water Security, and Create Universal Access to Communication and Information.[69]

POST-2015: WHAT'S NEXT?

There has been significant progress toward the MDGs as outlined in the previous sections. There was a decline in child mortality from 90 deaths per 1,000 live births in 1990 to almost half (48) in 2012, which means almost 18,000 fewer children are dying every day from preventable causes. But many of the goals were not fully achieved for all countries, and these disparities were highlighted in the previous sections as well. Within countries, the poorest continue to receive less than the rich and urban dwellers have better access to health care than rural populations. Gender discrimination and low education levels also contribute to inequities within countries, which are masked by countrywide statistics. Children of educated mothers are more likely to survive. In China and India, girls have a higher mortality rate than boys.[70] These are some of the reasons why a set of Sustainable Development Goals (SDGs) emerged in the post-2015 era—not to replace but to supplement and enlarge what began as the original MDGs. For instance, while child injury prevention did not make it into the MDGs, at least one injury-related health goal (traffic injury prevention) made it into the "zero" draft of the UN post-2015 SDGs (as of March 2015).

Some countries have already made progress. While many of the inequity findings suggest insurmountable odds, the experience in Brazil proves otherwise. There is a 5% annual reduction (ahead of target) in child deaths and a drop from 19.9% (1990) to 7.1% (2006) in stunting. This tremendous progress is attributed to a number of economic and health interventions accompanied by a committed political agenda, all of which will be woven into the new post-2015 SDGs, which will be finalized by the UN General Assembly in 2015.

Sustainable Development Goals

The SDGs will deepen and expand the MDGs because they will include social, environmental, and economic development goals; include goals focusing on all countries, not just developing countries; affect all aspects of public policy, not just those affecting children younger than 5; mobilize resources and global partnerships from all sections; and address health but also unemployment, inequality, hunger, agriculture, education, energy, climate change, ecosystems, and poverty. Governments around the world will have to recommit themselves in the post-2015 era, individually and through alliances, to continue working on decreasing

child mortality, poverty, maternal mortality, and injury and increasing education of women and children but also on more comprehensive goals focusing on overall outcomes from people and societies. Health systems and ecosystems must be improved to effectively implement effective policies, programs, and environments across the continuum of maternal, newborn, and pediatric care, in concert with an agenda that is universal, integrated, and transformational. Achieving safe, healthy, and educated children will be an outgrowth of these SDGs that emphasize well-being and sustainability for all countries.

KEY POINTS

- *Statistics.*
  - Global child mortality substantially declined over the last 25 years. Ramping up current efforts will result in continued decreases in death along with considerable economic benefit.
  - It is unacceptable that 18,000 children younger than 5 years die every day—most from preventable causes—and that 800 die daily from pregnancy- or childbirth-related causes.
- *Interventions.* The knowledge and tools to further decrease child and maternal mortality and morbidity exist.
  - Family planning
  - Maternal and neonatal care
  - Malaria control
  - Injury prevention
  - Addressing the HIV epidemic
  - Immunizations
  - Strengthening community-based services, such as the IMCI program, to improve child health
- *Political will.* More leaders and their governments need to understand the substantial benefits that increasing investment in programs, infrastructure, and health workforce will reap in the future.
- *Equity.* Infrastructure improvements must reach all people equitably, not only from one region to another but also within a country's borders.
- *Policy.* Two global policy documents that help set the stage for improvements in global child health are the MDGs and SDGs.

We cannot afford to sit on the sidelines and be content with the status quo. We need to be a loud voice for our children because if we care for them in a fair and equitable manner, we will pave the way to a more just society.

"It is health that is real wealth and not pieces of gold and silver."
— Mohandas Gandhi

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CHAPTER

2

Culture, Economics, Politics, and War: The Foundation of Global Child Health

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INTRODUCTION

Traditionally, pediatric training, like most medical education, has primarily focused on the biomedical causes, cures, and preventive modalities of disease that affect child health and well-being. Medical missions by small groups of pediatricians and other health professionals from lower-, middle-, and higher-income countries historically focused on curative, biomedical approaches. Such missions accomplish much good for the children they serve and for the medical teams involved.[1] Increasingly, pediatricians and students of child health are becoming interested in approaches reaching a wider spectrum of the population and whose effects are sustainable. Pediatricians in the United States, Canada, and other higher-income nations seek to partner with their colleagues in middle- and lower-income nations to bring about fundamental change in child health across the globe. Numerous national and pediatric organizations, including the Accreditation Council for Graduate Medical Education, the American Board of Pediatrics, the American Academy of Pediatrics, and the Federation of Pediatric Organizations, are actively involved in global child health as part of their core missions and strategic plans.

Critical to understanding child health dynamics across the globe is to appreciate the integrated roles of culture, economics, and politics on the well-being of children and their families. Indeed, much of the health disparity between and within nations can be attributed to the intersection of the biological basis of diseases and sociocultural and political economic context in which a child develops and matures.[2] Pediatricians and child health specialists who wish to work toward achieving improved global child health must be aware of these issues and their actions guided by this understanding.

This chapter reviews the effect on child global health of a range of social, political, and economic issues, including poverty and resource disparities; access to health care; homelessness; child labor; child prostitution; gender, ethnic, and racial inequalities; and war and civil unrest. The intersection of pediatrics with these concerns at the levels of policy, intervention, and health care, as well as local, national, and global advocacy for the well-being of children worldwide, are then discussed.

DEFINING CHILDHOOD AND ADOLESCENCE

The World Health Organization (WHO) defines children as 0 to 9 years of age and adolescents as 10 to 19 years of age. However, childhood and adolescence are age-based social constructions that vary historically and across cultures.[3–5] Concepts about child development and parenting are based in social and cultural contexts and may be strongly associated with values and ideals in relation to religion, kinship, and social and familial obligations.[6–10]

Not so long ago in the United States and Western Europe (and still in many societies today), children grew into adulthood with little of the transitional period demarcated in Western medicine and social sciences as adolescence.[9] This period of development emerged in the United States and Europe in the late 19th century as a part of industrialization and globalization as young people worked independently outside of an agrarian economy, stayed in school longer, and delayed marriage.[4]

A majority of mid-20th century research on childhood development and psychology was based in a Western-focused conceptualization of development categories. Such research normalized the Western models for childhood development, parenting, and even the clinical manifestations of disease.[11] However, in the last 25 years, social and medical sciences recognized and began describing the variations of childhood and adolescence across time and cultures and employing methodologies that improve cross-cultural research with children.[12]

EFFECT OF SOCIOCULTURAL, POLITICAL, AND ECONOMIC ISSUES ON GLOBAL CHILD HEALTH

Poverty and Resource Disparities

Tran lives with her husband on a small island in the South China Sea. Her husband is a fisherman and is away from home 2 to 3 weeks a month. During the rainy season, access to the mainland is often difficult. One afternoon, Tran's 3-year-old daughter begins acting fretful and develops a fever and very loose watery diarrhea. The trip to the hospital on the mainland is about 45 minutes away, but Tran is concerned because the water is very rough with heavy rains. Her husband is out fishing despite the conditions. Tran treats her daughter with soupy rice and tea made from leaves she grows in her garden. Her daughter's condition only worsens as she begins vomiting and having large watery stools every half hour. Tran goes to the pharmacy, where she obtains an antibiotic. However, her daughter cannot keep the liquids in her body and eventually is unable to take the fluids. She is no longer crying tears and is not responsive. She dies later that same evening.

An estimated 6.6 million children younger than 5 years die every year—and nearly 50% of these deaths are associated with malnutrition. Seventy-five percent of these deaths occur in Africa and Southeast Asia. Two-thirds of these deaths are preventable through access to low-cost interventions and effective primary care. The major causes of these deaths are pneumonia, diarrheal diseases, and malaria.[13]

Economic conditions and the distribution of resources within and between communities, regions, and nations have significant direct and indirect effects on the health of children of all ages. For example, the world's poorest children are 2.7 times less likely to have a skilled attendant at birth.[14] It is not possible to address global health without acknowledging the relationship between income and child health and well-being.

An examination of data presented in the annual United Nations Children's Fund (UNICEF) *State of the World's Children* report illustrates the parallel courses between economic and health disparities (www.unicef.org/publications). For example, *The State of the World's Children 2008: Child Survival*[15] reports that children younger than 5 years experience a mortality rate of 6 per 1,000 live births in countries with a gross national income (GNI) per capita greater than or equal to $37,000.[15] In countries with a per capita GNI of less than $2,000, children younger than 5 years experience a rate of 79 deaths per 1,000 live births (referred to hereafter as the younger-than-5 mortality rate). However, this relationship between income and childhood mortality is not absolute. For

example, among the 11 nations with a younger-than-5 mortality rate greater than 200 children per 1,000 live births, 3 have an annual GNI per capita greater than $800, while the remaining 8 nations have an annual GNI per capita less than $800. Also, among 47 nations with a GNI per capita less than $800, 36 report younger-than-5 mortality rates of less than 200 per 1,000 live births. Bangladesh and South Africa have a younger-than-5 mortality rate of 69 per 1,000 live births; yet, the annual per capita GNI of Bangladesh is $480 and of South Africa is $48,282. Similarly, Eritrea and Algeria, with GNIs of $200 and $33,351, respectively, have younger-than-5 mortality rates of 74 per 1,000 live births. These figures illustrate that while poverty and wealth are important, there are by no means simple correlations between countrywide income and child survival.

Resource disparities and distribution of wealth within countries also contribute to child mortality. Among countries in sub-Saharan Africa, with a younger-than-5 mortality rate of 160 per 1,000 live births, the poorest 40% of the population controls only 13% of the wealth, while the wealthiest 20% controls 55% of the wealth. In South Asia, where the per capita GNI of $777 is marginally lower than that of sub-Saharan Africa ($851), the poorest 40% of the population controls 19% of the resources, while the wealthiest 20% controls 46% of the wealth. The South Asian younger-than-5 mortality rate of 83 per 1,000 live births is roughly half the rate of sub-Saharan Africa and close to the global median of 72 per 1,000 live births.[15] These data suggest that more equitable distribution of even limited resources can affect child health.

Research suggests that income inequality (calculated as a ratio of the amount of income to the top 20% of households to the amount of income to the lowest 20% of households) in high-income countries has significant negative effects on child health and social and educational well-being. Among 21 high-income nations, the United States ranks first in income inequality, and evidence suggests that within the United States, those regions and states with greater inequality show higher rates for poor health outcomes, including low birth weight and infant mortality.[16]

Access to Health Care

Prana lives in Kolkata with her husband and 4 children. Prana heard from her neighbors and saw a flyer posted in the common area of her housing about a campaign taking place over the next 2 weeks to ensure that all children are immunized against polio. Vaccination will take place at a local site within a 5-minute walk from her residence. Prana's husband heard from some men with whom he works that the vaccine might be unsafe and cause infertility in their

children. Although Prana knows that her children are not vaccinated against polio and she would like for them to receive the vaccine, she is reluctant to go against her husband's decision. She decides not to participate in the campaign.

Related to poverty and inequitable access to resources is the issue of access to health care. Access to health care is mediated by multiple factors, including social, political, and economic conditions that can affect availability of care, particularly for poor or marginalized populations. While health care costs and lack of adequate numbers of health practitioners are the most obvious barriers, other barriers include language, social or legal status, gender inequalities, isolation or distance to travel to health facilities, traditional beliefs about disease etiologies, and distrust of the existing health system, as well as the disruption of health services from civil unrest and war. Evidence suggests that households with higher incomes are more likely to seek health care for their children and also receive higher quality of care. Meanwhile, children in the poorest households are at greatest risk for disease because of malnutrition, poor sanitation, and indoor pollutants, yet are the least likely to receive adequate health care.[17] Inequities in health care include high-cost procedures for small numbers of patients, medical programs that may discourage those in greatest need from accessing services, and disparities between local community members' perceptions of needed and desired programs and programming that is evidence based and supported by the scientific and medical community.[18,19]

There are significant differences among countries and regions in terms of numbers of available skilled health workers (eg, doctors, nurses, midwives). In the European region there are 78 nurses or midwives and 32 doctors for a population of 10,000. In Southeast Asia there are 12 nurses or midwives and 5 doctors, and in Africa there are 11 nurses or midwives and 2 doctors for a population of 10,000. In 2005, lower-income countries spent an estimated 4% of total public expenditures on health care, compared with 16% in high-income countries. As a consequence, in lower- and lower-middle–income countries, an estimated 90% of private health costs are out of pocket compared with 39% in high-income countries.[20]

In 1974, the WHO established the Expanded Program on Immunization (EPI). At that time, fewer than 5% of children living in lower-income countries were receiving vaccines that were readily available in high-income countries. Today, through the EPI, it is estimated that 83% of infants and children worldwide receive available vaccines against tetanus, pertussis, measles, diphtheria, and polio. In addition, *Haemophilus influenzae* type b, rubella, and mumps vaccines were

recently added to the EPI schedule in some countries. It is estimated that 3 million children's lives are saved annually as a result of EPI.[21,22]

Despite such significant accomplishments in vaccine coverage, more than 22 million infants are not immunized and 1.5 million children die annually from vaccine-preventable diseases.[21] Multiple integrated cultural, social, political, and economic factors contribute to the immunization status of children.[23] For example, worldviews that incorporate beliefs about balancing hot and cold elements within the body to maintain health can contribute to refusal to use certain vaccines as well as other Western medicines. In Vietnam, Western medicines, including vaccines and antibiotics, are considered hot. Infants and children are perceived as vulnerable to these hot elements, which is believed to cause them illness or delay their development.[24]

Access to health care can also affect children when parents or other caregivers or providers are unable to access care for themselves. Most notable in this respect is a woman's access to prenatal and antenatal care, as well as voluntary and accessible birth control. Access to health care during and after pregnancy can help improve a woman's nutritional status, provide access to tetanus toxoid immunization, and decrease risks for HIV and other sexually transmitted infections, malaria, and tuberculosis.[25] Access and communication with health care resources during pregnancy can also increase the likelihood of a household's participation in childhood immunization and other disease prevention programs (eg, use of insecticide-treated bed nets).[26] Research in Pakistan and Indonesia indicates that a woman's immunization for tetanus during pregnancy and her knowledge of the disease increased chances that her children received EPI immunizations.[27,28]

Human immunodeficiency virus/AIDS and access to antiretroviral therapy (ART) directly and indirectly affect child health. A woman's access to ART during pregnancy and delivery significantly decreases risks for her child. In addition, the death of one or both parents due to HIV/AIDS has left approximately 15 million children younger than 18 years orphaned worldwide. While many children are incorporated into other relatives' households, others become homeless or institutionalized. For all of these children, the effects of parental loss due to HIV/AIDS can include stigmatization, grief, and psychologic and emotional distress.[29,30]

Homelessness

Nguyen has worked selling postcards, books, and souvenirs to tourists since he was 9 years old. Now, at the age of 15, he lives in a one-room rental space with his 18-year-old brother. His mother lives outside the city. Nguyen works every day from early morning until late in the evening. On some days he is

"lucky" and makes several dollars, but most days he does not sell any postcards or just one or two. His diet primarily consists of noodles purchased from small snack stands on the street. When Nguyen is sick, he seeks advice from some of the women who also sell to tourists. However, he does not have the ability to receive care through public or private clinics. Throughout his years selling on the street, he is approached by men willing to pay him as much as $100 for sex. He knows other young men who participate in these sexual exchanges and is tempted to accept the offers when he has gone a long time with little or no money.

An estimated 100 to 200 million children and adolescents worldwide live in shelters or on the street.[4] Children and adolescents can become homeless as a result of their parents' loss of income, work, or housing; extreme poverty; natural disasters; warfare; becoming orphaned due to HIV/AIDS; or voluntarily leaving their residence. Brazil, which has the highest number of street children in Latin America, also has the greatest income inequality in the region.[31]

Some children live on the street to earn money for themselves or their family. Others want to escape overcrowded housing, family disapproval, or abusive conditions.[32] In lower- and middle-income countries, generally more boys than girls live on the street, although these numbers are more equal in high-income countries. Street children may have no contact with their families, may have some regular contact with family, or may be part of a family that has no permanent home.

Children living on the street are frequently represented as threats to social order. Their living conditions and associated poor health are normalized as the expected results of street life.[33] While living or working on the street can contribute to an increased likelihood of drug use and sexual and reproductive health issues, it is problematic to disassociate many other nutritional and health concerns among street children from those of all children living in extreme poverty.[31,34]

Child Labor

The role of children as workers within families and their contributions to household income vary significantly between cultures and higher- and lower/middle-income countries. In many societies in Africa and Asia, children are expected to contribute to the household and are raised to feel a lifelong obligation to support their parents and maintain their lineage. Within agrarian societies, children at early ages take on a range of chores, and work is a significant part of socialization and is not conceived as a violation of a child's rights. For example, in Kenya, an estimated 10% of children between the ages of 5 and 15 years are engaged in work. Even though a majority of these children are contributing to

family farm labor, these children can still be exposed to conditions that can negatively affect their well-being.[35] In Bangladesh, an estimated 19% of children between the ages of 5 and 14 years are in the labor force. While poverty and insufficient household income are reasons the children work, cultural perceptions of the children's role in the household and that children should not be idle contribute to rates of child labor.[36]

Child labor is of mounting concern as children are exposed to increasingly urbanized and industrialized settings.[5] Children often work in non-organized, informal work sectors (ie, selling on the streets) that lack regulations for safety or health. In middle- and lower-income countries, children also work in factories, mines, and domestic service. These children are exposed to dangerous chemicals and machinery and are frequently exploited and abused.[37] Children's biological and developmental characteristics can increase their risks in relation to carcinogenic and other toxic substances.[38] In the most extreme cases, children and adolescents from rural regions are sold and forced to work in manufacturing facilities, providing businesses with labor at little cost in an increasingly competitive global market.[39]

Child Prostitution

Liu works at a "massage parlor" 6 evenings a week. This massage parlor is set up to provide sexual services for local and traveling businessmen. Liu is now 17 and has worked at the parlor for about a year. Liu traveled to the city from the countryside where her parents have a small farm. Her father has a respiratory illness and is often unable to work.

Liu came to the city to work as a waitress but was only able to find part-time work that paid poorly. One of the girls at the rooming house where Liu was staying introduced her to work at the massage parlor. Liu was reluctant at first but was convinced to work for "just a short time" to make as much as $500 a month.

Liu has sexual relationships with about 10 men a week. Five or 6 of her clients are regulars, but most of them only come for one visit. Liu feels shame when she engages in sex with these men, as they are often verbally abusive to her and occasionally physically abusive. Liu was told about using condoms, but her regular clients and some of the one-time clients pay her extra to not use them.

The sex work industry is closely associated with multiple social, economic, and political changes, as well as organized crime, gangs, government corruption, and human trafficking. Sex work is illegal in most countries and workers and clients are frequently marginalized. Regardless of legal status, sex tourism brings money into lower- and middle-income countries and therefore is often "overlooked" by national and local government authorities.

Globally, the sex work industry generates approximately US $20 billion per year, with a quarter of that from child workers.[40] In 4 Asian countries (Malaysia, Thailand, Indonesia, and the Philippines), the sex industry is estimated to account for between 2% and 14% of the gross domestic product.[41] The main users of this sex industry are local men. The vastness of this industry is built on sociocultural factors including gender inequality, sexual stigma, and constructions of masculinity, as well as such economic factors as rural-to-urban migration and lack of accessible well-paid legal employment for the large populations of young people.[41–43]

Sex work often starts at an early age. Data suggest that in some regions of Asia, the prime age for entering into sex work is 12 to 16 years. One study indicates between 30% and 35% of sex workers in the Mekong Delta region are 12 to 17 years old.[37] Research in China indicates that many establishment-based (eg, massage parlors, karaoke bars) female sex workers are young, have little education, and come from rural areas.[44] In poor Kenyan rural coastal regions, it is estimated that 30% of girls (some as young as 12) and young women are engaged in some form of casual sex work.[45]

While most sex workers are female, young men also engage in the sex work industry. These young men are a particularly vulnerable population because of social and cultural taboos in many countries with regard to men having sex with men. These taboos create barriers to identifying and providing services for these young men.[41]

In addition to children and adolescents engaged in sex work within their own countries, trafficking of youth between countries results in forced engagement in sex work, physical abuse, and isolation from resources. In many instances, these youth or their parents are told that they will be working as domestics or in some other industry.[46] An estimated 1 million children, with estimates as high as 10 million, are forced into the sex work industry annually.[40]

Gender, Ethnic, and Racial Inequalities

Margarita came to the United States from a village in El Salvador at the age of 14 years to live with her aunt in an East Coast city. Margarita started school but found it very difficult and quit after about 6 months to work with her aunt cleaning office buildings. Margarita met Carlos, who was 20 years old, had his green card, and worked a steady construction job. Margarita and Carlos moved in together when they learned that Margarita was pregnant. They plan to get married as soon as Carlos becomes a US citizen. Margarita's neighborhood started to undergo many changes and they were forced to move out of

their apartment when it was bought to be redeveloped as condominiums. They moved outside of the city into a neighborhood where few people speak Spanish. Margarita needs to find a doctor to provide care during her pregnancy but is delaying because of her fears regarding language barriers, questions about her legal status, and concerns about the costs.

Ethnicity, race, and gender are social categories that are constructed and reconstructed across time and place. These categories are often naturalized as biological distinctions, thus providing an authenticity to the existing social order.[47] Characteristics of ethnicity, race, and gender further become imbedded within a society's structural and knowledge systems.[48]

Inequality affects children's access to education, housing, and adequate nutrition. Furthermore, inequalities and associated discriminations and recriminations can significantly compound issues such as health care access, negotiations between traditional and biomedical world views, and child health outcomes.[49,50] Analysis of the US National Survey of Children's Health for 2013 indicates Latino(a) respondents were more likely to be uninsured (22.4% versus 10.3% for white Americans and 17.0% for African Americans).[51] Other disparities between majority white American respondents and Latino(a), African American, First Nation, and Asian respondents included poor health outcomes (eg, higher rates of asthma) and lack of access to health facilities (eg, problems obtaining specialty care).[52] In other research with US farmworkers, of whom 87% are Latino(a), data indicate that these workers' children were 2 times more likely to be uninsured than other low-income US children.[53]

Constructed gender roles and responsibilities can significantly affect child and adolescent well-being. In some cultures, as girls reach puberty, they may be perceived as sexually vulnerable and consequently married at a young age. In many countries in South Asia and Africa, more than 50% of girls are married before the age of 18 years. Between 1998 and 2007 in Bangladesh, 64% of 20- to 24-year-old women respondents on national and international surveys were married prior to becoming 18 years old.[54] These young women experience pressure to produce children soon after marriage, resulting in low contraceptive use and high fertility. As a result, Bangladeshi women 15 to 19 years of age experience higher rates of mortality than young men of the same age.[55] In this instance, gender constructs intersect with high levels of poverty to increase these adolescent women's vulnerabilities to risks associated with early and multiple pregnancies.

Other health outcomes in relation to social inequalities for children and adolescents can include psychological distress and associated

syndromes, increased risks for sexually transmitted infections (ie, young women's abilities to negotiate condom use), and increased likelihood of incarceration.[56–58]

War and Civil Unrest

Iqbal is 16 years old and a soldier in his nation's army. He has not seen his parents for the 3 years he has been in the army. His family is very poor. When the army passed through his village on the way to war, he was told he would earn a lot of money, which would be sent to his parents. He has not seen the money and has not heard from his parents, so he does not know if they received it. He no longer wants to fight, but he is in another country and does not know how he could return home. Lately he has been alone on the night watch and spends much of the night crying.

The effects of war and disruptions of life during periods of civil unrest profoundly affect the well-being of children living in those nations engaged in war or those areas under political, economic, and social chaos during regional conflicts. These periods of extreme violence and volatility negatively affect every facet of childhood development and health.

Since the end of World War II, more than 250 major wars have taken the lives of more than 23 million people. Prior to World War I, an estimated 90% to 95% of direct war casualties were soldiers; in World War II, this ratio dropped precipitously to 50%. In modern-day wars, civilians account for approximately 90% of the casualties, with women and children accounting for 75% of those deaths.[59]

In modern time, wars are consistently prevalent, with most occurring within the boundaries of a nation.[60] The first decade of the 21st century hosted more than 3-dozen wars, most of which were also internal conflicts. Over the last 2 decades, an estimated 4 million children were killed as a consequence of war.[59,61] Many of these conflicts lasted longer than a decade, resulting in entire generations of children whose developmental trajectory from infancy through young adulthood was shaped by war.[62]

Direct mortality figures account for only a portion of the total negative effect of war 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*.[62] This document identifies and discusses 8 broad areas in which war negatively affects virtually all aspects of child well-being and development. In addition, children in military families face unique challenges during times of war whether or not they live in a country in which the conflict is being waged.

Disruption of Basic Child Health Pediatric Care and Services

War disrupts services essential for child well-being. Food and water supplies are interrupted, resulting in inadequate amounts and unsafe products; immunization programs are crippled; and health care practitioners may be unavailable. Most contemporary wars are occurring in lower-income nations, placing children with preexisting malnutrition or other health conditions in particularly vulnerable situations.[62] Tuberculosis and malaria are likely to reemerge even in countries where they were previously controlled. Studies in Angola demonstrate direct relationships between combat and rising rates of under-immunization and malnutrition with greater effects in areas most affected by war.[63] Child mortality rates increased nearly 50% during the Bangladesh war of independence, and Uganda immunization rates plummeted from more than 70% to less than 10% during wartime.[62]

Health facilities that provide preventive and curative services to children, including services to disabled children, may be destroyed by war, abandoned due to a lack of available personnel, or co-opted to provide for military needs. Reproductive health services, including family planning, prenatal and antenatal care, and testing and treatments for sexually transmitted infections, will often be curtailed because of limited health care practitioners and resources.[63]

The range of psychological assaults and potential disruption to identity formation, which children experience living through wars, are limitless, including post-traumatic stress disorder (PTSD), anxiety, depression, and behavioral problems. The response of an individual child to these exposures is widely variable, but children of both genders, regardless of age, may be affected.[64]

Gunfire, Land Mines, and Unexploded Ordinance

An estimated 110 million land mines contaminate at least 68 countries. Land mines and other unexploded ordinances are indiscriminate, exploding when triggered by friend or foe, child or adult, human or animal. All continents are affected, although Africa may be the most afflicted. Angola alone has an estimated 10 million land mines and, as of 1996, housed more than 70,000 amputees, including 8,000 children, as a result of land mine explosions.[62] Chechnya experienced nearly 1,400 land mine explosions in 2000 and 2001; one-quarter of the victims were children. Almost one-third of the children were injured while playing where explosives lay, and in some cases, curious children tampered with them.[65] Butterfly mines used extensively by the former Soviet Union are

brightly colored and appear to have wings. In Chechnya, children used mines as wheels for toy trucks and to play games.[62]

Children and adults also set off explosive devices while engaged in economic activities such as cultivating fields and foresting.[65] The affected individuals carrying out these activities are often among the poorest in the nation. Although antipersonnel mines are not designed to kill, children are more likely to die. In Cambodia, approximately 20% of childhood mine injuries result in death. For those who survive, adult or child, economic consequences are significant, with more than 60% of families of mine victims in debt in one study. It was estimated that clearing mines takes 100-fold longer than deploying and a $3 mine may require $1,000 to remove. Because most of the nations with land mines have severely constrained resources, national funds for their removal are often not available.[62]

Refugee Status

During times of conflict, families may feel that they have no option but to flee or send their children to safer locations. It is estimated that there are 23 million refugees worldwide, of whom approximately 40% are children younger than 18 years. In many instances, these children are not accompanied by parents or other adult guardians. Persons in flight are highly vulnerable during the escape, while in a refugee camp in their own or another country, and even when they successfully reach asylum. Children in refugee situations may experience PTSD, grief, loss, and separation anxiety. Diseases such as cholera and measles may sweep through the refugee camps, particularly where immunization programs were disrupted. Girls, in particular, may be vulnerable to rape and sexual abuse within these camps.[66]

Multiple models for working with refugee children have evolved over the years, including those that focus on the individual and a more biomedical or therapeutic approach and those based in a theory of sociocultural re-adaptation in which a safe and structured environment is established for the children.[67]

Destruction of the Environment and Chemical Toxins

War and conflict devastate natural environments. During the Gulf War, Kuwaiti oil wells were purposefully set on fire and crude oil spilled into waterways. During the 1970s and 1980s in Cambodia, 35% of the forest cover was destroyed. During the years of conflict in Angola, 90% of the wildlife was eradicated.[68]

During the Vietnam-American War, 77 million liters of herbicides, including nearly 50 million liters of Agent Orange/dioxin, were released over 2.6 million acres of forests and countryside.[69] Dioxins are stable and their half-life within the human body is from 7 to 11 years. Short-term effects of dioxins on humans include skin lesions and altered liver function. Long-term exposure compromises the immune system and effects development of the nervous, endocrine, and reproductive systems.[70] While negative health outcomes from exposure during the war are accepted, research continues to document potential effects from current exposure in regions affected during the war. Recent studies found elevated amounts of a dioxin consistent to exposure with Agent Orange in areas where the chemical was sprayed during the 1960s and 1970s.[71]

A meta-analysis of 22 studies indicates that parental exposure to Agent Orange appears to be associated with a range of birth defects among children born to US and Vietnamese veterans and Vietnamese nationals, with the magnitude of the association increasing with degree of exposure.[69] The US Department of Veteran Affairs currently recognizes association between multiple diseases and exposure including Hodgkin disease, multiple myeloma, non-Hodgkin lymphoma, prostate cancer, and multiple respiratory cancers and soft-tissue sarcomas.[72] In addition, the department provides benefits to children with spina bifida born to female veterans exposed to Agent Orange.[73]

Child Soldiers

At any given time, an estimated 250,000 to 300,000 children younger than 18 years are serving as soldiers.[74] They may be forcibly recruited, sold into armed service by their parents, or feel they have no other option for self-protection or protection of their families. Child soldiers may be used as messengers, martyrs, guards, foragers, or sexual servants. Given the developmental stage of these young adolescents, they are especially vulnerable to the pressures of group ideology, romantic illusions of martyrdom, and failure to appreciate the danger of violent situations.[2] Reentry of these children into society is typically not negotiated during cease-fire agreements and does not take into account the violence they suffered, witnessed, or perpetrated. They may have lost or not be welcomed by their families. A study among Nepali child soldiers found high rates of depression and PTSD.[62] A study among former Ugandan child soldiers describes symptoms extending beyond those of PTSD, suggesting the emerging diagnosis of developmental trauma disorder.[75]

Gender-Based Violence

Rape and other forms of gender-based violence, unlike murder and torture, are not widely recognized as war crimes. Adolescents (generally girls but also boys) are particularly at risk. The fine line between rape and sex for food or for survival during war underscores the importance of zero tolerance for gender-based violence. Rape also occurs frequently in detainment camps, not uncommonly by international soldiers and security personnel.

Educational Needs

Schooling is important for age-appropriate transfer of knowledge to the child as well as to maintain a sense of routine during the disruptions of war and conflict. However, schooling will generally be anything but normal during wartime, with a loss of teachers due to enlistment, draft, or displacement; possible attacks on or appropriation of school buildings for military purposes; an unstable student body with migration and population movement; and a lack of reliable resources (eg, schoolbooks, school supplies, water, electricity).

Deployment and Children

Families are profoundly affected when one or both parents are deployed. Deployment is associated with abuse, neglect, attachment problems, and inadequate coping skills, as well as increased outpatient mental health clinic visits among children in US military families.[76–78]

THE ROLE OF PEDIATRICS AND CHILD HEALTH SPECIALISTS

The examples in this chapter provide a brief overview of the many political, economic, and sociocultural factors with devastating implications for global child well-being. Two overarching concerns are poverty and inequitable distribution of resources within and between countries and gender, ethnic, and racial inequalities. Economic decision-making and priority setting are deeply entwined within politics and health care, whether at a local, national, or global level. It is essential that pediatricians be part of the political process to guide decisions about distribution of much-needed resources.

Such advocacy must be well-informed and consistent with other child welfare advocates. However, pediatricians have unique roles in these efforts. First, evidence-based programs are important in industrialized countries; they are critical in lower- and middle-income countries.[79] Pediatricians can help guide policy makers in such approaches.[54,79] There are a vast number of reviews and meta-analyses of programs addressing high-impact issues in lower-income countries. For example, Bhutta

and colleagues published a comprehensive review that examined 186 studies, including 64 community-based studies.[80] Although the authors found significant gaps in the literature, they were able to identify several groups of intervention approaches for which there is credible evidence of high impact on important outcomes. Likewise, the Cochrane Collaboration conducted intervention reviews on 26 topics of importance in lower- and middle-income countries, including nutritional, education, and perinatal-neonatal survival interventions and tobacco cessation programs.[81]

When pediatricians are invited to work in other settings or asked to help develop programs in new settings, it is their responsibility to be well-versed in outcomes literature addressing the programs in which they will be involved. Obtaining these reviews and becoming familiar with successful programs (and program components) as well as unsuccessful programs will allow the visiting pediatrician to contribute to the host country rather than simply take away experience.

At the same time, it is important to recognize that change comes slowly, and often programs in place that are not evidence based (or are even contrary to the existing evidence base) have their own history and reason for existence within a community. Equally important for physicians are health outcomes that are epidemiologically important but for which no evidence base exists or are only for countries with a very different socioeconomic and health structure. In such situations, the pediatrician may share with the hosts data that do exist and possibly work with the hosts to develop an intervention trial.

Many of the issues discussed in this chapter are difficult to research, and limited baseline information is available about the extent of effects on child health and well-being. For example, child prostitution is illegal and often well-hidden. There remains insufficient data on the numbers of children involved, as well as the morbidity and mortality rates associated with these exploitative practices.[40,82] Pediatricians and other health professionals can contribute through collaborative efforts with local organizations to develop, implement, and evaluate intervention programming. At a national and international level, pediatricians can advocate for stronger policies addressing the exploitation of these children and work for more funding to increase knowledge about the health status of these children to develop more targeted and effective programs.[40]

War, civil disorder, and other conflicts present multiple challenges for intervention. Pediatricians have uniquely important roles in sustaining services through these political actions by supporting combat-free immunization days (in which they may participate if they are in the country)

and group efforts such as the World Food Programme, which seeks to establish reliable food chains, and working as long-term volunteers in refugee camps with established groups such as Doctors Without Borders.

Pediatricians can play a key role in protecting children from land mines by working with schools, parents, and children in countries where land mines and unexploded ordnance remain. Pediatricians can teach them how to recognize these devices, regard them as serious weapons, and discourage their use as toys. Pediatricians can also support international political action prohibiting the use of land mines and creating funds to clear mines, such as the UN Voluntary Trust Fund for Assistance in Mine Action.[62]

Pediatricians can work to rejoin children with their nuclear or extended families. UNICEF developed emergency kits to facilitate the work of volunteer relief workers; pediatricians planning to work in such settings should be familiar with these kits to ensure that their well-intended actions are actually helping. Likewise, if pediatricians are in a situation to advise families living in combat zones about evacuation of children, parents should be encouraged to do so with care and knowledge of the proposed routes and detailed documentation of persons responsible for conveying and receiving the children to avoid risks of child trafficking.[62]

Pediatricians, whether working in regions of conflict or attending to the needs of children in safe-haven or refugee settings, can help youth who lived in war-torn nations by

- Assisting parents in reconstructing their social networks and rebuilding a secure home life
- Encouraging youth to be involved in normal school routines and, where possible, community-building efforts
- Integrating psychological support for the child and parent in routine clinical and preventive care
- Avoiding questioning youth about painful memories while at the same time inviting them to discuss issues that might be disturbing them
- Being knowledgeable about local accessible mental health services to offer the family and youth if needed

Pediatricians should serve as champions for continued education and be knowledgeable about existing resources. For example, relief agencies have long known of the importance of continued schooling. The United Nations Educational, Scientific and Cultural Organization, UNICEF, and others developed teacher's emergency packs to aid teachers in delivering education during the first few months of war while more sustainable strategies for education are developed. In refugee situations, pediatricians

should attempt to find out where children can receive education to guide families, as often, refugees will not be permitted to attend public school in host countries. Pediatricians may also play an advocacy role, reminding local government and donor agencies that in addition to reconstructing the physical infrastructure, resources must be focused on teacher recruitment, retention, and training.[62]

Pediatricians can help by offering to speak to military personnel about their responsibilities to civilian women and children and to support measures designed to encourage reporting and treating rape as a war crime. Pediatricians can work with international efforts to identify rape and exploitation of children as specific war crimes.[67] As long as leaders in the global society condone this action through their silence, it will continue unabated. Pediatricians can play a critical role in this regard. Further, they can and should provide reproductive and psychological support to victims of gender-based crimes.[64] Pediatricians may also be in a position to advocate for the special educational and mental needs of former child soldiers. Pediatricians should join international efforts, whether at home or abroad, to prohibit the use of soldiers younger than 18 years.

It is likely that wherever a pediatrician practices, he or she will have patients whose family was deployed. Being aware of the deployment status, openly acknowledging and inquiring about the possible stresses facing the family (including the children), and being aware of local services to address concerns are important services to these families and their children.

The UNICEF *The State of the World's Children 2008: Child Survival* identifies 7 broad precepts about improved global health. These precepts contain economic implications and can serve as useful guides to pediatricians working abroad. Although a visiting pediatrician will generally not be in the position to develop entirely new systems, he or she can help make a difference, regardless of the size and cost of the health plan, by following these guiding precepts.

1. Focus on countries and communities with the highest mortality rates.
2. Package essential services to improve coverage and efficacy.
3. Actively engage the community to develop programs that will be sustained after the pediatrician leaves.
4. Provide a continuum of care linking communities to health care facilities.
5. Develop a strategic, result-oriented approach to health care in which maternal, infant, and child care are central.

6. Recognize the importance of political partnerships and the need to incorporate sustained financing into program development.
7. Work collaboratively with other health partners.

KEY POINTS

- As pediatricians from higher-, middle-, and lower-income countries partner to address global child health issues, the dynamic intersection of biological, sociocultural, and political-economic factors need to be recognized and addressed through education, research, and practice.
- A nation's gross national profit and/or per capita income, as well as wealth distribution among its inhabitants, are all closely associated with child morbidity and mortality indicators, but there are notable exceptions, demonstrating that economic development is essential but not sufficient for improved child health.
- Access to health care is affected by the health care system, transportation systems, numbers of trained providers, gender and ethnic inequalities, social factors such as decision-making within a family, access to funds, personal belief systems, and political factors, including violence and war.
- While the global EPI initiative has dramatically increased immunization rates across the globe, an estimated 1.5 million children still die annually from vaccine preventable diseases. Lack of access to health care for women and children in some regions of the world continues to hinder the delivery of these basic lifesaving preventive measures. Rates of vaccine-preventable diseases are substantially higher in countries facing social unrest and war.
- Multiple sociocultural and political-economic conditions result in homelessness and child labor. Children may be homeless and living with their family, or they may be street children living independently all or part of the time. These children have less access to health care services and are vulnerable to physical and sexual violence, substance abuse, and poor nutrition
- Globally, the sex work industry generates approximately US $20 billion dollars per year, with one quarter of that from child workers. These children and adolescents are at a high risk for substance abuse; exposure to sexually transmitted infections, including HIV; and victimization from physical and sexual violence.
- War and civil unrest are significant causes of malnutrition, low immunization rates, increased mortality, and physical and mental health disorders among the whole population, with the greatest effect on children. Children suffer these multitude of health-related negative outcomes from exposure to land mines and unexploded ordinances,

chemical warfare, conscription as soldiers, disruption of basic health and educational services, and forced emigration and living in refugee settings.

- Pediatricians can serve in many roles to positively affect global child health.
  - —Advocate for children's rights and access to health care.
  - —Participate in research and practice that increases the number of evidence-based programs in middle- and lower-income countries.
  - —Collaborate and volunteer with local nongovernmental organizations and governments in the development and implementation of interventions directed at vulnerable children (eg, those living on the street, engaged in sex work) to decrease risks of negative social, emotional, psychological, and physical outcomes.

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CHAPTER

3

Medical Anthropology

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INTRODUCTION

Practices related to maintaining health and treating sickness are grounded in a culture's belief system, which provides a framework for understanding and explaining illnesses, diseases, symptoms, causes, and treatments. This chapter explores the discipline of medical anthropology and provides cross-cultural examples of ethnomedical systems and the accompanying illness causation theories, diagnosis processes, and treatment beliefs. As partners in pediatric health care, medical anthropologists explore the cultural context of health and healing and facilitate the incorporation of cross-cultural knowledge in medical education and health services research.

ANTHROPOLOGY

Anthropology is broadly defined as the holistic study of humans, past and present. Anthropology is unique among social sciences in that "the focus of anthropology is on clusters of people—how they differ in form and behavior from other clusters of people—and how the largest cluster of people, the human species itself, relates to other species."[1] Anthropologists focus on culture as it exists throughout all levels and domains of societies throughout the world. A principle aim of the discipline of anthropology is to describe varying ways of life without devaluing the cultural differences found among societies.[2]

Culture

Anthropologists study culture, which is defined as "that complex whole which includes knowledge, belief, art, morals, law, custom, and any other capabilities and habits acquired by man as a member of society."[3] Culture includes the behaviors and ideas we take for granted in everyday life, from following traffic signals, to the language one speaks, to recognizing national symbols, such as the bald eagle in the United States. Culture encompasses our daily lives, consciously and unconsciously. It is not static; rather, culture is constantly responding to economic, political, and social forces. Culture is learned through communication and observation in the process of enculturation, wherein children and adults learn the norms, values, beliefs, customs, and traditions that govern behavior in society.

Anthropologists use qualitative and quantitative methodologies to study culture. The primary qualitative methodology in anthropology is participant observation, wherein the anthropologist participates in everyday, community activities and observes the quotidian activities of the culture invisible to the casual observer.[4] The goal of participant observation is to gain an in-depth understanding of the study population and the power structures that affect a culture.

All cultures have health care systems. It is within the purview of medical anthropology to explore the epidemiology, health perceptions, definitions of illness and disease, role of the curer, and appropriate medical treatment within and across cultures.

MEDICAL ANTHROPOLOGY

Medical anthropology is the study of health, illness, and healing across the range of human societies and over the course of the human experience.[5] Specifically, medical anthropologists explore how different cultures explain the causes of illness, the types of treatment they deem acceptable, and to whom they turn for treatment.[6] The anthropologic study of health care systems and "primitive medicine" was pioneered in the 1940s by Erwin H. Ackerknecht. In these early days of anthropologic study, much of the literature was published in medical journals rather than anthropologic publications.

By focusing on the intersection of culture and health, medical anthropologists bring with them the qualitative methodological experience indicative of anthropology and a commitment to exploring health, medicine, and healing in a cultural context. This includes examining the greater political, economic, and social webs of power in society to assess the effect of class, race, gender, and age on health and health outcomes.

Often, medical anthropologists have focused their gaze on child and adolescent health across cultures.[7–13]

Health, Disease, and Illness

A guiding principle in medical anthropology is that health, disease, and illness are culturally defined. The World Health Organization defines *health* as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity."[14] A *disease* is a health threat that is externally verifiable, often through a clinical or scientific process.[15] It can be genetic in origin or caused by bacterial, viral, fungal, or parasitic agents or other pathogens. Alternatively, *illness* is a condition of poor health felt by the individual—a perception.[6] Therefore, it is possible to become ill without a disease or have a disease without being ill. This nuance is important to consider when developing therapies, treatments, and healing prescriptions for patients of diverse cultural backgrounds. Overcoming cultural dissonance that exists among individuals from divergent medical systems is possible, as examples in this chapter will demonstrate.

CULTURE AND ETHNOMEDICAL SYSTEMS: BRIDGING BELIEF AND UNDERSTANDING

A medical system encompasses the "cultural beliefs and practices that are learned and shared by a group of people."[15] *Ethnomedicine* is defined as "culturally constructed medical systems."[15] Both definitions rely on the notion that a medical system is a product of the culture in which it exists. The central focus in ethnomedical approaches to studying healing is to understand the "group's conceptualizations of illness, its causes and cures, the role of healers, and the relationship between concepts of disease and cosmology."[16] The ethnomedical approach focuses on understanding how medical systems are constructed cross-culturally, how they are similar and different cross-culturally, and ways in which they reflect cultural norms and values. For example, spiritualism in Mexico is as culturally based as biomedicine because each system is specific to the culture's beliefs. Similarly, the biomedical belief in prescription drugs is a cultural construct based on the metaphor that the body is a machine, while another culture might believe that the body is an extension of the natural environment and logically rely on herbal treatment. Because a fundamental theoretic foundation of medical anthropology is that all medical systems are bound by cultural beliefs, a disciplinary priority is to examine biomedicine as a form of ethnomedicine alongside all other medical systems.[17] All ethnomedical systems have a theory of illness

causation or etiology, mechanisms for diagnosing the cause of illness, and norms for prescribing appropriate diagnosis-based therapy.[15]

Etiology

All ethnomedical systems provide a framework for understanding the cause of disease and illness. There are 3 primary etiologic theories: naturalistic, personalistic, and emotionalistic.[18,19] Originally created to aid in the cross-cultural comparisons of non-Western medical systems, cultural etiologies of disease and illness help us understand potential options for diagnosis and treatment.

Naturalistic Disease Theory

Naturalistic disease theories explain disease through scientifically identified agents. Due to the causes attributed to disease and illness in naturalistic theories, a specialist in symptomatic treatment is required for healing. Health is accomplished through equilibrium and balance. Preventive measures can generally be described as "things not to do," such as abstaining from smoking or drinking. Hippocrates' humoral system of health, which revolves around the balance of 4 bodily liquids, is considered a naturalistic disease framework. Within this framework, diseases are thought to derive from natural forces, thus causing an imbalance of bodily elements. This imbalance may be caused by cold, heat, wind, and dampness.[18] Belief in the humoral system is centralized in Asia, Latin American, and parts of the Middle East. Additionally, Western biomedicine is considered an ethnomedical system that uses the naturalistic disease theory characterized by externally testable variables observed and measured within controlled conditions.

Personalistic Disease Theory

Personalistic disease theory explains disease and illness as caused by the active or purposeful intervention of an agent. That agent may be human (witch or sorcerer), nonhuman (animal), or supernatural (ancestral spirit or ghost). Individuals are victims of personalistic disease for reasons known only to them. Consequently, personalistic disease etiology remains at the individual, not population, level. Personalistic disease theory situates poor health as the result of individual behavior, wherein the victim acted in such a way as to cause the illness.

Emotionalistic Disease Theory

According to Foster and Anderson,[19] there exists a third disease theory in which emotional states cause disease and illness; this is referred to as emotionalistic disease theory. In this framework, intense anger,

jealousy, shame, grief, fright, and other extreme emotions result in illness. Symptoms are psychologic and physical in nature, as someone may report disassociation from daily life, persistent lethargy, and other withdrawal symptoms.[19] In addition, individuals report loss of appetite, sudden weight loss, and insomnia. Healers include shamans, household members, and other culturally appropriate community members.

Diagnosis and Treatment in Cross-cultural Perspective: Culture-Bound Syndromes

To illustrate the variety of options available when health is situated within diverse ethnomedical systems, the following examples of culture-bound syndromes unravel the mechanisms for diagnosing and treating disease and illness cross-culturally. Culture-bound syndromes are illnesses specific to a particular society or cultural tradition and treated in a specific way.[20] These examples illustrate the complexity of maintaining good health in an ever-increasingly globalized world where individuals and households experience health and wellness through multiple etiologic lenses. In the course of medical care, a patient may or may not describe an ethnomedical belief system with causal or etiologic information. Indeed, a patient may begin to describe poor health conditions by explaining the culturally appropriate mode of treatment or therapy, which will, in turn, assist the medical practitioner with framing the individual's course of care. Therefore, the examples also provide cultural information that sheds light on pathways to culturally appropriate and complementary treatment and therapy options for the practicing biomedical physician.

Nervios

Nervios, or nerves, is an emotionalistic disease found throughout Latin America and the Mediterranean. Nervios attacks include shaking, feelings of heat or pressure in the chest, difficulty moving limbs, feelings of the mind "going blank," and loss of consciousness (Table 3-1). Symptoms result from a slow buildup stemming from the problems one experiences in life, especially concerning household and financial issues, culminating in an acute attack. Nervios attacks afflict adults and children. Children experience heartache, extreme sadness, and feelings of despair and loss that may lead to acts of anger. Reports indicate that nervios can result in children harming themselves or attempting suicide.

Nervios attacks are more likely to occur in children coping with a parent who has migrated, often to the United States. Children experience frustration, lack of control, and feelings of abandonment as their parents, particularly their fathers, migrate for work.[21] Nervios often persists

Table 3-1. Summary of Culture-Bound Illnesses

ILLNESS	SYMPTOMS	POSSIBLE CAUSES
Nervios	Shaking, feelings of heat/pressure in the chest, difficulty moving limbs, mind "going blank," loss of consciousness, heartache, extreme sadness, feelings of despair and loss, anger	Biomedical explanation includes anxiety, depression, panic attacks stemming from low social or socioeconomic status.
Brain fag	Visual (blinded by light) or auditory sensory disturbance, impairment of intellectual activity, emotional disturbances, inability to read, inability to understand or recall what is being read, head and neck pain, fatigue	Pressure for group achievement in schools but individual personality, motivation, emotion, stimulant use, and sleep deprivation may be factors.
Susto	Appetite and weight loss, distraction, lethargy, diarrhea, vomiting, fever, sleeplessness, crying	Believed by locals to be caused by the loss of the soul through sudden fright; no agreed-on biomedical explanation

in children even after their households are reunited, a result of the constant uncertainty inherent in today's globalized world. The social, political, and economic status of Latinos and Latino Americans reveals a widespread "sense of hopelessness, helplessness, and lack of control,"[22] often experienced disproportionately by women,[23] that manifests as nervios.

Nervios is an example that illustrates the concept of social suffering that "results from what political, economic, and institutional power does to people and, reciprocally, from how these forms of power themselves influence responses to social problems."[24] Through ethnographic research with individuals afflicted by nervios, we are able to connect the illness to the transnational migrant work networks that result from global economic inequalities. Thus, the illness, while experienced by individuals, is also bound to populations most affected by larger, structural factors.[25,26]

Brain Fag

Brain fag syndrome was first described by Prince[27] among Nigerian students. The name *brain fag* is derived from his patients describing the cause of their illness as fatigue of the brain from extensive brain work. Symptoms generally arise during periods of intense reading or studying or following periods of intense study.[27,28] The syndrome has the

following 4 classes of symptoms: sensory disturbances, impairment of intellectual activity, emotional disturbances, and somatic complaints. Intellectual impairment manifests itself as an inability to read, grasp content, or recall what was just read. Sensory disturbances are chiefly visual but sometimes auditory. The patient's vision is often altered in a way he finds difficult to describe, sometimes using the phrase "blinded by a light." Most commonly, patients complain of head and neck pain as well as a general weakness of the body and easy fatigability. Emotional effects are the least stressed but could be expressed as depressive symptoms[27] (see Table 3-1).

Onset is usually gradual, with somatic symptoms arising prior to intellectual impairment. It is seen particularly among Western Africans in non-African educational systems in which success is measured by individual achievement. West African societies are collectivist and often measure success by the achievements of the group. Genetics, intelligence, or parental literacy are not thought to be directly related to the eitiology.[27] Instead, this syndrome may have a multifactorial etiology, including personality, motivation and emotion, stimulant use, and sleep deprivation.[28]

Susto

Susto is a fright illness believed to cause soul loss after a person experiences a fearful situation or a sudden, loud disturbance.[29,30] Commonly found in Latin America and Latin American immigrant populations,[31] symptoms include loss of appetite, weight loss, distraction, and lethargy,[32] as well as diarrhea, vomiting, fever, sleeplessness, and crying in children[33,34] (see Table 3-1). In children, susto is often cured by their mothers, an elder female, or shamans called curanderos, who perform rituals that call the soul back to the body and aim to restore the psychologic and spiritual balance of the patient.[35] Mothers with children suffering from susto report that biomedical physicians cannot cure the disease because the cause of susto is not pathologic; therefore, very few children are taken to a biomedical doctor's office.[33]

In addition, susto sufferers have higher rates of morbidity and mortality than control groups.[32] Individuals who suffer from susto are at great risk for suffering from poor mental health.[29] Interestingly, individuals with susto do not meet the biomedical criteria for depression, as was commonly thought, although individuals with depression are likely to report previous experience with susto (and nervios). It is hypothesized that individuals use the culture-bound syndrome of susto to express psychologic distress and seek assistance in an effort to curtail the likelihood that the illness escalates to depression.[29] Furthermore, it is notable that

susto is associated with diseases such as Type 2 diabetes in explanatory models of illness in culturally diverse populations.[36,37]

With an understanding of ethnomedical systems and etiologies, the examples in this chapter illustrate that various symptoms are interpreted and explained in different ways by people with diverse cultural worldviews. The diversity of symptoms that individuals express is indeed linked to their beliefs of illness causation and is subsequently connected to their diagnosis. Thus, familiarizing oneself with the possibilities for causation models and diagnosis options necessarily leads to reflections on treatment and therapy. For example, nervios is categorized as an emotionalistic disease caused by mental distress, but the diagnostic symptoms of weight loss and diarrhea are 2 commonly accepted health problems within a biomedical system.

APPLYING MEDICAL ANTHROPOLOGY TO CHILD HEALTH

As a result of globalization, acculturation, and the increase in biomedical training worldwide, cultural groups often believe in multiple disease theory systems. Belief in and practicing multiple disease and illness causation theories is referred to as *pluralistic health care practices,* as Pelto and Pelto[38] assert.

> *In most areas where traditional care predominated in the 1940s and 1950s, there is now widespread acceptance of many aspects of cosmopolitan medicine, often without any apparent sharp reduction in traditional beliefs and healing practices. Studies in Asia, Africa, and Latin America have shown that families utilize both indigenous and cosmopolitan health care resources, sometimes serially, sometimes simultaneously.*

Therefore, challenges for the biomedical clinician are to seek an understanding of a person's disease causation theory, validate the reality of that belief, and seek mutually acceptable modes of therapy and treatment.[39] Medical anthropologists partner with biomedical practitioners, indigenous healers, and health care institutions around the world to incorporate the cultural diversity of health and healing beliefs. The partnership between medical anthropologists and medical educators is leading to improvements in the quality of health care through an "anthropology devoted to helping health practitioners do their work better."[40]

Medical Education: Incorporating Cross-cultural Content to Enhance Patient Care

One result of this collaborative research with medical practitioners is the introduction of the culture concept and various ethnomedical systems in the medical curricula to reflect the plurality on health care practices worldwide.[41] Institutions commonly require medical and nursing students to complete introductory anthropology or medical anthropology courses to increase exposure to diverse cultures. Additionally, the Accreditation Council for Graduate Medical Education has mandated cross-cultural education in medical training.

In medical education, books such as Anne Fadiman's *The Spirit Catches You and You Fall Down: A Hmong Child, Her American Doctors, and the Collision of Two Cultures*[42] and Emily Benedek's *Beyond the Four Corners of the World: A Navajo Woman's Journey*[43] describe the tensions and misunderstandings between indigenous cultural beliefs and Western biomedical culture. Both texts present compelling arguments for cultural competency, sensitivity, and humility in providing health care. Effective cross-cultural medical education uses anthropologic understandings of the vitality of culture and focuses on the acquisition of skills, such as knowledge of various disease etiologies, diagnosis models, and treatment options, to develop collaborative relationships between the clinician and patient to develop mutually acceptable treatment plans.

Furthermore, medical anthropologists have worked to ensure that medical education does not place culture as a protagonist when different notions of health and healing collide, which could lead one to blame culture as one would any other character for disastrous and tragic outcomes. Medical anthropology serves to remind us that "'Culture' is not a 'thing,' somewhere 'out there,' that books are 'about.' It is a process of making meanings, making social relations, and making the world that we inhabit, in which all of us are engaged—when we read and teach, or when we diagnose and treat…."[44]

Improving the Pediatric Health Care Delivery System

Medical anthropologists are concerned with improving children's health services research by examining the "structure, processes, and outcomes of health services for children for the ultimate purpose of improving the health and well-being of children."[45]

Specifically, research exposing communication dissonance between practitioners and the patient or household members is a focus of medical anthropology. Foundational to this body of literature is the notion that improved communication, at all levels, is a vehicle for enhancing the

delivery of health services. This research demonstrates that as a result of increased trust and disclosure, communication between practitioners and household members improves the quality of care and outcomes for the pediatric patient.[46–49] A pediatrician who understands the concepts and practices of different cultures will be better at communicating with the patient and her household and improving health outcomes.[50] Similarly, pediatricians who reflexively recognize their health care system as one that is culturally constructed will be better positioned to assist their patients in negotiating possible cultural divides.[51]

Through the lens of medical anthropology, this chapter focused on the intersection of culture and health. Medical anthropologists study culture to understand the ways that cultural groups diagnose and treat illness and disease. When unpacked, the relationship between culture and health can provide valuable insight into factors that differently affect the health of populations living in a culture, structural factors that affect some cultural populations disproportionately, and ways health care practitioners can improve their sensitivity to cultural difference to provide effective health interventions. Threads of culture connect populations by weaving different historical, political, and economic experiences. Medical anthropologists, with their commitment to understanding variety and difference and to placing concepts and social situations in a holistic framework, are uniquely qualified to explore these variables in ways that make them useful for pediatric practice and research.

KEY POINTS

- Anthropologists study *culture,* defined as behaviors, ideas, and processes that guide everyday life.
- Medical anthropologists examine the relationship between culture and health, illness, and healing.
- All cultures possess an ethnomedical belief system that includes theories of illness causation, mechanisms for diagnosing cause of illness, and norms for prescribing appropriate, diagnosis-based therapy.
- Culture-bound syndromes, such as nervios, are often treated with pluralistic medical systems and therefore require health care practitioners to negotiate mutually agreeable, collaborative treatment plans.
- Medical anthropologists apply their cross-cultural research to enhance medical education and strengthen health services to improve pediatric care and outcomes across the globe.

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CHAPTER

4

Cultural Humility in Pediatric Practice

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INTRODUCTION

There is a significant need for culturally effective health care services based in cultural humility to address existing health disparities for minority children and mend fragmented systems of care in which some receive better services than others. Cultural humility is a lifelong process of reflection and critique that considers one's own biases in addition to the patient's perspectives. Investigating one's own assumptions about health, medicine, and culture is often neglected in trainings on cultural competence and effectiveness. In addition, cultural humility can be difficult to achieve with families and children because culture itself is translated through parents, family, and community members. Pediatricians may not see a family's cultural differences because they are not physically apparent (eg, belief systems, religion, socioeconomic status). In addition, children may identify with several cultures simultaneously or have a different cultural presentation than their parents, further complicating their beliefs, behaviors, and resources related to health care.

Pediatricians may not understand the culture of some families and children because they maintain stereotypic views of particular culturally different groups. Ultimately, if caregivers do not feel understood or do not feel involved in their children's health care, the result may be that

families are marginalized from the health care system, do not function as good advocates for their children, and engage in poor medical adherence to their children's treatment. The purpose of cultural humility is to reject stereotypic or generalized understandings of culture and instead turn toward more nuanced, individualized, patient-centered care. Complex global changes in demographic diversity, cultural health beliefs, decreased health equity, pediatric practice abroad, and relevant policies and standards demand cultural sensitivity, awareness, and competence in pediatric practice. Cultural humility requires continuous effort and reflection to ensure that practitioners are meeting the needs of patients and families.

CHANGING DEMOGRAPHICS

We are an increasingly diverse society with an explosion of social, linguistic, religious, and cultural differences. The startling rate of globalization is due to advances in economic and geopolitical activity, telecommunications, and transportation. Worldwide, there are changes in the composition of populations, with increases in foreign-born children and families from diverse nations. In the United States, it is estimated that by 2060, close to 70% of school-aged Americans will be of racial or ethnic minority groups (nonwhites).[1] This diversity is further complicated by increases in the number of internationally adopted children in Europe and the United States and the increase of refugee children worldwide, as well as the growing numbers of multicultural families in which parents come from different backgrounds (eg, nationality, religion, race, ethnicity) and children display hybridization and alternation between 2 or more cultures.

These growing diverse communities may have varied health beliefs, values, and practices, as well as diverse social factors that affect their lives. Countries like the United States, Canada, Australia, and Britain have large Southeast and East Asian communities. Large immigrant communities like these, and existing African and Caribbean communities in Britain, can lead to an increased perception of cultural distance within societies. In addition, growing multicultural societies create culture shock and opportunities for intercultural adjustment. These phenomena do not only affect immigrants adjusting to new cultures but also people within society who interact with these diverse communities in their daily lives.

Along with foreign-born families to societies worldwide, linguistic diversity is on the rise. There are an estimated 5,000 to 6,000 different languages spoken worldwide. In the United States, there are more

than 329 languages spoken, with 61 million people speaking a language other than English at home.[2] Eight-hundred forty-eight million people across 13 countries speak Mandarin Chinese—the most spoken language in the world—as a native language. Spanish is now the second most spoken language in the world, with approximately 406 million native speakers across 31 countries. English follows with 335 million people across 101 countries, and then Hindi with 260 million speakers across 4 countries.[3] It is clear that there are many multicultural nations with multiple languages spoken daily, requiring increased health services resources.

HEALTH EQUITY

Families and children worldwide face stark realities of health disparities and commiserate lack of health equity. In general, there are widening disparities in health and human rights worldwide and, simultaneously, patient populations are becoming increasingly more vulnerable (eg, advancing age, growing diversity, higher burden of chronic illness, socioeconomic decline[4]). The big problems in global health are defined as HIV/AIDS, malnutrition, lack of access to medical care, and lack of adequate resources.[5]

There is much less research on health disparities in ethnic minority youths in the United States and worldwide. Relatively few studies address whether minority youths receive important procedures and are prescribed intensive treatments at the same rate as majority youths. However, there is some evidence that disparities exist in this area. For example, US data indicate that the ethnicity of children with asthma is associated with physicians not adhering to national care guidelines,[6] minority adolescents receiving fewer services,[7] racial or ethnic differences in the probability of children receiving prescription medications,[8] and US Latino children receiving lower quality health care, including fewer laboratory tests, radiographic examinations, and prescriptions for nebulizers after asthma-related hospitalizations.[9] In addition, the US Department of Health and Human Services reported health disparities in access and quality of care in all ethnic groups as compared with white Americans, defining the health care of minorities and low-income individuals as "suboptimal."[10] The American Academy of Pediatrics (AAP) Committee on Pediatric Research specifically called for more research on racial, ethnic, and socioeconomic disparities in treatment and clinical outcomes for minority youths.[11]

To fully understand the severity of health disparities and increase health equity globally, there must be joint consideration of race and ethnicity combined with social class and culture. Many social and contextual factors affect how patients view their illness, and this may affect

how and if the treatment regimen is followed (medical adherence). In addition, health and well-being are increasingly recognized as contextually based, composed of a complex set of factors (eg, poverty; air pollution; racism; inadequate housing and income inequalities; other social, economic, and physical environment factors) that contribute to the disproportionate burden of disease experienced by marginalized communities.[12,13] Globally, pediatricians must practice cultural competence so that these global health disparities are acknowledged and addressed, thereby increasing health equity worldwide.

GLOBAL PEDIATRICS

With amplified internationalization and globalization and simultaneous world population growth and migration, the world has become a smaller place. As such, pediatric trainees and physicians across the United States have traveled and experienced more of the world than most other generations. In addition, educational institutions and organizations have a growing interest in addressing global health challenges and disparities,[14] which takes pediatricians increasingly into non-US settings. The proliferation of study-abroad programs, international travel, incorporation of global health content into medical curricula, medical training occurring outside of birth country, and international humanitarian efforts[15,16] all require the practice of cultural humility in a different cultural context than at home.

Cultural humility in pediatric practice is needed anywhere in the world, and lessons learned abroad about culturally effective health care based in cultural humility can be applied at home and vice versa.[17] As early as 1969, an editorial in *JAMA: The Journal of the American Medical Association* encouraged young US doctors to spend time working in a developing country to practice "better medicine at home and abroad."[18] Supporting the notion of global pediatrics, the American Board of Pediatrics is collaborating with other countries to establish the Global Pediatric Education Consortium, a working group to share the tasks of developing common standards for postgraduate training.[19]

CULTURE AND HEALTH

Health is defined broadly to include physical, mental, social, and spiritual well-being; this definition is similar to the one offered by the World Health Organization (WHO). The breadth of the definition emphasizes an inextricable link between health and culture. The definition of culture eludes most, perhaps because of the complexity of the concept and the many disparate definitions previously suggested. There is lack of consensus about the meaning of culture, and yet the notion seems to permeate

so many aspects of our lives, including personal tastes, manners, beliefs, values, worldviews, and actions. Although culture is usually thought of as national identity, the scope has broadened to include many aspects of social difference, including, but not limited to, race, ethnicity, gender, social class, religion, and sexuality. Even though much of culture in the nationalistic sense is tangible and visual (eg, food, clothing, housing, rituals), many elements cannot be seen, such as socioeconomic status, religion, and sexual orientation.

A broader definition of culture is an integrated pattern of learned beliefs and behaviors that are shared among groups. These beliefs and behaviors include thoughts, communication styles, ways of interacting, views of roles and relationships, values, practices, and customs.[20,21] We are all culturally different given our different family backgrounds, religions, occupations, disabilities, gender, socioeconomic status, and sexual orientation. Beyond race and ethnicity, we all are part of and influenced by multiple cultures. Each of us is a multicultural individual with many sets of cultures in different contexts, which may or may not coincide.[22]

Traditionally, culture has been considered the purview of anthropologists. In the medical field, the concept of culture is often oversimplified to refer to language, and cultural clashes are viewed as problems solved simply by an interpreter. Neutralization of cultural differences has also been attempted using mandatory diversity training in many organizations, during which employees purportedly learn to embrace the more superficial aspects of culture and celebrate multiculturalism.[22] It is important to remember that one size does not fit all. All cultures cannot be defined and understood in the same way because culture is a combination of many different elements, such as history, economic activity, and religion. However, the overarching characteristics seem to be that culture, in general, is shared, reflects an interaction between humans and their environment, and is carried over across generations and time periods.[23]

Aspects of Culture Affecting Pediatric Practice in a Global Context

Across the globe, there have been paradigmatic shifts in the goals of and approach to health and the definition of health itself. First, the goal of medicine has changed from simply being an eradication of illness to prevention of disease and promotion of health through the adoption of a healthy lifestyle. The definition of health has changed to include social and mental well-being. With the expansion of this definition, there is a corresponding focus on social and behavioral sciences to explain the roots of health problems.[24] This underscores the importance of context via community-based approaches and the important role that

sociocultural, behavioral, and environmental factors play in health, such as poverty, social support, medical adherence or compliance with treatment regimen, resilience, acculturation, immigration, and even shared water sources. In addition, there is more consideration of culturally sensitive approaches to health care as well as indigenous and alternative forms of healing as legitimate forms of treatment. Particular aspects of culture have a major effect on pediatric practice, including cultural health beliefs and behaviors, immigration and related acculturation stressors, and culture-bound syndromes.

Cultural Health Beliefs and Behavior

Cultural backgrounds significantly affect people's beliefs and attributions about health, illness, and medical care in ways that have important implications for health care practitioners.[25,26] Individuals may attribute causes of illness to internal factors (ie, bad habits or negative emotional states), factors within the natural environment (ie, pollution and germs), factors associated with others or the social world (ie, interpersonal stress, medical facilities, and actions of others), and supernatural factors (ie, God, destiny, and indigenous beliefs such as witchcraft or voodoo).[27] For instance, African Americans in the United States are likely to make external attributions related to the will of God, destiny, and the power of prayer.[28] On the other hand, there is evidence that white Americans are likely to attribute disease to individual behavior and perceive treatment as mechanistic and unrelated to religion, family, or other systems.[25,29]

The varied belief systems that exist across cultural groups differ in multiple factors, including disease models, perceptions of providers, specific disorders and diagnoses, and use of unique treatments and health care practices. Some traditional cultures attribute a soul to all natural objects, including human beings. These cultures may perceive illness as stemming from moral and theologic thought, with the ultimate cause of illness being disharmony in the relationship between the sick person and another being.[30] Individuals of the Mixtec culture in Mexico believe that illness can occur through exposure to disruptive forces, including extreme temperature, negative social relationships and interactions, or evil spiritual entities.[31]

Differences in causal attribution translate to differences in perceived cures. Because Westerners tend to attribute illness to individual or environmental factors, they typically believe that illness can be treated without reference to family, community, or deities. People from nonindustrialized countries often attribute illness externally to social factors or the will of God or the supernatural and, as such, may have a very

different perception of what is an appropriate or effective treatment or may not follow expected health-seeking behaviors.

Immigration and Acculturation

Immigration profoundly affects health. Immigrants are exposed to a host of conditions that may make them more susceptible to illness. Many diseases are simply endemic to the country of origin and stress because of economic hardship; disrupted family and social networks will only exacerbate illness. In the country of arrival, immigrants frequently work in low-paying jobs, face poverty, lack health insurance, have limited access to health care and social services, and have communication difficulties because of language differences. Immigration can take a toll on children in particular, as they are forced to adjust to an unfamiliar environment during formative years. Immigrant children can have infectious diseases that Western pediatricians are not used to diagnosing and treating. In addition, immigrant children often lack adequate immunization. Psychosocial factors of immigration may impose additional stressors on immigrant children (eg, disparities in social, economic, and professional status from the family's country of origin). Immigrant children may experience ongoing mental health issues because of relocation and potential atrocities experienced in their home country as well as adaptation issues with school and peer groups. Like their parents, immigrant children may lack a larger social support network of family and friends, which was present in their country of origin.[32]

Immigrants can be further disadvantaged when it comes to receiving health care. They may not be able to afford quality health care or a means of getting to a hospital; language and cultural barriers complicate the process even more, possibly making the immigrant feel uncomfortable or discriminated against. Immigrants may simply lack the knowledge of a new and complex health care system and what services are available to them. Foreign-born immigrants are twice as likely to lack health insurance as those born in the United States.[33] Recent immigrants to the United States have less contact in general and less timely contact with the health care system[34] and are more likely to have infectious diseases, especially tuberculosis, hepatitis B, and parasitic infections, as compared with US natives.[35]

Not only can immigrants suffer from a loss of social support, but they can also be negatively affected by *acculturation*—the process of adapting to a new environment. Acculturative stress occurs as immigrants lose touch with self-identifying constants, values, and social institutions of their former homeland and can lead to depression and other mental disorders. Acculturation can have negative implications for children and

their parents and family who experience uncertainty about the future, along with heightened levels of anxiety. These tensions may contribute to family dysfunction, which can manifest as strict and authoritarian child-rearing practices, including harsh disciplinary methods and possible severe physical abuse.[24,36,37] Additionally, in households in which both parents work, children may be left unsupervised or neglected and, in some cases, left behind in their native country. These circumstances can increase conflicts surrounding relationships, gender roles, and respect issues.[36]

Culture-Bound Syndromes

There are physical and mental illnesses that are unique to particular cultures, directly influenced by cultural belief systems. The *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association defines such illnesses not recognized by Western medicine as *culture-bound*. For example, mal de ojo (evil eye) in Latin America refers to the illness experienced by a child when they are surveyed admiringly by a more powerful adult. According to Latin American culture, children who have experienced mal de ojo are fussy, cannot sleep, and may even have seizures. Treatment for evil eye can include physical contact or touch from the perpetrator, typically on the head, or prayer and ritual with an egg.[38]

Cultural ideals of beauty can also be the culprit for illnesses such as eating disorders. Eating disorders span physical and mental boundaries of cultural health and, especially in highly industrialized societies, incidence continues to rise.[39] Although, in some cultures, being stout and plump is associated with good health and prosperity, the cultural ideal of women being thin and fit has increased in popularity.[39,40] In the Western world, especially among young women, the cultural notion of thinness as the ideal body image makes it clear that culture definitely influences attitudes toward body size and shape and eating behaviors.[40]

Physical ailments caused by stress or emotional distress (somatization) are common, especially in collectivistic societies, perhaps because people avoid expressing psychologic complaints to families and friends.[39] A person suffering from depression or anxiety might use somatization as a culturally sanctioned way to signal distress.[41] Recognizing that there are culture-bound syndromes and that the expression and formation differs culturally paves the way for practicing culturally sensitive medicine and psychotherapy. Otherwise, misdiagnosis can occur when ethnic and cultural differences are not considered.

FROM CULTURAL COMPETENCE TO CULTURAL HUMILITY

The term *cultural competence* is commonly used in medicine to describe effective attitudes, behaviors, knowledge, and policies in cross-cultural situations or about a specific demographic.[42] While the goal of integrating cultural competence into medical care is admirable, the direct application is not always universal to specific groups. For example, next-door neighbors may be of the same ethnicity or religion but have different customs based on other aspects of their individual culture. Anne Fadiman captured this phenomenon very well in her book *The Spirit Catches You and You Fall Down* as she described the misunderstandings of medical practitioners and family in the care of a Hmong child who suffered from seizures. Attention to the importance of such differences in cultural understanding has caused the concept of cultural competence to come under scrutiny.

Many educational bodies now focus on the concept of cultural humility. Cultural humility was first well described in 1998 by Tervalon and Murray-García.[43] Their definition of cultural humility is "a process that requires humility as individuals continually engage in self-reflection and self-critique as lifelong learners and reflective practitioners. It is a process that requires humility in how physicians bring into check the power imbalances that exist in the dynamics of physician-patient communication by using patient-focused interviewing and care." They add that knowing as much as possible about health practices in a culture is quite important; however, the competence about a specific culture's needs should not lead a practitioner to develop stereotypes. An increase in knowledge without changes in attitude or behavior would not benefit a practitioner or patient. Juarez et al add that "cultural humility…allows the physician to consciously be aware of culture and patient uniqueness during each visit."[44]

Cultural humility is described throughout the literature in many different settings and has slightly different definitions in each realm, but common themes emerge. Most authors concentrate on the importance of patient-focused interactions, the role community plays in health care, a health care practitioner's role as a learner rather than knower, avoiding the paternalistic position of a physician, a willingness to partner with the patient and help find a common ground for treatments, and a dedication to lifelong learning and self-reflection rather than simply knowledge acquisition.

The AAP uses the term *culturally effective pediatric care,* which refers to "the delivery of care within the context of appropriate physician knowledge, understanding, and appreciation of all cultural distinctions leading

to optimal health outcomes."[45] Culturally effective pediatric care is preferred over cultural competence because outcomes of the physician and patient or family interaction are considered. The AAP further recognizes the complexities of the term *culture* and includes all distinct attributes of population groups within its definition as well as the importance of traditional aspects of culture. The AAP emphasizes barriers to accessing care and how these barriers may relate to low levels of health literacy or particular health care needs of population groups.

In addition, the US Office of Minority Health (OMH) established national standards for culturally and linguistically appropriate services (CLAS) in health care.[46] The OMH CLAS standards were designed to promote health services as more responsive to all patients and consumers and ultimately to improve the health of all Americans and contribute to the elimination of racial and ethnic health disparities.

APPROACHES TO CULTURAL HUMILITY RELEVANT FOR PEDIATRICS

The need for culturally effective approaches to medical care based in cultural humility has become more important as recognition of the overwhelming link between cultural and health beliefs and outcomes increases. To address the need for culturally effective medical practice, many institutions have implemented cultural competence training into the undergraduate curriculum. Despite these efforts, research indicates that this training is largely ineffective.[47–49] In addition, health care professionals may not feel adequately prepared to practice cultural humility or provide competent care. For example, one study indicates that while only 1% of residents felt ill-prepared to perform a procedure in their specialty, 25% did not feel adequately trained to care for patients with health beliefs that contradict Western medicine, recent immigrants, or those with religious beliefs that differed from their own.[50]

Many health care institutions incorporate linguistic competence into their services and employ interpreters and translators to manage linguistic diversity for their patients. However, being linguistically competent is not the same as practicing cultural humility. For example, although a site may have interpreters available for patients, the site may still impose a Western biomedical values-based health care environment (eg, lack of religious accommodations, such as nondenominational spaces for prayer; not observing certain feeding practices and dietary mandates).

With the growing diversity of populations worldwide, the need for cultural humility within medicine is strong. Many institutions are shifting their cultural educational focus away from competence toward humility. Development of curricula and teaching of cultural humility varies by institution but is not exclusive to students. Faculty members

are also being trained in cultural humility to adequately prepare students. The introduction of cultural humility is noted as important as early as the medical school years but continues through residency and beyond. Nursing education also developed a focus on cultural humility for those in training. Levi has described the importance of cultural humility in the context of ethical nursing care for trainees in the United States and abroad.[51]

Cultural humility is often referenced in the field of global health, particularly in developing countries. One must not overlook the importance of cultural humility within the United States and developed nations practicing Western medicine. The role of cultural humility is a necessity for every patient encounter with every health care practitioner for the best outcomes to be achieved. Perhaps the importance of cultural humility is best described by Chang et al: "When sociocultural differences between healthcare professionals and patients are explored, understood, and appreciated, the result is patient satisfaction, better medical adherence, and improved health outcomes. By becoming the patient's student, the healthcare professional is not only caring for patients from her mind, but also from the heart."[52]

Incorporating ideas of cultural humility, the Vaughn and Phillips model of intercultural adjustment includes the ability for reflection and self-awareness (intrapersonal competence) and relationships with others (interpersonal competence).[53] *Intrapersonal* competence refers to the cultivation of self-understanding and self-discovery. A person who achieves intrapersonal competence recognizes her own judgments and biases and the human tendency to want to categorize people and use generalizations to make better sense of the world. Intrapersonal competence also infers a kind of flexibility in thinking, an ease in assimilating new schemas and ideas into one's existing bank of knowledge.

The second component of the Vaughn and Phillips model is *interpersonal* competence. As the name suggests, this kind of competence has to do with an individual's relationship to other people. An interpersonally skilled person is able to relate to others with a background different than his own. Bochner[54] empirically confirmed that poor interpersonal skills have adverse effects in intercultural situations. Interpersonally, people prefer others who they perceive as similar to themselves, which is known as the *similarity-attraction hypothesis*.[55] This makes interpersonal competence difficult to achieve because we might not put the energy or time into interpersonal relationships with people whom we perceive as different.

Given the complex interplay of psychologic, social, physical, and spiritual influences within culture, health care practitioners may become overwhelmed and disempowered given the complex, multifaceted, and often misunderstood needs of children. Pediatricians may need to address and advocate for the family or child in many nontraditional ways for medical care to be effective. As such, it is helpful if practitioners are informed of more creative strategies that do not rely on traditional approaches of changing the people involved but instead focus on different ways to manage the system as a whole. Several nontraditional approaches to culturally effective pediatric care include the life domains approach, cultural brokers, and lay health workers.

The *life domains approach* stresses the importance of examining the many different facets of a given culture to better understand that culture's relationship to health beliefs and practices.[56] Using this strategy, health care practitioners may choose to investigate the many things that comprise a cultural identity, including language, daily living habits, education, work, intimate relations, child rearing, and special celebrations.

Because physicians often lack time to do a thorough cultural assessment or go to the depth that may be necessary with some families or patients, other intermediaries, such as cultural brokers and lay health workers, should be considered. *Cultural brokers* are patient advocates who can help bridge the gap between physician and patient by working to understand the patient's background and facilitating a successful health outcome.[57] *Lay health workers*—often termed *promatores* in Latino communities—are members of the community who provide basic public health services to low-resource populations. Because lay health workers are embedded in the very community in which they serve, it is easy for them to adopt the perspective of their patients.[58] In fact, the WHO describes qualities of a 21st century "5-star doctor" to be community oriented, reconciling individual and community needs, and initiating actions on behalf of the community.[59]

There is good evidence that these types of models work because they are culturally appropriate and integrated into communities.[60] In pediatric care, research suggests that lay health worker interventions lead to improvements in symptoms, parental psychosocial outcomes, and care-seeking behaviors and create lasting effects that continue after the intervention ends. [61]

PRACTITIONER GROWTH IN CULTURAL HUMILITY

Development of cultural humility is a lifelong and incremental process. One does not achieve cultural humility by taking a particular class or

serving abroad. Rather, pediatricians must develop an orientation of critical consciousness and social justice[62] that "places medicine in a social, cultural, and historical context," recognizes societal problems, and works toward achieving contextually appropriate solutions. As such, all children across the globe, regardless of background, are treated fairly and receive high-quality pediatric care. Such an orientation combines the best aspects of physician professionalism, humanism, and compassion with cultural openness and humility.

To truly appreciate culture, physicians must go deeper than an "Epcot Center approach,"[22,63] which focuses on food, dances, and customs and minimizes more serious issues like health disparities and racism. Practicing or studying abroad, particularly in developing countries, certainly exposes various social contexts of enormous health and economic disparities, but this is not enough. Similarly, essentializing or simplifying culture ignores the many contextual factors that contribute to experiences of culture.[34] In addition, such an approach does not acknowledge multiple cultural groups to which an individual may belong based on race, ethnicity, religion, sexual orientation, or other identifiers. Physicians need to make a personal commitment to culturally responsive practice and growth throughout their career. To continue growth in cultural humility, physicians must strive to attain what McPhatter terms "enlightened consciousness, a grounded knowledge base, and cumulative skill proficiency."[64] This includes a shift in worldview and recognition of one's own socialization and cultural background, critical analysis and reflection to reframe one's existing knowledge base and incorporate a multicultural framework, and systematic and motivated efforts to ensure that all children, regardless of cultural background (eg, nationality, race, ethnicity, poverty, religion) and context (ie, at home or abroad), experience compassionate, accepting, and equal pediatric care. Because culture is fluid and context dependent, cultural humility requires continuous reflection and effort to provide effective care.[65]

KEY POINTS

- Complex global changes require culturally effective pediatric services based in cultural humility.
- Demographic diversity, cultural health beliefs, decreased health equity, pediatric practice abroad, and relevant policies and standards contribute to the need for proficiency in culturally responsive pediatric practice.
- Culture and health are broadly defined and include multiple and complex factors.

- Particular aspects of culture have a major effect on pediatric practice, including cultural health beliefs, immigration and acculturation, and culture-bound syndromes.
- Training in cultural humility is a necessity in medicine; more global and creative models include intercultural adjustment and nontraditional approaches to pediatric care.
- Practitioners can achieve growth in cultural humility through consistent efforts at an enlightened consciousness, a grounded knowledge base, and cumulative skill proficiency.

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CHAPTER

5

International Law and Health

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DIAGNOSING THE PROBLEM OF CHILDREN'S HEALTH: THE ROLE OF LAW AND GOVERNANCE

From a medical perspective, we already know the leading causes of child mortality: acute respiratory infections, diarrheal diseases, and neonatal infections.[1] For the vast majority of cases, we also know the appropriate medical treatments. The difficult challenge and tragedy of global children's health lies in applying proven solutions to known problems. The United Nations Children's Fund (UNICEF) identifies some of the "[u]nderlying and structural causes of maternal and child mortality."[2] Among other factors, UNICEF lists "[p]oorly resourced…health and nutrition services," "[l]ack of hygiene and access to safe water or adequate sanitation," and exclusion from essential health services "due to poverty and geographic or political marginalization."[2]

This list hints at structural concerns that raise basic issues of governance, not medicine. UNICEF further acknowledges that these are complex and multidimensional problems in need of multidimensional solutions: "Their wide-ranging nature and interrelatedness require them to be addressed at different levels—household, community, service provider, local government, and international community—in an integrated manner to maximize effectiveness and reach."[2] This daunting challenge is ultimately one of effective governance, calling for frameworks that can facilitate effective forms of cooperation.

The medical implications of unclean water and poor sanitation are clear:

> *An estimated 1.2 million children die before the age of 5 from diarrhoea. Poor urban areas where insufficient water supply and sanitation coverage combine with overcrowded conditions tend to maximize the possibility of faecal contamination.…Without sufficient access to safe drinking water and an adequate water supply for basic hygiene, children's health suffers. Improving access remains vital to reducing child mortality and morbidity.*[3]

Understandings of the link between health and sanitation, characteristic of the "great sanitary awakening," predate scientific understandings of the causes of disease.[4] Furthermore, the basic solutions to these problems are well understood. Thus, the issue is not what to do but how to do it. There can be no clean water or proper sanitation without effective forms of local cooperation, highlighting the often hidden link between governance and health. As such, the presence of clean water and proper sanitation can be used as a proxy for the existence of effective governance. Conversely, poor sanitation indicates, among other things, the absence of effective forms of local cooperation.

Making the diagnosis is easier than remedying its causes. Providing clean water and proper sanitation requires surmounting all the historical challenges involved in establishing effective forms of local governance in the first place. Indeed, the baseline expectation should be that structures enabling effective cooperation are the exception and not the rule, as they are difficult to establish and maintain. Moreover, areas where effective structures of local governance have not historically taken root (as witnessed by the absence of clean water and sanitation) are likely to be among the most difficult settings in which to build cooperative frameworks. Sustainable public health progress, however, is not possible if one focuses on clean water without also focusing on governance. Developing countries are full of wells donated by organizations that quickly fall into disrepair because technology was inserted in the absence of a supportive social infrastructure.

The underlying lessons are even broader. Improved governance is critical for almost every aspect of improving maternal and child health. For example, UNICEF recognizes the importance of establishing a "continuum of care" linking households, communities, and health facilities.[2] There are important, although often not stated, dimensions of governance behind every aspect of this continuum of care. But to classify the problem of children's health in terms of governance is to

open a Pandora's box of problems. Specific interfaces of the continuum of care are multiple and varied, calling not only for various effective local actions but complicated inter-linkages from the local through national and ultimately to the international community. As such, useful notions of law and governance must also be open, flexible, and multidimensional.

APPRECIATING THE MULTIDIMENSIONAL NATURE OF LAW AND GOVERNANCE

No single or simple answer exists for the question, "What is law?" Popular conceptions often view law as a series of commands—a list of things citizens must do or must refrain from doing. Other popular conceptions view law as a series of entitlements—enforceable demands that citizens can make against the state. Both understandings assume that whatever law is, it can be enforced and its violations punished. There are certainly domains in which these views ring true and provide workable frameworks to understand what law is and what it can do.

In the domain of global health governance, which exists within the realm of international law, neither of these understandings is very useful. With the notable exceptions of the World Trade Organization (WTO) mandatory dispute resolution process and certain matters under the purview of the UN Security Council, there are few established enforcement mechanisms for the breach of international law. So while international law may declare the existence of a right to health, this right inevitably means something different than a comparable declaration would mean in a domestic setting where legal mandates are backed by a state's police powers. The perennial challenge of law and governance in the international setting is to establish goals, set objectives, and enable effective forms of cooperation in the absence of traditional state enforcement mechanisms.

Defining the issue in this manner rightly suggests that the problem of global health governance has more in common with private law than public law. Private actors (individuals, businesses, and nonprofit and nongovernmental organizations [NGOs]) often face the challenge of forging effective voluntary agreements in the face of remote (or costly) state enforcement prospects. How private actors do this, what models and techniques they use, and how these methods map to a wide range of varied local conditions are potentially fruitful avenues of investigation. Ironically, business school, rather than law school, might be a better source of inspiration for physicians and public health advocates concerned with global health governance.

This is not to say that law and institutional structures do not matter; they do. What is important about law in this setting is not its ability to command, which it cannot, but its ability to help establish frameworks that can facilitate forms of voluntary cooperation. Again, the sources of inspiration may be surprising. The best primer for those concerned about global health governance may be a course in institutional economics, which covers focused training in the role of incentives, transaction costs, information failures, coordination, collective action, and agency problems.[5,6] Institutional economics teaches an important set of tools, but it also counsels a different temperament in approaching policy making.

One hallmark of institutional economics is the value of institutional agnosticism, with a focus on function, not form. The same public health function can be provided through a wide range of different institutional forms: public-regulatory, private-market, or hybrid public-private partnerships. No one form is appropriate in all settings. Moreover, the desired form will often be influenced, in a path-dependent manner, by a country's historical mix of institutional structures. In this setting, policy making should consist of a rigorous exercise in comparative institutional analysis—objectively comparing the plausible range of institutional solutions and selecting the least worse. This is an intensely empirical investigation of alternatives in which evidence should matter. Prior ideologic beliefs about the competing virtues of the state and market are best left aside.

While no unitary model of governance emerges from this analysis, one can produce fairly systemized processes of decision-making as to how governance problems can be approached. Consistent with mainstream economics and international relations theory, the basic behavioral assumption adopted here is that actors, state and non-state, act in what they believe to be their own best interest, although the values underlying each actor's perceived self-interest may vary widely. A flowchart for addressing public health issues can take the following form:

Problem → Bases of Cooperation → Tools → Strategy

1. Clearly understand the nature of the public health problem.
2. Identify the range of potential bases of cooperation that can build self-interested coalitions for action around the problem.
3. Examine the range of possible tools and models available through which to act.

These 3 steps can lead to the construction of appropriate public health strategies or policies.

Such a problem-driven approach depends on an honest and thorough understanding of the public health problem. Appropriate strategies will

change, sometimes radically, as the nature of the public health problem changes. An authentic understanding of the problem will suggest which bases of cooperation are possible. While neither are exhaustive nor mutually exclusive, the following list includes potential useful bases of cooperation for global public health problems. Different coalitions and different actors will have different motivations. Bases of cooperation include

- Health as security
- Health as a global public good
- Health as development
- Health as a human right
- Health as a humanitarian concern

The list suggests a hierarchy in terms of each mandate's strength, at least from a traditional nation-state perspective. States are most likely to act when there is a security threat and are least likely to act when confronted by a predominately humanitarian or human rights concern. Different international organizations and NGOs often define their missions in a manner more consistent with one basis of cooperation than another. The World Bank, for example, is chiefly motivated by health as development, while the World Health Organization (WHO) functions more comfortably within the model of health as a human right or humanitarian concern.

Each basis for cooperation, in combination with each particular problem, creates its own mandate for action. The strength of these mandates varies widely, with some more effective than others. At the same time, each basis for cooperation has its own boundaries and limits. Bioterrorism and highly contagious infectious diseases have clear national security implications, while childhood diarrhea clearly does not. Correspondingly, the security mandate for action in the former case will be stronger than the latter.

The international surveillance function necessary to detect emerging infectious diseases and public health threats is one of the best examples of a genuine global public good. As such, the mandate for action underlying the WHO revised International Health Regulations,[7] a combination of security threats and a global public good, was particularly strong. Yet the literature tends to overstate the reach of the public-good mandate. Not every public health concern is a genuine global public good. Moreover, the nature of public goods can change at different units of analysis. What may be a public good at the local or national level may not be a public good at the international level.

Caution is appropriate; when the mandate for action is misidentified or overstated, the very foundation for building an effective framework for cooperation can be undermined from the beginning. If effective coalitions are to be built, it is important to be brutally honest about which bases of cooperation are implicated, as well as the strength of their various warrants. To do otherwise is akin to building a house on sand. The sad reality is that global children's health implicates a range of weaker warrants for international cooperation: health as development, health as a human right, and health as a humanitarian concern. It is wiser to be creative and effective within these realms than to attempt to overstretch other potential bases of cooperation.

Once the problem and bases of cooperation are understood, policy makers need to examine the range of available tools and models for action. The choice of tools depends on the nature of the problem and whether action is intended at the international, national, or local level. At the international level, the range of available tools and models might consist of

- Hard-law legal instruments, such as traditional treaties (Convention on the Rights of the Child [1989])[8] or the treaty-based convention-protocol framework (WHO Framework Convention on Tobacco Control [2003])[9]
- Soft-law recommendations, statements, declarations, or goals (Declaration of Alma-Ata [1978],[10] Millennium Development Goals [MDGs],[11] WHO International Code of Marketing of Breast-milk Substitutes)[12]
- Creation of a new international organization (The Global Fund to Fight AIDS, Tuberculosis and Malaria)[13] or a looser network-based coalition of existing international organizations and national governmental organizations and NGOs (Gavi, The Vaccine Alliance)[14]
- A range of possible public-private partnerships (Malaria Vaccine Initiative)

The process of understanding the problem and selecting appropriate bases of cooperation and proper set of tools ultimately produces a strategy for taking action on the issue. While this discussion focuses primarily on the international level, the same heuristic approach can also be applied at the national and local levels.

INTERNATIONAL LAW AND GOVERNANCE IN THE SERVICE OF CHILDREN'S HEALTH

Every global effort to assist children's health has some aspect of governance. What is lacking is a systematic appreciation of the importance of governance and the need for structures that can better coordinate disparate and often uncoordinated initiatives. This section examines a broad range of undertakings: the historic role of treaty making to improve children's health, different forms of network-based actions to improve public health, and efforts to facilitate more effective local governance and grassroots participation.

Role and Limits of Classic International Law in Children's Health

International lawyers commonly distinguish between *hard law* and *soft law*. Hard law, what most people associate with international law, consists of formal treaty obligations negotiated and assented to by individual sovereign states. Soft law consists of a range of nonbinding resolutions, recommendations, and policy statements issued by various international organizations and institutions.

There is no shortage of hard law concerning children's health. Standard references include the WHO Constitution[15]; the International Covenant on Economic, Social and Cultural Rights (1966)[16]; and the Convention on the Rights of the Child (1989).[8] These instruments can collectively be interpreted as creating a "right" to health.[17]

The WHO Constitution speaks of a fundamental right to health, defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity."[15] The WHO Constitution makes only 2 express references to children. The first is in the preamble: "Healthy development of the child is of basic importance; the ability to live harmoniously in a changing total environment is essential to such development."[15] The second reference is in article 2, stating that one of the basic functions of WHO is "to promote maternal and child health and welfare and to foster the ability to live harmoniously in a changing total environment."[15]

The International Covenant on Economic, Social and Cultural Rights further elaborates on the "right" to health.[16] Article 12 of the covenant broadly defines a right to health as "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health."[16] Among other measures, the covenant obligates signatories to take all steps necessary for the "reduction of the stillbirth rate and of infant mortality and for the healthy development of the child."[16]

In terms of children's health, the most important treaty is the Convention on the Rights of the Child.[8] Article 24 of the convention deals with health. Among other things, the provision requires nations to take appropriate measures to "diminish infant and child mortality," "ensure the provision of necessary medical assistance," "combat disease and malnutrition," "ensure appropriate pre-natal and post-natal health care for mothers," and "develop preventive health care, guidance for parents and family planning education and services."[8]

In addition to hard law, countless soft-law declarations and resolutions address children's health. The most important are probably the Declaration of Alma-Ata[10] and the MDGs.[11] In 1978, the Declaration of Alma-Ata reaffirmed health as a fundamental human right and called for "the attainment by all peoples of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life."[10] The declaration advocated a focus on primary health care that included, among other things, particular attention to "an adequate supply of safe water and basic sanitation"; "maternal and child health care, including family planning"; and "immunization against the major infectious diseases."[10]

The MDGs are a set of 8 quantifiable targets that members of the international community committed themselves to obtain by 2015.[11] While each target has implications for children's health, MDG 1 (poverty/nutrition), MDG 4 (child mortality), MDG 5 (maternal health), MDG 6 (combating HIV/malaria), MDG 7 (clean water and sanitation), and MDG 8 (global partnerships) are particularly salient.[11] To their credit, the MDGs have provided an effective framework to help coordinate activities by the international community in pursuit of these objectives. Indeed, this soft-law instrument, through its efforts to create more effective frameworks for cooperation, has probably done more to advance children's health than any hard-law instrument.

When reading the various hard- and soft-law instruments, 2 equally strong reactions are common. The first is a genuine respect for the scope, depth, and intensity of the formal international commitment to children's health as a basic human right. The second is a sense of the large gap that exists between the aspirational goals established by these international instruments and the actual facts. These dual impressions help delineate the strengths and limitations of international law as a tool for improving children's health.

Shortcomings of traditional international law are well known. First, it is difficult to speak of meaningful rights in the absence of enforcement mechanisms, yet the absence of effective means of enforcement

is a defining hallmark of international law. Human rights are typically enforced through a process of naming and shaming—report writing and commission findings. In the end, however, there is little the international community can do if a country fails to comply with its obligations (although extreme cases of human rights abuses can generate ad hoc regimes of economic and political sanctions). A second limitation is that positive rights, like the right to health, are substantively self-constrained by the principle of *progressive realization*. At most, countries commit themselves to do the best they can, given the resources they have, rather than fully honoring the right outright.

Despite these limitations, the human rights paradigm has a role to play. Human rights are particularly important in the hands of individuals and advocacy groups because they are the principal means that individuals have to make claims on the international community. Traditionally, international law was the exclusive domain of the nation-state. Not only was there no participatory role for the individual in this game, but international law imposed no obligations on the state's conduct toward its own people. The development of the human rights concept marked a radical change in this orientation. The international community now recognizes that nations have obligations to their citizens and that, in limited ways, individuals can press their claims against states in an international setting.

Indeed, these tools should be more aggressively pursued. Human rights lawyers must join ranks with epidemiologists and other public health experts to do this more effectively. New and creative ways need to be developed to demonstrate that insufficient resources are being devoted to children's health, even under the constraints of the doctrine of progressive realization. Cross-sector analyses can be conducted under defensible measures of social welfare to show that money could be more efficiently reallocated to public health. Analogies could be drawn to emerging trade law, such as under the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (1995),[18] where article 5(5) permits the disparate treatment of "like risks" to be used as a basis for inferring discriminatory treatment.[18,19] As applied to public health, disparate treatment by governments of comparable sectors of public spending could be used to demonstrate a failure of the state to progressively realize its commitment to children's health.

Even this use of human rights law, however, is ultimately a tactic to establish political pressure. The real power of human rights is not that they are an effective source of legal entitlement but that they can be effective levers for social change. This change happens not only at the

policy level but also at the level of redefining social norms and values. The human rights framework can build bridges of empathy to socially and geographically distant, disadvantaged communities that can be the basis for reordering international priorities. As such, the human rights paradigm is most useful in combination with other bases of cooperation, such as health as development or as a humanitarian concern, in the formation of workable frameworks for cooperation. Human rights act as a catalyzing force and glue that helps hold these coalitions together. On its own, however, its force is fairly limited.

From Nations to Networks: The Role of Cooperative Frameworks

Law is more than a source of mandates or entitlements, and the international community is more than a collection of independent nation-states. One of the most important functions of law is its ability to establish cooperative frameworks. This approach to law provides a more useful template for addressing issues of global governance, particularly when confronting complicated social problems such as public health or the environment. But this vision of law must be combined with a pragmatic understanding of the international community that reaches beyond the nation-state as the only relevant building block for action. International organizations and other non-state actors must also be part of the solution. We need to move from nations to *networks* as the primary unit for addressing public health problems such as children's health.[20]

In 2002, Dodgson and Lee provided a useful mapping of the actors involved in global health governance.[21] Placed within the tightest circle are WHO, the World Bank, and the US government—3 actors that approach public health from very different perspectives and have very different understandings of their own missions and self-interests. For purposes of children's health, UNICEF would have to be added to the inner circle as well. One circle removed, Dodgson and Lee list developed countries (along with their bilateral aid agencies), developing countries, the WTO, and a range of UN agencies with health-related mandates. The next circle includes various groups of non-state actors comprising global civil society—religious groups, social movements, individuals, media, epistemic communities, and research institutions. As an illustration of how fast things are changing, the Bill & Melinda Gates Foundation and the Global Fund to Fight AIDS, Tuberculosis and Malaria would now have to be added to the map and placed at or near the inner circle.

Mapping of actors is just the first step. For effective action to take place, there must be mutual understanding of the nature of the problem to be addressed, an agreed-to strategy consistent with the missions

and perceived self-interest of the leading actors (a basis for cooperation), and an organizational structure through which the strategy can be implemented. As suggested earlier, there are no one-size-fits-all solutions to these problems. The relevant actors must sit around the proverbial negotiating table and hammer out a solution that best fits the relevant problem. This is an exercise in which creativity and problem solving are essential skills, and there are a number of different models that can serve as sources of inspiration. Each of these illustrates a different type of network-based cooperation. Three examples will be considered here: the WHO Framework Convention on Tobacco Control,[9] Gavi,[14] and the Global Fund to Fight AIDS, Tuberculosis and Malaria.[13]

The WHO Framework Convention on Tobacco Control serves as one model.[9] Formally, the convention is a treaty and, therefore, an instrument of hard international law. There are 2 things that distinguish this exercise from traditional treaty-making processes. First, the convention-protocol framework is dynamic in nature and initiates an ongoing governance process. The convention establishes a general commitment by all members to broad goals and establishes a governance structure that enables the international community to continue to work the issue. Series of specific protocols can then be negotiated and adopted (each also a treaty) to address particular aspects of the larger social problem. The second distinguishing factor is how, through the auspices of WHO, the broader epistemic community of public health professionals played a substantial role in pushing forward the tobacco control agenda and shaping the treaty's contents.[22,23] This process was substantially different from the exclusive nation-state orientation of traditional treaty making. Both aspects of the WHO Framework Convention on Tobacco Control make it an interesting model for future cooperative action in public health. For example, Larry Gostin has advocated the use of the convention-protocol framework as the basis for addressing a wide range of global public health problems.[24,25]

The second example, Gavi, is a looser network-based form of action. In the face of stalled international progress, the Gates Foundation spearheaded efforts to renew international action concerning childhood immunizations.[14] Gavi was formed rather than starting a brand new international organization or working exclusively through an existing international organization. The structure of Gavi enables more effective cooperation and action among existing stakeholders in the campaign for childhood vaccinations. Gavi has a lean secretariat housed in UNICEF offices in Geneva. It has a 12-member board consisting of representatives from developing world governments, WHO, UNICEF,

World Bank, pharmaceutical companies, NGOs, research institutes, and the Gates Foundation. "The strategy was to create an inclusive decision-making body to bring new coordination to a disjointed, inefficient marketplace."[14]

Finally, the Global Fund represents an innovative effort to combat 3 diseases plaguing the international community. Legally a private foundation registered under Swiss law, the government of Switzerland entered into a headquarters agreement with the Global Fund that recognizes it as an international legal personality and grants it certain legal privileges and immunities similar to those granted to intergovernmental organizations.[13] Voting members of the board consist of representatives from developed (8 members) and developing (7 members) countries, as well as representatives of civil society and the private sector (5 members). Representatives from WHO, the Joint United Nations Programme on HIV/AIDS, and the World Bank, as well as a Swiss citizen, serve as ex officio board members. Funding proposals are generated by and implemented through a newly created, nation-based infrastructure of country coordinating mechanisms, which themselves comprise new forms of public-private partnerships. The Global Fund stands as an ambitious example of an innovative type of network-based cooperation in the service of global health governance.

Costello and Osrin have argued for new network-based action with respect to maternal and child health.[26] Their proposal is consistent with the views proposed here: the need to develop frameworks that enable more effective forms of cooperation. They advocate for the creation of a new global fund dedicated to meeting the needs of maternal, neonatal, and child health but acknowledge that there are many challenges to making sustained improvements in children's health. Many developing countries have limited public health infrastructures and limited capacity at the national level to oversee or coordinate the multiplicity of international, bilateral, and nongovernmental actors working in the field. What could a new global fund do to help? In addition to attracting additional resources, a new global fund could play important administrative and governance functions. "Donor countries want assurances that their investments are managed well, transparently accounted for, and achieve results."[26] Costello and Osrin outline how these functions might be structured and performed. The governance functions need not take the exact form these authors advocate, but their proposal highlights the need to pay more attention to the role of governance, as well as the need for new frameworks to facilitate more effective forms of cooperation among existing actors in the name of public health.

Contemplating which bases of cooperation might support an initiative, such as a new global fund for maternal and child health, suggests the many challenges that any such effort would face. To begin, the problems of children in developing countries do not constitute a direct security threat, eliminating a strong security mandate. While aspects of the public health infrastructure necessary to address children's health (clean water and sanitation) might constitute a public good from a local and perhaps even national perspective, it is difficult to characterize them as a global public good. There is no strong global public good mandate.

Health as development raises more difficult questions. There are undoubtedly some economic benefits from investing in basic children's health. However, from an economic perspective, the value of such an investment is immediately discounted by the young age of the child and the potentially high background rate of child mortality. This obviously sounds harsh, but most developing societies implicitly recognize this same harsh reality by having compensatory high numbers of children. Similarly, in some cultures with high rates of child mortality, families postpone naming children and forming other types of bonds until the child reaches an age at which survival is more likely. From a short or intermediate time frame, the health as development mandate is relatively weaker for children's health than other public health investments. In contrast, AIDS was considered a particularly strong threat to the economies of developing countries because it hit people in the most productive years of their economic lives. Significantly, the development case for children's health is stronger when one examines basic infrastructure investments (ie, water, sanitation, and education) that have potential crossover benefits, as well as public health investments that protect the health of the mother and hence the entire family. There is a development case to be made, but it is of a more targeted and selective nature.

The ultimate cooperative bases for children's health must be found in the relatively weaker warrants of health as a human right and health as a humanitarian concern, with health as development playing a supporting role. Children's health rates particularly high on human rights and humanitarian scales. The challenge is to creatively leverage these bases of cooperation into more effective frameworks for network-based action. Many dimensions of improved governance in this regard are fairly self-evident and would be commonly acknowledged. Efforts to think holistically in terms of integrated packages of services, continuums of care, and more cost-effective forms of intervention need to be extended. More effective donor coordination (a governance function), as well as better

planning that makes the connection between global and local dimensions of governance more seamless, is certainly in order.

Linking Global and Local: Building Governance at the Grassroots Level

In the developing world, most children die outside the reach of health facilities. Children's health cannot be sustainably improved until a global public health infrastructure is established that can effectively reach into individual homes in the world's most remote rural communities. This requires creative thinking about governance at the most grassroots levels. There is good news and bad news in this regard. The bad news is that in many countries, the notion of the village is completely unrelated to any notion of established administrative structures providing public services.[27] All too often, the notion of the village is also unrelated to notions of strong communal bonds or ties. The good news is that the potential bases of cooperation on behalf of children's health at the local level are much stronger than at the international level. The challenge at the global level is that the health of children in third-world countries does not affect the direct self-interests of developed countries. The story is very different at the household and village level where these children live and die.

The health of the mother (wife/daughter/sister) and child directly affects the well-being of the family and, by extension, the community and village. The strongest self-interest and, therefore, the strongest allies are potentially at the local level. To be sure, there are substantial obstacles to effective local cooperation as well. For example, health status typically tracks socioeconomic status.[3] As a result, the sickest members of society are often the most politically marginalized and disenfranchised. Gender and the status of women add additional complications. Effective action requires surmounting numerous social, economic, cultural, and political barriers. Nevertheless, empowering stakeholders at the local level and encouraging various forms of participation and cooperation are potentially fruitful strategies.

Again, these views reflect an emerging consensus in the field of public health on the importance of greater grassroots participation. The challenge is how to best accomplish this objective and how to conceptualize the role of local participation within a larger integrated framework of global network-based governance. For example, UNICEF supports the innovative Seth Koma program in Cambodia, in partnership with parallel processes fostering deconcentration and decentralization of state functions, to empower women in participation with village development councils in a process to improve public health.[28] Building on these and other successes, the Global Fund to Fight AIDS, Tuberculosis and Malaria

now targets community systems strengthening as a central component of its future action.[29]

Building frameworks of cooperation from the grassroots level up is one of the most important frontiers in global public health. But local participation is not a panacea for public health problems, and establishing effective local cooperation will not be easy. Just as at the international level, building frameworks for effective network-based participation at the local level requires identifying bases of cooperation that could lead to a convergence of the perceived self-interest of disparate actors. Too often, participation becomes a tactic used by international organizations to implement preestablished agendas. Such efforts cannot establish real or effective grassroots participation. The participation of local stakeholders must be authentic and self-sustaining, and local actors' views must help shape the agenda of any cooperative undertaking. Effective local cooperation and governance cannot be maintained if international objectives do not correspond to the perceived needs and self-interest of local actors and if local actors are not given proper incentives to participate.

CONCLUSION

Governance is critical to global children's health, and a more considered understanding of governance is essential for the construction of more effective public health programming. Nation-states, particularly in developing countries, are often constrained by the limited reach of their administrative structures and underdeveloped and ineffective status of their bureaucratic institutions. Health ministries often have difficulties projecting power beyond the nation's capital and the largest provincial towns. International organizations are constrained in different ways but face their own challenges in extending programming to remote areas. This is a serious problem, as the basic needs of children require effective and ongoing forms of public health services that can only be provided at the most local of levels. Without more effective forms of public health governance, substantial progress cannot be made in improving children's health. National and international actors have had only sporadic success in effectively connecting the international and national apparatus to the local level. This remains the most important challenge to law, governance, and public health.

In the last half-decade, important progress has been made on this front. The WHO Positive Synergy Campaign spearheaded international efforts to address health system strengthening.[30] Health systems constitute the invisible and often overlooked infrastructure providing all health services.[31] In tandem with the work of WHO, other international

organizations, such as the Global Fund, have completely redefined their approach to "health system" and "community system" strengthening, making significant advancements.

But not all news is positive. Just as substantial progress was being made with respect to health system strengthening, the Global Fund canceled round 11 of its grant cycle in the wake of the global financial crisis. The Global Fund has emerged with a new funding formula, which should be understood as a new proposed framework for prospective international cooperation. The real questions moving forward are what will be the fate of the WHO Positive Synergy Campaign, recent efforts at health system strengthening, and the new Global Fund funding formula. Governance issues lay at the heart of each of these questions. More creative understandings of law and an express appreciation of the need to create frameworks that enable more effective forms of cooperation offer partial insights into ways to move forward.

KEY POINTS

- Some of the most important obstacles for improving children's health concern issues of law and governance, not medicine.
- International law can be interpreted as creating a fundamental right to children's health, but a large gap exists between the aspirational goals set by this right and the reality the world confronts.
- International law is best approached not as a set of mandates but as tools and tactics that can help establish frameworks that can facilitate more effective forms of cooperation.
- A flowchart for addressing public health issues can take the following form:

  Problem → Bases of Cooperation → Tools → Strategy
- Bases of cooperation for international law include
  - Health as security
  - Health as a global public good
  - Health as development
  - Health as a human right
  - Health as a humanitarian concern
- Progress on children's health will require building multidimensional networks of cooperation effectively linking global, national, and grassroots efforts.

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CHAPTER
6

Maltreatment and Advocacy

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INTRODUCTION

Not only are large numbers of the world's children adversely affected by economics, politics, and war, but they are also harmed by immediate and long-term effects of child abuse and neglect.[1] Studies in countries throughout the world have documented the growing recognition of harmful parental and societal practices.[2–5] Pediatricians and other professionals caring for children, in addition to their training and experience in recognizing and responding to child abuse and neglect, will have to incorporate into their practices the many international variations in cultures, parenting, and reporting laws and practices.

The United Nations Convention on the Rights of the Child (UNCRC) was enforced in 1990 (General Assembly Resolution 44/25) subsequent to being ratified by all countries except the United States and Somalia.[6] Specific provisions deal with a child's right to protection from all forms of violence, abuse, and exploitation; this applies to all children with their families, refugees, and those in armed conflict. It also contains provisions addressing economic, sexual, and other forms of exploitation and torture.

By ratification, 193 countries committed themselves and are legally bound to respect, protect, and fulfill the rights of children. These countries also took many legislative, social, and other measures to bring their laws and practices into compliance with the UNCRC. In addition, nongovernmental organizations (NGOs), United Nations Children's Fund

(UNICEF), and other UN agencies with growing involvement of professional groups, such as pediatricians and the corporate sector, support the UNCRC implementation.[7,8]

It is in the context of varying levels of national commitment to and implementation of the UNCRC that the pediatrician will face varying definitions, legal procedures, and societal responses to child maltreatment and exploitation. Professionals caring for children outside the United States should acquaint themselves with local cultural and legal practices and community resources to best provide for the health, safety, and protection of children. While injury pathophysiology, biomechanics, and stress mechanisms do not change from continent to continent or country to country, the pediatrician should not expect the same level of systematic societal response to child maltreatment in developing countries as it might receive in the United States. Depending on cultural background and exposure, the pediatrician will also face a variety of parenting practices, poverty, socially accepted norms, and physical discipline that will test sensitivity to and understanding of complementary and alternative medicine practices.

DEFINITIONS

While a variety of definitions have been used, *child maltreatment* generally falls into 5 types: physical abuse, sexual abuse, neglect, psychological maltreatment, and other exploitation. The World Health Organization (WHO) broadly defined these types of maltreatment for data collection and intervention (Box 6-1). The UNCRC states that a child is "[e]very human being below the age of eighteen years unless, under the law applicable to the child, majority is attained earlier" and that child maltreatment consists of "all forms of physical or mental violence, injury and abuse, neglect or negligent treatment, maltreatment or exploitation, including sexual abuse."

Child maltreatment occurs primarily in the family but also in schools, alternative care institutions and detention facilities, places where children work, and communities. The definition was extended to include exploitation of children in inappropriate work settings that are likely to be hazardous or interfere with the child's education or are harmful to the child's health or physical, mental, spiritual, moral, or social development. Children who are exploited in armed conflict generally fall outside these child maltreatment regulations but are covered under other local and international statutes and the mandate of the UN Office of the Special Representative of the Secretary-General for Children and Armed Conflict.

Box 6-1. World Health Organization Conceptual Definitions of Child Maltreatment

PHYSICAL ABUSE
Intentional use of force against a child that results in, or has a high likelihood of resulting in, harm to the child's health, survival, development, or dignity, which includes hitting, beating, kicking, shaking, biting, strangling, scalding, burning, poisoning, and suffocating. This may or may not be with the objective of punishment.

SEXUAL ABUSE
Involvement of a child in sexual activity that he or she does not fully comprehend, to which he or she is unable to give informed consent or for which the child is not developmentally prepared, or that violates the laws or social taboos of society. This can be by adults or other children who, by virtue of their age or development, are in a position of responsibility, trust, or power over the child.

PSYCHOLOGICAL MALTREATMENT
A pattern of failure over time on the part of the parent or caregiver to provide bonding and a developmentally appropriate and emotionally supportive environment; other acts include restricting movement, belittling, blaming, threatening, frightening, discriminating against, ridiculing, and other nonphysical hostile treatment.

NEGLECT
Isolated incidents and patterns of failure over time on the part of the parent or caregiver, when in a position to provide food, clothing, shelter, health, education, nutrition, and safety for the child.

EXPLOITATION
Commercial or other exploitation of a child refers to use of the child in work or other activities for the benefit of others. This includes, but is not limited to, child labor and child prostitution. These activities are to the detriment of the child's physical or mental health, education, or spiritual, moral, or social-emotional development.

Adapted from World Health Organization. *Preventing Child Maltreatment: A Guide to Taking Action and Generating Evidence.* Geneva, Switzerland: World Health Organization; 2006; and World Health Organization. *Report of the Consultation on Child Abuse Prevention.* Geneva, Switzerland: World Health Organization; 1999.

An additional form of child maltreatment, *medical neglect* or medical care neglect, was defined separately from neglect in some jurisdictions. For example, 7 US states specifically define medical neglect as failing to provide any special medical treatment or mental health care that a child needs.[9] In addition, 4 US states define medical neglect as withholding medical treatment or nutrition from disabled infants with life-threatening conditions. The American Academy of Pediatrics (AAP) notes that medical neglect usually takes 1 of 2 forms: failure to heed obvious signs of serious illness or failure to follow a physician's instructions once medical advice is sought. Either of these situations can be fatal or lead to chronic disability.[10] Several factors are considered necessary for diagnosing medical neglect.

1. A child is harmed or is at risk of harm from lack of health care.
2. The recommended health care offers significant net benefit to the child.
3. The anticipated benefit of the treatment is significantly greater than its morbidity so that reasonable caregivers would choose treatment over nontreatment.
4. It can be demonstrated that access to health care is available and not used.
5. The caregiver understands the medical advice given.

A caveat applies when medical resources are limited or nonexistent. Medical care neglect usually identifies that the family failed to provide needed care when otherwise able to do so. Thus, the pediatrician will have to consider the resources available in addition to parental factors when considering this form of child maltreatment.

EPIDEMIOLOGY OF CHILD MALTREATMENT ACROSS THE WORLD

As the United Nations reports, child maltreatment is "a global problem" with "reports of cruel and humiliating punishment, genital mutilation of girls, neglect, sexual abuse, homicide, and other forms of violence against children…long recorded, but the grave and urgent nature of this global problem has only recently been revealed."[11]

It is difficult to precisely determine the incidence and prevalence of child maltreatment across the world due to variations in the application of definitions in law and practice, different numbers of cases generated with voluntary versus mandated reports, parenting and cultural practices, acceptability of corporal punishment and other family violence, and resources available for systematic epidemiologic case ascertainment. Some jurisdictions have little or no information about child maltreatment, while data systems have been in place in many countries for more than 20 years.[12] Several models were developed in various countries to capture the number of children coming to the attention of social services or legal authorities or the prevalence of behaviors that place children at risk for child maltreatment.[13] Population-based surveys using the parent-child Conflict Tactics Scale, the Adverse Childhood Experiences questionnaire, the Lifetime Victimization Screening Questionnaire, and International Society for the Prevention of Child Abuse and Neglect screening tools have all been variably used to assess child maltreatment worldwide.[4]

The United States, Canada, England, and Australia often report all types of child maltreatment rates at 3% to 5% with fewer than half receiving investigation and fewer than a quarter being legally

substantiated. Increasingly, non–English-speaking countries, such as the Netherlands, Greece, and Croatia, are reporting population-based rates that are not substantially different.[12] When individual countries such as the United States possess the resources to accurately count child maltreatment cases, additional obstacles often prevent an accurate comparison. Organizations such as WHO have decried poor public health surveillance of child maltreatment across the world, and there is active discussion on the world stage about measuring and reporting strategies. Each country (and sometimes provinces or states) has its own policy and practice around child maltreatment definitions and reporting and whether a report is substantiated. Such difficulties occur within countries over time as well.

Fatality and hospital discharge data have been compared across continents, but research comparisons are limited by the application of commonly used *International Classification of Diseases* coding and underutilization of external cause-of-injury codes (E codes).[14] The homicide rate of children in 2002 was twice as high in lower-income countries compared with higher-income countries (2.58 versus 1.21 per 100,000 population). The highest child homicide rates occur in adolescents, especially boys between the ages of 15 and 17 years (3.28 for girls; 9.06 for boys) and among newborns to children 4 years of age (1.99 for girls; 2.09 for boys). The following information was determined using limited country-level data:

- An estimated 53,000 children died worldwide in 2002 as a result of homicide.
- Eighty percent to 98% of children suffered physical punishment in their homes.
- One-third or more of children experienced severe physical punishment from the use of implements.
- Twenty percent to 65% of school-aged children were verbally or physically bullied in the past 30 days.
- One hundred and fifty million girls and 73 million boys younger than 18 years experienced forced sexual intercourse or other forms of sexual violence in 2002.
- One-hundred million to 140 million girls and women worldwide underwent some form of female genital mutilation (FGM) or cutting.
- One-point-eight million children were sexually exploited in prostitution and pornography in 2000 according to estimates by the International Labour Organization.[11]

Variations in the use of corporal punishment were identified. Among 124,916 children in 28 developing and transitional countries, a majority

(83%) of African children experienced psychological abuse, with moderate and severe physical abuse affecting 64% and 43%, respectively.[15] At one end of the spectrum, the use of any violent punishment by parents is noted in even greater numbers (>75%) in countries such as Guyana, Iraq, Gambia, Jamaica, Ghana, Togo, Cameroon, Vietnam, and Yemen.[12] Corporal punishment was noted to be highly accepted in some countries—92% in Syria and 56% in Sierra Leone.[15] At the other end of the spectrum, the secretive nature of human trafficking makes information about these children even more difficult to ascertain; their plight is thought to be more perilous.[16]

While studies of risk and protective factors among countries are problematic due to methodological and definitional differences, studies clearly confirm child maltreatment to be an international problem with common themes among countries. Recent studies found rates in line with comparable North American research; for example, rates for sexual abuse ranged from 7% to 36% for women and 3% to 29% for men.[3,17] Most studies find females to be sexually abused 1 to 3 times more than males. Economic development of the country, socioeconomic status of the survivor, age, and gender are among the many factors associated with the risk of lethal violence. Studies suggest that young children are at greatest risk of physical violence, while sexual violence predominantly affects those who reached puberty or adolescence. Boys are at greater risk of physical violence than girls, while girls face greater risk of sexual violence, neglect, and forced prostitution. The rise in commercial sexual exploitation of children in the United States highlights practices the pediatrician will now encounter throughout the world. Those caring for potential survivors need to be able to recognize and treat the short- and long-term health effects as well as respond to their extreme social and psychological vulnerability. In 2015, the AAP published a clinical report to assist in the safe and effective evaluation of children who experience commercial sexual exploitation.[18]

Stable family units can be a powerful source of protection from violence for children in all settings. Factors that are likely to be protective in the home and other settings include good parenting, strong bonds between parents and children, and positive nonviolent discipline. Factors that are likely to protect against violence at school include school-wide policies and effective curricula that support the development of nonviolent and nondiscriminatory attitudes and behaviors. High levels of social cohesion are shown to have a protective effect against violence in the community, even when other risk factors are present. International initiatives are underway to expand knowledge

about the epidemiology of child maltreatment beyond currently available statistics.[19,20]

VARIATIONS IN PARENTING METHODS AND PRACTICES

While many cultural practices exist, pediatricians will encounter complementary and alternative medicines and variations in parenting across the world that potentially cross over into child abuse and neglect, including the use of physical discipline and corporal punishment, FGM, cupping, moxibustion, therapeutic burning, and coining.

Physical Discipline and Corporal Punishment

Effective discipline requires 3 essential components: a positive, supportive, loving relationship between the parent(s) and child; positive reinforcement strategies to increase desired behaviors; and removing reinforcement or punishment to reduce or eliminate undesired behaviors.[21] Punishment can be verbal or corporal and can range from restraining or slapping the hand of a child about to touch a hot stove to identifiable child abuse, such as beating, scalding, and burning.

Spanking and other forms of corporal punishment are widely accepted and used throughout the world. Nearly all 14,239 mothers surveyed in Brazil, Chile, Egypt, India, Philippines, and the United States used nonviolent discipline and verbal or psychological punishment.[22] Spanking rates (open hand on buttocks) ranged from a low of 15% in an educated community in India to a high of 76% in a Philippine community. Similarly, there was a wide range in the rates of children who were hit with objects (9% to 74% [median: 39%]) or beaten by their parents (0.1% to 28.5%).

Spanking and less traumatic forms of physical discipline were found to increase the chance of physical injury, and the child may not understand the connection between the behavior and the punishment.[21] Spanking and threats of spanking lead to strained parent-child relationships, making discipline substantially more difficult when physical punishment is no longer an option, such as with adolescents. Spanking is no more effective as a long-term strategy than other methods of discipline, and relying on spanking makes other discipline strategies less effective.[23] The more children are spanked, the more anger they report as adults, the more likely they are to spank their own children and approve of hitting a spouse, and the more marital conflict they experience. Spanking is associated with higher rates of physical aggression, more substance abuse, and increased risk of crime and violence.[23]

There is consensus against using harsh methods of physical punishment, such as burning or smothering, which are rare in all countries.

Shaking continues to be used; 20% of parents in 9 communities admitted shaking children younger than 2 years.[22] In a larger survey of discipline practices by Gray,[12] 33% to 94% of children reported receiving violent punishment in countries ranging from Bosnia and Herzegovina (33%) to Yemen (94%); 1% to 44% experienced severe physical discipline. More violent discipline is used in countries where more domestic violence, polygamy, and child labor is reported. More education and more books in the home were associated with a greater use of nonviolent discipline strategies.

Corporal punishment in schools has been prohibited in at least 108 countries worldwide. However, at least 78 of these did not prohibit corporal punishment as a disciplinary measure in penal institutions for children in conflict with the law, and 43 did not prohibit it as a judicial sentence of the courts for young people convicted of an offense.[24] Box 6-2 shows the nations that have specific laws protecting children from all corporal punishment and the year the law was instituted.

Box 6-2. Nations With Specific Laws Protecting Children From All Corporal Punishment

Benin (2015)	Venezuela (2007)
Andorra (2014)	Uruguay (2007)
Estonia (2014)	Portugal (2007)
Nicaragua (2014)	New Zealand (2007)
San Marino (2014)	Netherlands (2007)
Argentina (2014)	Togo (2007)
Bolivia (2014)	Greece (2006)
Brazil (2014)	Hungary (2005)
Malta (2014)	Romania (2004)
Cabo Verde (2013)	Ukraine (2004)
Honduras (2013)	Iceland (2003)
TFYR Macedonia (2013)	Turkmenistan (2002)
South Sudan (2011)	Germany (2000)
Albania (2010)	Israel (2000)
Congo, Republic of (2010)	Bulgaria (2000)
Kenya (2010)	Croatia (1999)
Tunisia (2010)	Latvia (1998)
Poland (2010)	Denmark (1997)
Liechtenstein (2008)	Cyprus (1994)
Luxembourg (2008)	Austria (1989)
Republic of Moldova (2008)	Norway (1987)
Costa Rica (2008)	Finland (1983)
Spain (2007)	Sweden (1979)

From Global Initiative to End All Corporal Punishment of Children. States with full abolition. http://www.endcorporalpunishment.org/progress/prohibiting-states. Accessed June 30, 2015

Female Genital Mutilation

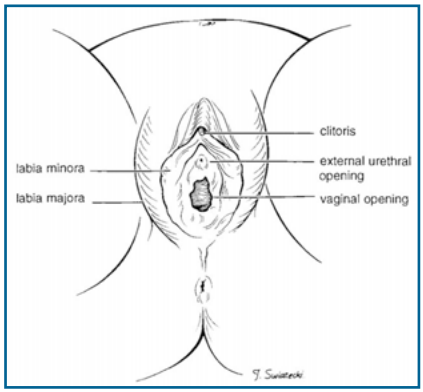
Female genital mutilation, also referred to as female genital cutting and female circumcision, includes procedures that physically or symbolically alter or injure female genitalia for nonmedical reasons. The practice is most common in the western, eastern, and northeastern regions of Africa; in some countries in Asia and the Middle East; and among certain immigrant communities in North America and Europe. In Africa, about 92 million girls 10 years and older are estimated to have undergone FGM, with the most severe types performed among Somalian and Sudanese populations.

Female genital mutilation is mostly carried out on young girls sometime between infancy and 15 years of age, although it is performed on newborns in certain countries. According to WHO, FGM is classified into the following 4 major types (Figure 6-1 shows normal female genitalia):

- *Type 1: clitoridectomy.* Partially or totally removing the clitoris and, in very rare cases, only the prepuce (Figure 6-2).
- *Type 2: excision.* Partially or totally removing the clitoris and the labia minora with or without excising the labia majora (Figure 6-3).
- *Type 3: infibulation (most severe).* Narrowing the vaginal opening by creating a covering seal that is formed by cutting and repositioning the inner or outer labia with or without removing the clitoris (Figure 6-4).
- *Type 4:* All other harmful procedures to the female genitalia for nonmedical purposes (eg, pricking, piercing, incising, scraping, cauterizing the genital area).[25]

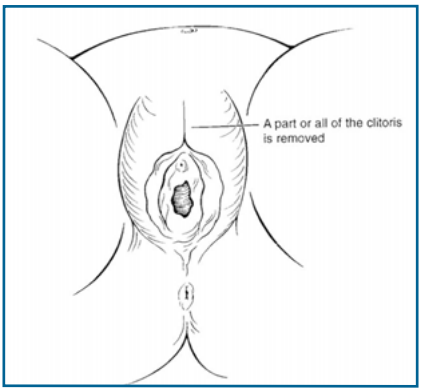
Female genital mutilation has no health benefits but does have adverse effects. Complications depend on the degree of FGM and how it is performed. The practice is often carried out by non-medically trained operators with rare administration of antibiotics and anesthesia. Equipment includes old, rusty scissors, knives, or pebbles that are not usually washed. A girl's legs are subsequently bound around the ankles and thighs and she is kept in bed for a week. Immediate complications include severe pain, shock, bleeding (hemorrhage, anemia, and death), tetanus or sepsis, urine retention, open sores in the genital region, and injury to nearby genital tissue. Long-term complications are more common in types 2 and 3, including urinary complications (urethral strictures, meatal obstruction, chronic urinary tract infection, meatitis, and urinary crystals), scarring (fibrosis, keloids, partial fusion, complete fusion, hematocolpos, inclusion/sebaceous cyst, and vulvar abscess), pain (neuromas, chronic vaginal infections, dyspareunia, vaginismus, dysmenorrhea, and menorrhagia), and infertility (vaginal stenosis, infibulated scar, dyspareunia, and apareunia).

Figure 6-1. Normal Female Genital Anatomy



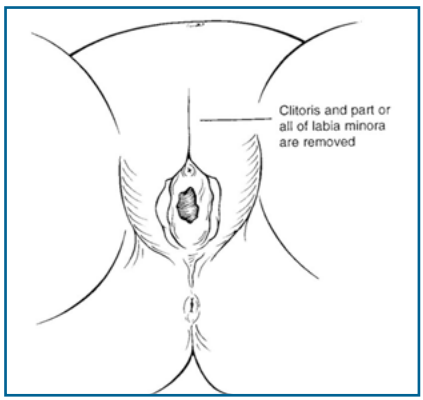
From American Academy of Pediatrics Committee on Bioethics. Ritual genital cutting of female minors. *Pediatrics.* 2010;125(5):1088–1093.

Figure 6-2. Type 1 Female Genital Mutilation—Clitoridectomy



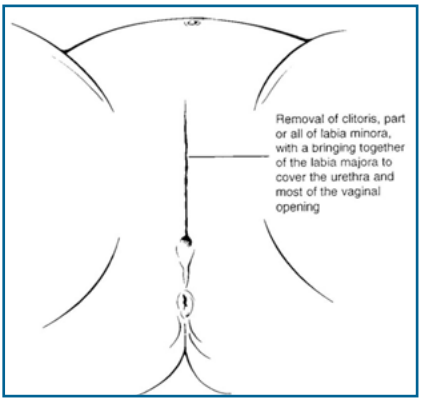
From American Academy of Pediatrics Committee on Bioethics. Ritual genital cutting of female minors. *Pediatrics.* 2010;125(5):1088–1093.

Figure 6-3. Type 2 Female Genital Mutilation—Excision



From American Academy of Pediatrics Committee on Bioethics. Ritual genital cutting of female minors. *Pediatrics.* 2010;125(5):1088–1093.

Figure 6-4. Type 3 Female Genital Mutilation—Infibulation



From American Academy of Pediatrics Committee on Bioethics. Ritual genital cutting of female minors. *Pediatrics.* 2010;125(5):1088–1093.

Female genital mutilation has been performed due to a mix of cultural, religious, and social factors within families and communities. Where FGM is a social convention, the social pressure to conform to what others do and have been doing is a strong motivation to perpetuate the practice. Parents initiate the practice for their daughters and, as most females in those regions underwent the procedure, many females do not feel they themselves are mutilated. Female genital mutilation is often motivated by beliefs about what is considered proper sexual

behavior, linking the procedure to premarital virginity and marital fidelity. Although no religious scripts require the practice, practitioners often believe it has religious support.

Female genital mutilation is considered a form of child abuse in the United States and a violation of human rights by WHO and UNICEF. It is illegal and subject to criminal prosecution in several countries, including Sweden, Norway, Australia, and the United Kingdom. In 1997, WHO issued a joint statement with UNICEF and the United Nations Population Fund against the practice of FGM. A new statement, with wider UN support, was then issued in February 2008 to support increased advocacy for FGM abandonment.[26] In December 2012, the UN General Assembly adopted a resolution on the elimination of FGM.

The WHO strongly urges health professionals to not perform such procedures. However, because of immigration, pediatricians, obstetricians, and gynecologists increasingly encounter girls and women who are survivors of this practice; parents may even request that a physician perform the procedure on their daughter. The AAP reaffirmed its position opposing all FGM, including the clitoral nick, which is forbidden under US federal law. The AAP counsels its members not to perform such procedures, as they can be life-threatening, and those who escape death are still vulnerable to sterility, infection, and psychological trauma. Members are urged to provide patients and their parents with compassionate education about the harms while remaining sensitive to the cultural and religious reasons that motivate parents to seek this procedure for their daughters.[27]

Therapeutic Cultural Practices

Various cultural practices are used to treat diseases around the world. Parents may seek these forms of therapy because of cultural beliefs in their benefit or limited access to medical care. Although not intentionally abusive, these practices can have many adverse effects and may result in findings that mimic child abuse. Furthermore, they may result in the delay or refusal of standard medical practices. It is important to be sensitive to other cultures yet help parents understand the importance of not taking health risks that can affect their children. Frequently, patients and families do not offer this information when they see their physician out of embarrassment and fear of judgment.

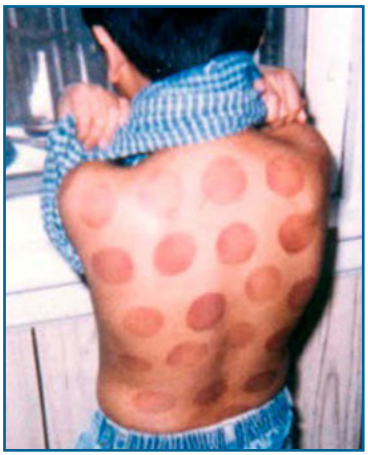
Cupping

Cupping is one of the oldest methods of traditional Chinese medicine. In China, cupping is used primarily to treat respiratory conditions such as bronchitis, asthma, and congestion; arthritis; gastrointestinal

disorders; and certain types of pain. Some practitioners also use cupping to treat depression and reduce swelling. Fleshy parts on the body, such as the back and abdomen (and to a lesser extent, arms and legs), are the preferred sites for treatment. A cup is placed over the skin and the skin is then drawn up into the cup; this is believed to open the skin's pores, stimulate blood flow, break up obstructions, and create an avenue to draw out toxins in the body.

Today, most practitioners use cups made of thick glass or plastic, although bamboo, iron, and pottery cups are still used in some countries. In a typical session, glass cups are warmed using a cotton ball or other flammable substance which is soaked in alcohol, ignited, and then placed inside the cup. As the substance burns, the cup is turned upside down so the practitioner can place it over a specific area of the body. The vacuum that is created anchors the cup to the skin and pulls it upward as the air inside cools. Depending on the condition being treated, the cup will be left in place for 5 to 10 minutes; several cups may be placed on a patient's body at the same time. Some practitioners will also apply small amounts of lubricants or medicated or herbal oils to the skin before the cupping procedure. Lubricants are used to move the cup around once it is placed on the skin to cover a wider area, which results in linear purpuric streaks rather than circular (Figure 6-5). Other variations to the technique include wet cupping, which involves incising the skin before the cup is placed or during the process of suctioning, with needles placed at the base of the cup being used. Modern appliances that use a manual hand pump to create the suction are also currently available and used.

Figure 6-5. Cupping—Circular Areas of Erythema Over the Back



From American Academy of Pediatrics. *Visual Diagnosis of Child Abuse on CD ROM.* 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008.

In a systematic literature review of 550 clinical studies published between 1959 and 2008, the majority of studies show potential benefit for pain conditions, herpes zoster, and other diseases. However, further rigorous trials in relevant conditions are warranted to support its use in practice.[28]

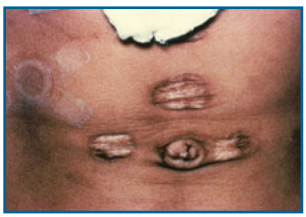
While cupping is considered relatively safe, it can cause some swelling and bruising. As the skin is drawn up under the cup, superficial blood

vessels in the papillary dermis are broken, thereby creating distinctive circular cutaneous lesions and bruises on the areas where the cups were applied. Because the procedure is slow and controlled, the application of the cup and subsequent bruises are usually painless, and any marks disappear within a few days of treatment; however, these marks can be confused with physical abuse.[29] Lubricants can cause contact dermatitis with erythema, edema, blisters, and scaling in areas of direct contact. Cutaneous burns may result when proper attention is not exhibited during the procedure, resulting in heating the cup too much as well as the air inside it. Children with significant pain from cupping, long-lasting marks, or inappropriate use of the procedure can be considered abused or neglected. Patients with inflamed skin, high fever, or convulsions, or who bleed easily, are not suitable candidates for cupping. Pregnant women should not have cupping on their abdomen or lower back. Cupping should not cross bony areas, such as spine ridges or shoulder blades.

Moxibustion

Moxibustion is a traditional Chinese medicine technique for all ages that involves burning the herb mugwort (*Artemisia vulgaris,* also known as moxa and traveler's herb) to facilitate healing. Its purpose is to strengthen the blood, stimulate the flow of body energy (referred to as chi), and maintain general health. In direct moxibustion, a small, cone-shaped amount of moxa is placed on top of an acupuncture point and burned. This type of moxibustion is categorized into 2 types, scarring and non-scarring. With scarring moxibustion, the moxa is placed on a point, ignited, and allowed to remain on the point until it burns out completely. This may lead to localized blisters and scarring after healing (Figure 6-6). With non-scarring moxibustion, the moxa is placed on the point and lit but is extinguished or removed before it burns the skin. The patient will experience a sensation of heat that penetrates deep into the skin but should not experience any pain, blistering, or scarring unless the moxa is left in place for too long. In indirect moxibustion, a practitioner lights one end of a moxa stick and holds it close to the area being treated until the area turns red. Another form uses acupuncture needles and moxa. A needle

Figure 6-6. Moxibustion—Scars Resulting From Burns Surrounding the Umbilicus



From Feldman KW. Pseudoabusive burns in Asian refugees. *Am J Dis Child.* 1984;138(8):768–769. Copyright © 1984 American Medical Association. All rights reserved.

is inserted into an acupoint and retained. The tip of the needle is then wrapped in moxa and ignited, generating heat to the point and surrounding area.

Moxibustion is usually taught as part of a qualified acupuncture or traditional Chinese medicine degree program. Although there are no licensing or accreditation requirements, a practitioner in the United States must have an acupuncture license to perform moxibustion. In Western medicine, moxibustion has successfully been used to turn breech babies into a normal head-down position prior to childbirth; one study published in 1998 found that up to 75% of women with breech presentations had fetuses rotated to the normal position after receiving moxibustion.[30] Other studies show that moxibustion increases the fetus' movement in pregnant women and may reduce the symptoms of menstrual cramps when used in conjunction with traditional acupuncture.[30,31]

Children with direct moxibustion can have significant pain and scarring after the procedure. It can result in circular or target-like burns and sometimes scarring, which may be confused with intentional child abuse, particularly cigarette burns. Burning moxa also produces a great deal of smoke and a pungent odor and can cause respiratory problems in susceptible individuals. Children with significant pain, scarring, or respiratory effects can be considered abused or neglected.

Maqua (Therapeutic Burning)

Maqua is a form of therapeutic burning used by healers in some parts of the Middle East and Africa. This therapy uses a red-hot iron, a burning coal, or a pinch of hot cinder to cauterize and burn the skin, resulting in full-thickness burns that are usually limited to small circular areas (Figure 6-7). Therapeutic burning can result in many complications, including infections, septicemia, contractures, and even death.[32]

Coining

One of the most common folk remedies practiced among Southeast Asians is coining. Also called coin rubbing or cao gio, coining is a dermabrasion therapy used to relieve a variety of illnesses, such as aches, pains, fever, seizures, chills, headaches,

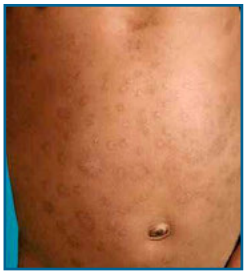


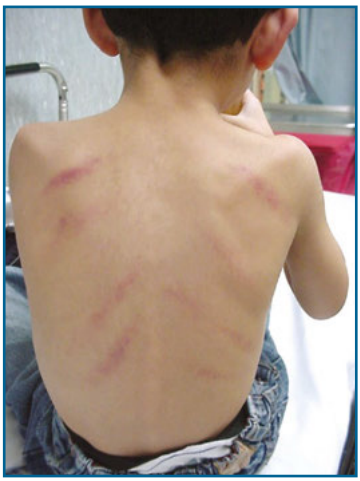
Figure 6-7. Maqua (Therapeutic Burns) in a Child With Abdominal Pain (Notice the circular scars on her chest and abdomen.)

From Nazer D, Smyth M. Cutaneous conditions mimicking child abuse. In: Palusci VJ, Fischer H, eds. *Child Abuse and Neglect: A Diagnostic Guide for Physicians, Surgeons, Pathologists, Dentists, Nurses, and Social Workers.* London, UK: Taylor & Francis; 2010:69–90. Copyright © 2010. Reproduced by permission of Taylor and Francis Books UK.

cough, vomiting, colds, nausea, abdominal pain, and symptoms related to changes in the weather. These illnesses are caused by an excess of "wind" in the body, which can be treated by "releasing" it from the body. Coining pulls the wind to the surface of the body and creates a pathway for its release. The amount of wind is measured by the degree of redness that appears on the body after coining. Balms or oils, such as Tiger Balm or liquid herbal medicines containing camphor, methanol, wintergreen oil, eucalyptus oil, peppermint oil, and cinnamon oil, are most commonly used. The skin is first lubricated with a balm or oil and the coin rubbed firmly and repeatedly in a linear pattern until blood appears under the skin, usually along the spine and ribs (Figure 6-8).[29] The technique is considered effective when it produces prominent marks that usually last only a few days.

There are complications associated with coining and misunderstanding the red marks found on patients. Children usually describe the procedure as soothing, but pain and bruising can result when the procedure is misapplied. Hyperpigmentation may also persist after the marks resolve. The lubricants used may cause burns, contact dermatitis, and toxicity. Tiger Balm or other oils contain camphor, which is absorbed transdermally when applied or rubbed on the skin. The effectiveness of coining to treat ailments such as aches and pains can be attributed to these balms and oils, but their therapeutic use in children is limited and toxicities have been described.[33] Children with significant pain, bruising, scarring, or toxicity can be considered abused or neglected.

Figure 6-8. Coining—Linear Lines of Petechiae and Ecchymoses on a Child's Back



From American Academy of Pediatrics. *Visual Diagnosis of Child Abuse on CD ROM.* 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008.

Other Cultural Practices

Other folk remedies have caused confusion with child abuse or have resulted in adverse health effects and even death. The therapeutic use of garlic has been reported to cause chemical burns after prolonged application.[29] Rue is a material sometimes used to treat the Hispanic folk illness mal de ojo (evil eye) and empacho (presumed intestinal blockage). Rue may cause phytophotodermatitis, which may be mistaken for abusive burns. Herbal teas, folk remedies containing lead, and compounds

containing theophylline, opium, caffeine, aspirin, or acetaminophen can poison children. In addition to the danger imposed, their use may be confused with intentional poisoning. Salting newborns by applying salt to the skin is an Asian custom that is still practiced in some areas of Turkey. It is thought to keep the skin healthy but may lead to hypernatremia if the skin is damaged and the salt is absorbed.

Some cultures believe that scarification can serve as a preventive measure in infancy to ensure lifelong health. Scarification is also called cicatrization and is a form of body modification in which a design or pattern is cut, etched, or scratched into human skin to make a permanent scar. Like most body modifications, there are many reasons why people choose to be scarified. Sometimes it is for cultural identity; sometimes, for health treatment. Scarification is frequent in Africa and may be as significant an issue as cupping and coining.[34]

INTERNATIONAL ISSUES IN CHILD MALTREATMENT REPORTING

When practicing in a new country, pediatricians should acquaint themselves with local practices and standards applied to child maltreatment identification and reporting. While reporting is required in all US states and territories, there are variable mandated and voluntary reporting requirements in several countries depending on laws and resources (Box 6-3). Reporting can be mandated by law, allowed by law (voluntary reporting), or not specifically enumerated in a country's laws or regulations. Sexual abuse and sexual assault are often covered more specifically by criminal statutes than child protection regulations. It is important to realize that these can result in severe criminal penalties in certain jurisdictions and that a report can result in the death penalty on conviction or severe ostracism for the child and family.[35–37]

Countries with mandated reporting may have laws that apply only to licensed professionals, such as medical practitioners and pediatricians. The pediatrician should ascertain whether the regulations in these countries apply to them in their visiting capacity and what exactly is required. A full listing of specific country and regional laws is beyond the scope of this chapter, but the pediatrician needs to realize that while many countries do have legally required reporting, they may only require that the most serious forms of physical and sexual abuse be reported (neglect and psychological abuse not being reportable); the basis for such reports may differ from the US "reasonable cause to suspect" standard; there are varying legal protections for making reports; and reports may go to police, governmental child protective services or community-based NGOs, social workers, or other special centers. For

Box 6-3. Child Maltreatment Reporting Requirements by Country

PROFESSIONAL REPORTING REQUIRED BY LAW

Argentina
Armenia
Australia
Bangladesh
Belarus
Benin
Bolivia
Bosnia and Herzegovina
Brazil
Bulgaria
Canada
Chile
Colombia
Denmark
Democratic Republic of Congo
Egypt
England
Estonia
Ethiopia
Finland
France
Greece
Guatemala
Honduras
Hungary
Iceland
India
Israel
Italy
Japan
Korea
Kyrgyzstan
Lebanon
Malaysia
Mauritius
Mexico
Mongolia
Montenegro
Morocco
Nepal
Peru
Philippines
Portugal
Romania
Russia
Rwanda
Serbia
Sierra Leone
South Africa
Spain
Sweden
Taiwan
Tajikistan
Thailand
Togo
Turkey
Turkmenistan
Ukraine
United States
Yemen
Zambia

PROFESSIONAL REPORTING ALLOWED BY LAW

Afghanistan
Bahrain
Cameroon
China
Fiji
Germany
Hong Kong, SARC
Netherlands
New Zealand
Nigeria
Pakistan
Poland
Portugal
Saint Lucia
Scotland
Singapore
Sri Lanka
Switzerland
Uganda

NO COUNTRYWIDE REPORTING SYSTEM

Albania
Georgia
Iraq
Ivory Coast
Saudi Arabia
Somalia
Syria

Adapted from Daro D, ed. *World Perspectives on Child Abuse.* 7th ed. Aurora, CO: International Society for Prevention of Child Abuse and Neglect; 2006; and Daro D, ed. *World Perspectives on Child Abuse.* 8th ed. Aurora, CO: International Society for Prevention of Child Abuse and Neglect; 2009.

example, confidential doctors have been used in the Netherlands to investigate possible child maltreatment and to direct services without resorting to public reporting systems.[38]

Several countries have voluntary professional reporting or generalized reporting requirements that are not specific for pediatricians. A voluntary reporting system offers the pediatrician the flexibility to better understand child maltreatment issues in a family, assist with services, and preserve the family unit's integrity and child's safety. However, the pediatrician must also realize that poverty, a lack of follow-up, and the potential for future harm may mitigate the ability to effectively intervene. This is heightened in countries with no specific reporting requirements where the pediatrician's only choice may be to call law enforcement authorities. Pragmatically, a police report may result in services and protection for the child, but it may also result in punishment of the child or family or no response at all when little or no resources are available or corruption has made the police response ineffective. The pediatrician should consult other practitioners and NGOs when practicing outside the United States to determine child maltreatment reporting requirements and best practices for services for families and children affected by child maltreatment.

STEPS FOR THE VISITING PEDIATRICIAN

The visiting pediatrician will be faced with varying cultures, parenting practices, child maltreatment definitions, laws, and reporting requirements when practicing outside the United States. The pediatrician seeking to improve child health and advocate for the needs of the child and family will have to proactively prepare for specific cultural and legal practices that apply to the jurisdiction where that pediatrician will practice. International practice requires pediatricians to become knowledgeable about specific types of child maltreatment identified in local law and custom as well as specific requirements and processes for reporting child maltreatment. They should learn specific steps to take when they suspect abuse so as to comply with local law and custom, assist in governmental intervention, and best treat the child and family without creating inappropriate family ridicule or endangerment. Pediatricians also need to learn about services and agencies available to provide ongoing social and psychological support to prevent child maltreatment in high-risk families after it occurs.

Pediatricians should talk with culturally knowledgeable leaders and practitioners to understand the use of alternative and complementary medical practices in the community and local opinion about their proper use and abuse. When certain practices are known to be harmful

or injurious, a health care professional may have little recourse other than working with the family to mitigate harm or working within local systems to provide services and assistance for children and families. Steps available to protect the child and reduce harm need to be thought out *before* the maltreated child is brought for medical care.

Beyond practice, several recommendations have been made by international child maltreatment professionals.[39] To improve social context, pediatricians can participate in movements to create, implement, or monitor a national plan to prevent violence. They can also work to strengthen and expand child maltreatment primary prevention activities as well as treatment options for child maltreatment victims, including international models for medical team responses to child maltreatment.[40] This includes evaluating whether successful prevention programs, such as home visiting, can be adapted for local use.[41] Perhaps most importantly, a pediatrician practicing outside the United States should be nonjudgmental and assume that parents, if they were provided with adequate personal, social, and financial resources, would optimally care for their children and protect them from abuse and neglect. It is in the best tradition of pediatrics and the special physician-family relationship for the pediatrician to recognize and respond to the psychosocial needs of families, to protect their health and safety, and to advocate for their needs in the medical system and within society.

KEY POINTS

- Child maltreatment consists of all forms of physical or mental violence, injury and abuse, neglect or negligent treatment, and maltreatment or exploitation, including sexual abuse, and includes intentional use of physical force or power, threatened or actual, against a child, that results in or has a high likelihood of resulting in actual or potential harm to the child's health, survival, development, or dignity.
- Although difficult to precisely determine its incidence, child maltreatment is a global problem. Professionals caring for children will have to incorporate into their practices the many international variations in cultures, parenting, and reporting laws and practices. They will also have to acquaint themselves with community resources to best provide for the health, safety, and protection of children.
- Corporal punishment is one of the parenting practices a pediatrician will encounter that may cross over into child abuse. Some forms, like spanking, are widely accepted and used throughout the world. Pediatricians should educate parents against the use of corporal punishment on children. In addition to the physical injuries that may result, corporal punishment is an ineffective mode of discipline and

associated with higher rates of physical aggression, more substance abuse, and increased risk of crime and violence.

- Many cultural practices may have potentially harmful side effects or may mimic findings after abuse. Pediatricians, while sensitive to parents' cultural and religious reasons, need to dissuade parents from practices that are harmful to children.
  - Female genital mutilation is a form of child abuse and a violation of human rights. Pediatricians are urged not to perform such procedures and to educate their parents about the harms of such procedures.
  - Other alternative medical practices may result in bruises (eg, coining, cupping) or burns (eg, moxibustion, maqua). In addition to their harmful side effects, they may be confused with injuries from child abuse. Pediatricians need to be aware of such practices and educate parents about their use in a culturally sensitive way.
- Pediatricians visiting other countries should become more knowledgeable about varying definitions of child maltreatment and reporting laws and resources available for families. They need to be nonjudgmental and culturally sensitive to different practices. They need to be first and foremost advocates for children and educators for families in an effort to prevent child maltreatment globally and to improve child health.

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CHAPTER

7

Environmental Hazards

Ruth A. Etzel, MD, PhD, FAAP

INTRODUCTION

Children's exposure to pollutants in the air, water, food, and soil, whether in the form of short-term, high-level or long-term, low-level exposure, is a major contributor to increased morbidity and mortality, especially in low- and middle-income countries. The World Health Organization (WHO) estimates that approximately one-third of the disease burden in developing countries is attributed to modifiable environmental factors, including indoor and outdoor air pollution, unsafe water, inadequate sanitation, and hygiene. This is 2 to 3 times higher than the attributable portion in the most developed countries. Box 7-1 shows the WHO definition of the modifiable environment.[1] Figure 7-1 shows the higher burden of disease in African and Asian countries due to air, water, food, and soil contamination compared with the countries of North America and Europe.[2,3]

INDOOR AIR POLLUTION

Smoke From Biomass Fuel Combustion

Almost 3 billion people use solid fuels (biomass or coal) for cooking and breathe the air that is heavily polluted from burning these fuels. Ninety percent of rural households in low-income countries use biomass fuels for cooking or heating. The smoke contains particulates, carbon monoxide (CO), nitrogen oxides, sulfur oxides, benzene, formaldehyde, and polycyclic aromatic hydrocarbons. Indoor concentrations of particulate matter less than 10 μm in aerodynamic diameter (PM_{10}) up to 2,000 μg/

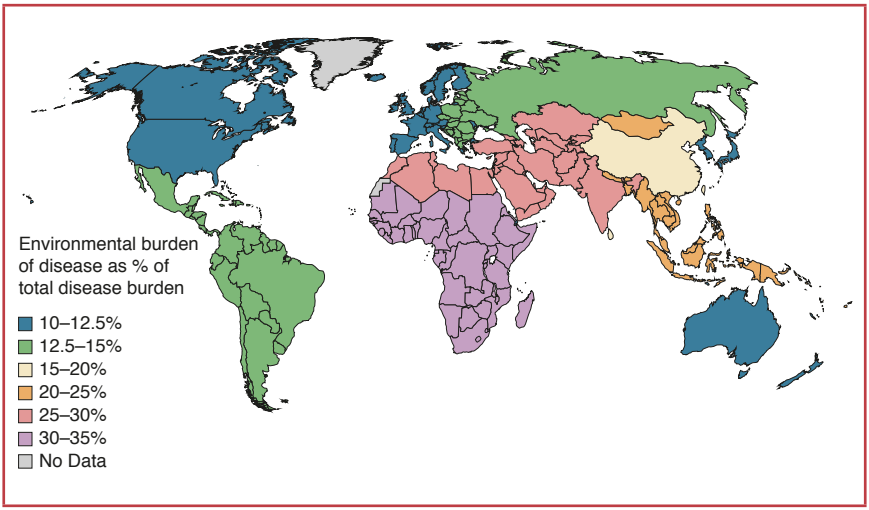
Box 7-1. Definition of the Modifiable Environment

- Air, soil, and water pollution with chemicals or biological agents
- Ultraviolet and ionizing radiation
- Built environment
- Noise, electromagnetic fields
- Occupational risks
- Agricultural methods, irrigation schemes
- Anthropogenic climate changes, ecosystem degradation
- Individual behaviors related to the environment, such as hand washing and food contamination with unsafe water or dirty hands

Excluded from the definition: Individual choices, such as alcohol and tobacco consumption, drug abuse, and diet; natural environments that cannot reasonably be modified (eg, rivers); unemployment (provided that it is not linked to the degradation of the environment); natural biological agents (eg, pollen); and person-to-person transmission that cannot reasonably be prevented by environmental interventions.

Adapted from World Health Organization. *Preventing Disease Through Healthy Environments: Towards an Estimate of the Environmental Burden of Disease*. Geneva, Switzerland: World Health Organization; 2006. http://www.who.int/quantifying_ehimpacts/publications/preventingdisease/en. Accessed June 10, 2015.

Figure 7-1. Environmental Burden of Disease Globally



From World Health Organization Health and Environmental Linkages Initiative. Priority environmental and health risks. http://www.who.int/heli/risks/en. Accessed June 10, 2015.

m^3 are produced by burning biomass fuel (much higher than the WHO air quality guidelines [Table 7-1]).[4] Figure 7-2 shows the population of the world using solid fuels in 2013.

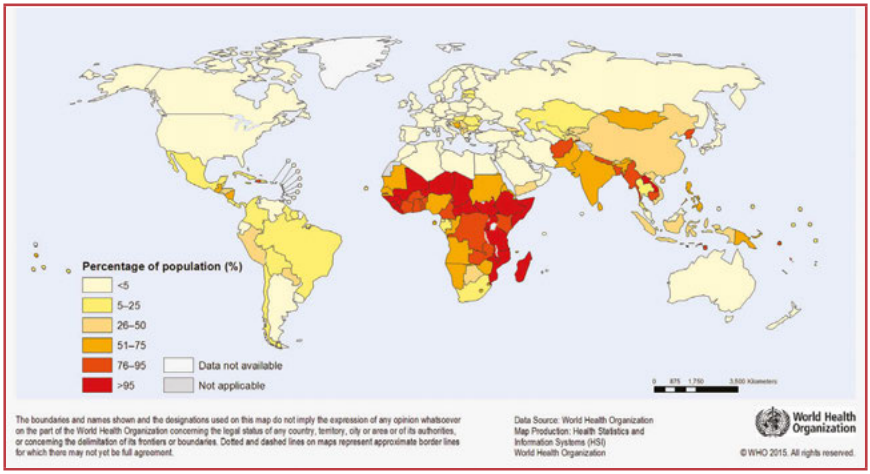
Most of the particulate matter from burning solid fuels is fine particles smaller than 2.5 μm in aerodynamic diameter. Infants and young children

Table 7-1. World Health Organization Air Quality Guidelines

POLLUTANT	AIR QUALITY GUIDELINE VALUE	AVERAGING TIME
Carbon monoxide	100 mg/m³ 60 mg/m³ 30 mg/m³ 10 mg/m³	15 min 30 min 1 h 8 h
Nitrogen dioxide	200 µg/m³ 40 µg/m³	1 h annual
Ozone	100 µg/m³	8 h, daily maximum
Sulfur dioxide	500 µg/m³ 20 µg/m³	10 min 24 h
Particulate Matter		
$PM_{2.5}$	10 µg/m³ 25 µg/m³	1 y 24 h
PM_{10}	20 µg/m³ 50 µg/m³	1 y 24 h

Adapted from World Health Organization. *Air Quality Guidelines Global Update 2005*. Copenhagen, Denmark: World Health Organization; 2006. http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf. Accessed June 10, 2015.

Figure 7-2. Population Using Solid Fuels (%), 2013



From World Health Organization. Global Health Observatory Map Gallery. http://gamapserver.who.int/mapLibrary/Files/Maps/Global_iap_exposure_2013.png. Access June 1, 2015.

spend many hours very close to fires while their mothers cook.[5] High concentrations of indoor air pollution and long periods of exposure increase the risk of lower respiratory illness and tuberculosis among children.[6–9] Globally, 4.3 million deaths were attributable to household air pollution in 2012, almost all in low- and middle-income countries. Thirteen percent of these deaths (534,000) were among children younger than 5 years, and the deaths were primarily from lower respiratory illnesses.[10]

In addition to cleaner-burning stoves and fuels, behavioral interventions, such as keeping children away from the stove while their mother is cooking, using dry wood, and cooking outdoors whenever possible, can help reduce children's exposure to smoke from biomass fuel combustion.[11]

Tobacco Smoke

More than 1 billion adults smoke worldwide. Tobacco, more than any other agent, kills almost 6 million people a year.[12] Tobacco will kill 8 million people a year by 2030; 70% of these deaths will be in developing countries. Around 700 million children, almost half of the world's children, breathe air that is polluted by secondhand smoke. Secondhand smoke contains particulate matter and more than 4,000 different chemical compounds, many of which are poisons. Exposure to high levels of secondhand smoke causes mucous membrane irritation and respiratory effects that result in rhinitis, cough, exacerbation of asthma, headache, nausea, eye irritation, sudden infant death syndrome, and some cancers.[13,14] Exposure to secondhand smoke may also increase tuberculosis risk.[15] Using data from 192 countries, WHO estimated the burden of disease worldwide from exposure to secondhand smoke to be approximately 1% of total mortality and 0.7% of total worldwide burden of disease in disability-adjusted life years.[16] There is no safe level of exposure to secondhand smoke. The WHO urged all countries to pass laws requiring that all indoor public places be 100% smoke free.[17] Pediatricians can take an active role in educating parents and supporting smoke-free public policies. Blending smoking cessation counseling with secondhand smoke exposure reduction counseling can increase the attempts to quit made by mothers with young children.[18] Smoke-free laws have been associated with substantial reductions in preterm births and hospital admissions for childhood asthma.[19]

Carbon Monoxide

Carbon monoxide is produced by incomplete fuel combustion. Sources of CO include heating and cooking fuels, automobile exhaust, and cigarettes. The symptoms and signs of mild CO poisoning (headache, nausea, vomiting, light-headedness, general malaise, dyspnea, confusion, and syncope) are nonspecific and may resemble influenza, tension or migraine headache, gastroenteritis, food poisoning, or depression. Children with higher exposures to CO may have seizures, coma, or dysrhythmias. A high index of suspicion is needed to identify CO poisoning.

Biological Particles

Exposures to airborne biological matter, including pollen and fungi, are associated with increased respiratory illness in children. Exposure to high levels of airborne fungi in damp and water-damaged indoor environments is linked to asthma exacerbations in children[20] and acute pulmonary hemorrhage in infants.[21]

OUTDOOR AIR POLLUTION

Children may be exposed outdoors to various mixtures of air contaminants (particulate matter, nitrogen dioxide, sulfur dioxide, ozone, and other photochemical oxidants) depending on where they live and attend school, as well as other factors, such as how near their homes and schools are to polluting industries, power plants, areas of high traffic, and outdoor waste burning. Rapid industrialization has resulted in very high levels of particulate matter in some Asian cities.[22] Children exposed to outdoor air pollution and very high concentrations of particulate matter have an increased risk of acute and chronic respiratory diseases and decrements in lung function. The smallest particles result in the greatest lung damage. The air quality guidelines in Table 7-1 are recommended everywhere (indoors and outdoors) to significantly reduce the adverse health effects of pollution.[4] Efforts to reduce coal-burning emissions and the environmental effects of industrialization have generated measurable health benefits.[23]

WATER POLLUTION

Unsafe Water, Poor Sanitation, and Hygiene

Nearly 1.1 billion people throughout the world are without access to safe drinking water. Nearly 2.6 billion people, including half of all Asians, lack access to sanitary means to dispose excreta.[24] Proper sanitation and hygiene and safe drinking water can decrease diarrhea by 22% and

decrease deaths resulting from diarrhea by 65%. Diarrhea accounts for 12% of deaths of children younger than 5 years.

Contaminated water causes a range of water-related diseases. A variety of viruses, bacteria, and parasites can contaminate drinking water and cause gastrointestinal diseases in infants and young children. Mortality and morbidity due to waterborne gastrointestinal diseases, mainly diarrheal, are still high in countries and communities where a substantial proportion of the population does not have access to proper water and sanitation. Effects from a lack of safe water and sanitation may also be indirect and long term; eg, repeated gastrointestinal infections represent a secondary cause of impaired growth, cognitive development, and school performance.[25,26]

Hygiene and household water treatment interventions have the greatest effect on diarrheal illness.[27] Eliminating open defecation should be a priority, along with promoting the construction of basic sanitation facilities in households and providing safe water facilities close to people's homes that the community can operate and maintain.

Arsenic

Children are exposed to arsenic mainly through drinking water. Arsenic is naturally high in water in some areas of the world, including West Bengal, India; Bangladesh; Mongolia; China; Chile; and some parts of Africa. Arsenic is deposited in river systems over thousands of years from arsenic-rich material. Approximately 45 years ago, local authorities installed tube wells in Bangladesh and other areas to provide a clean source of drinking water uncontaminated by biological agents. In 1993, however, high levels of arsenic were discovered in the ground water in Bangladesh. A testing program revealed that about 1 in 5 tube wells were using water with high arsenic levels (greater than 50 parts per billion). A massive information campaign is teaching people in Bangladesh about the dangers of drinking water with high arsenic levels.[28]

In addition to its natural presence in water, arsenic is also produced by a variety of activities, such as smelting and coal burning. Food crops, such as cassava, cocoyam, and other tuber crops grown in communities with mining and smelting activities, can take up arsenic from the soil.[29] Arsenic also is found in some herbal remedies.[30–32]

Overt symptoms of arsenic poisoning are rare in children but are seen in children as young as 3 years in Inner Mongolia.[33] After 20 or more years of exposure to high arsenic levels in drinking water, arsenic causes bladder, kidney, lung, and skin cancers. Neurologic effects, cardiovascular and pulmonary disease, skin lesions, and diabetes are also associated with arsenic exposure from drinking water.[34–36]

Fluoride

Drinking water in some parts of the world is contaminated with high levels of fluoride. Fluorosis is a potentially crippling disease caused by ingesting too much fluoride. Fluorosis is widespread in the eastern part of Africa and some parts of China. High concentrations of fluoride in water can affect children's growth and intelligence.[37] Endemic goiter in children living in 6 villages in South Africa was associated with an excess of fluoride in the drinking water, presumably due to its influence on thyroid hormones.[38] Although drinking water is traditionally considered the main source of fluoride, food items may be a contributing factor in areas with high concentrations of fluoride in the soil.[39]

FOOD-BORNE HAZARDS

Contamination of food with viruses and bacteria is a major cause of food-borne illnesses. Children are also at risk from a variety of chemical food-borne hazards in the environment, which include natural hazards such as mycotoxins and persistent organic pollutants.

Mycotoxins

Mycotoxins are toxic chemicals produced by certain fungi that can grow on crops in the field or during storage. Fungi growth on grains, nuts, and other crops is influenced by temperature, humidity, and rainfall. Mycotoxins can harm children's immune systems and lead to acute respiratory illness, gastrointestinal illness, tremors, and cancer.

Aflatoxins

Aflatoxins are poisonous substances that occur as a result of mold growth on peanuts and corn. High levels of aflatoxin cause acute aflatoxicosis.[40] Aflatoxin exposure during pregnancy (30% or more in tropical Africa) results in poor growth in the child's first year of life.[41] Aflatoxins are associated with jaundice in newborns and may be a cause of kwashiorkor.[42] In some parts of West Africa, about one-third of children are exposed to food contaminated with more than 100 ppb aflatoxins[43]; these high levels of aflatoxin exposure may reduce secretory IgA in saliva.[44] In parts of East Africa, 49% of milk samples have high levels of aflatoxin M_1.[45]

Ochratoxin A

Ochratoxin A, produced by some molds, is toxic to the kidneys. Ochratoxin A contaminates many foods, including cereals, cereal-derived foods, dry fruits, beans, cocoa, coffee, beer, wine, poultry, eggs, pork, and milk.[46] Ochratoxin A is teratogenic, immunotoxic,

genotoxic, mutagenic, and carcinogenic. In some parts of West Africa, approximately 35% of healthy people have ochratoxin in their blood.[46]

Fumonisins

Fumonisins are contaminants of cornmeal and cereals. Eating foods contaminated with fumonisins increases the risk of having a child with a neural tube defect and the risk of developing esophageal cancer during adulthood.

In developing countries, there is a need to ensure that children's foods do not contain excessive amounts of aflatoxins, ochratoxin A, or fumonisins.[47] This is especially important considering the emerging evidence linking mycotoxin exposures to stunted growth in children.[48]

Other Chemicals

Persistent Organic Pollutants

Persistent organic pollutants include compounds such as polychlorinated biphenyls and dioxins, which are very resistant to biological degradation and remain in the environment for decades. The major source of children's exposure to persistent organic pollutants is through food.[49] The effects of these chemicals include neurotoxicity and carcinogenesis.

Mercury

Mercury comes from combustion sources such as municipal waste incinerators and coal-burning power plants because coal contains mercury. Mercury is deposited into lakes and rivers and converted into methylmercury by bacteria, which then accumulates in fish that mothers and children eat. Methylmercury is toxic to the nervous system and can produce adverse neurodevelopmental effects on the fetus through the maternal diet.[13]

OTHER CONTAMINANTS

Lead

Children can be exposed to lead from a wide variety of sources. Leaded gasoline (petrol) was previously a major source of lead exposure. Currently, all but 4 countries have phased out leaded gasoline. Children also may be exposed from the use of lead ore in eye cosmetics and from lead in ceramic dishes or paint. Lead paint has long been outlawed in developed countries, but no legislation prevents lead paint from being sold in many parts of Asia and India.[50] Children may be exposed from backyard cottage industries (eg, battery recycling).[51] Children also may be exposed from living or playing near areas where mining occurs. A

mass lead intoxication in northern Nigeria during 2010 resulted in the deaths of more than 200 children whose parents were engaged in small-scale gold-mining activities.[52]

Lead is toxic to the nervous system; effects are particularly severe during the early development of the central nervous system.[53] Children with elevated lead levels have lower intelligence scores, more language difficulties, attention problems, and behavior disorders.[53] These adverse effects on children's intellectual development are seen at blood lead concentrations below 10 µg/dL.[54] In 2012, the US Centers for Disease Control and Prevention defined a reference level of 5 µg/dL to identify children with elevated blood lead levels. Blood lead concentrations well above this level are frequently reported in children from Africa and Asia.[55,56]

Mercury

Children in low- and middle-income countries may be exposed to mercury from many sources.[57] For example, mercury is used in small-scale gold-mining activities. Gold is extracted using mercury amalgamation, which poses a threat to human health.[58] Unmonitored releases of mercury from gold amalgamation have caused considerable environmental contamination and human health complications in the Amazon basin in South America and in rural sub-Saharan Africa.[59,60]

Skin lightening (bleaching) cosmetics and toiletries are widely used in some African countries. The active ingredients in these cosmetic products are mercury, hydroquinone, and corticosteroids. Skin absorption of mercury is enhanced because these products are used for a long duration on a large body surface area and under hot and humid conditions; fatalities have occurred.[61]

Waste Sites

Uncontrolled hazardous waste sites may pose a hazard to children; these sites include waste storage and treatment facilities, landfills, former industrial sites, military facilities, waste recycling facilities, and unsanctioned wastewater discharge. Some of the substances found in uncontrolled waste sites include heavy metals such as lead, chromium, and arsenic and organic solvents such as trichloroethylene and benzene.

Chemicals From Electronic Waste

Poor countries have become a destination for electronic waste (e-waste), including many tons of used desktop computers, fax machines, cell phones, and other electronic equipment. Although many of these machines can be repaired and resold, up to 75% of the electronics

shipped to Africa is junk.[62] When dumped, this equipment may leach lead, mercury, and cadmium into the environment; when burned, it may release carcinogenic dioxins and polycyclic aromatic hydrocarbons into the air.[63] Children living in towns where primitive e-waste recycling occurs may have high blood levels of lead and cadmium.[64] Negative associations between blood chromium concentrations and forced vital capacity have been documented among children aged 11 and 13 years from an e-waste recycling area.[65,66]

Pesticides

Pesticides (especially anticholinesterase type) are some of the most common causes of acute poisonings among children in low-income countries.[67] Even at low levels, these pesticides adversely affect children, including neurotoxicity and possibly endocrine disruption. Children heavily exposed to pesticides performed significantly worse on developmental tests than those less heavily exposed.[68]

Some of the older pesticides were designed to persist and can still be found in water and soil worldwide. Newer pesticides degrade more quickly but still contaminate water and soil and, consequently, food.

RADIATION

Ionizing Radiation

Children can be significantly exposed to ionizing radiation from radioactive fallout (ie, after disasters such as those at the Fukushima and Chernobyl nuclear power plants)[69] and medical diagnostic equipment (ie, x-ray and radioisotopes). Abandoned medical scanners, food processing devices, and mining equipment that contains radioactive metals such as cesium 137 and cobalt 60 are often picked up by scrap collectors and sold to recyclers. Such items may be hidden inside beer kegs and lead pipes to prevent detection. Smelting these items contaminates recycled metal used to make new products (including consumer goods) and the furnaces that process the material. Many atomic devices were not licensed when they were first widely used by industry in the 1970s. Although most countries tightened regulations, it is difficult to track first-generation equipment that is now coming to the end of its useful life.

Acute effects of overexposure to ionizing radiation include acute radiation sickness (nausea, vomiting, diarrhea, declining white blood cell count, and thrombocytopenia), epilation (loss of hair), and death. Delayed effects are largely caused by mutagenesis, teratogenesis, and carcinogenesis. Ionizing radiation causes chromosome breaks in

somatic cells (eg, lymphocytes, skin fibroblasts) that presumably account for the increased rates of cancer observed after exposure in childhood or adulthood.[70]

An excess of thyroid cancer occurred in Japanese children who were exposed to the atomic bomb beginning at 11 years of age. Thyroid cancer developed in hundreds of children in Ukraine and Belarus after a latent period of only 3 years following the partial meltdown of the nuclear reactor in Chernobyl in 1986.[71] Intrauterine exposure to ionizing radiation may cause small head size alone or severe mental retardation. Children are more sensitive to radiation than middle-aged adults by a factor of 10.[72] The health effects are greater if children are iodine deficient.

Radon

Children are constantly exposed to radon, which accounts for a large proportion of background radiation. Radon gas comes from radioactive decay of radium, a product of uranium deposits in rocks and soil. Radon enters homes through cracks in the foundation, porous cinder blocks, and granite walls. Most of the dose of radon and radon decay products is delivered to the lungs, resulting in an increased risk of lung cancer during adulthood; some of the dose goes to the bone marrow. One study has documented an increased risk of leukemia or cancer among children living in an area with high indoor radon concentrations.[73] Pediatricians should advise families about the hazards of radon exposure and point out that cigarette smoking adds to the radon-induced risk of lung cancer.

GLOBAL CLIMATE CHANGE

Many of the main global killers, such as malaria, diarrhea, and malnutrition, are closely associated with climatic conditions. Climate change will affect children's health as a result of their exposure to extreme temperatures and precipitation; food insecurity; transmission rates of vector-borne diseases; and increases in air pollution from molds, pollens, and burning fossil fuels.[74] Food insecurity, water scarcity, damp housing, waterborne and vector-borne diseases, mycotoxin-related illnesses, and natural disasters such as floods and hurricanes will worsen as temperatures and sea levels rise. The effects will be felt most among young children in low- and middle-income countries.

Exposure of children to the environmental hazards mentioned in this chapter is preventable. Pediatricians need to be aware of the adverse health effects from these hazards and work toward their control and eventual elimination.

KEY POINTS

- With indoor air pollution, the main risks for child health include
  - Increased incidence and severity of respiratory disorders such as acute lower respiratory tract illness, bronchitis, and asthma
  - Mucous membrane irritation, headache, and discomfort
- With outdoor air pollution, the main effects on child health include
  - Increased incidence and severity of respiratory disorders such as acute lower respiratory tract infections, bronchitis, and asthma
  - Long-term effects: chronic respiratory illness
- With poor water supply, inadequate sanitation, and food contamination, the main effects on child health include
  - Increased incidence and severity of diarrheal disease
  - Indirect effects: impaired growth due to repeated infections
- With poisoning, the main risks for child health include
  - Acute toxicity (lead, mercury, or organophosphate poisoning)
  - Chronic neurotoxicity: lower IQ, neurodevelopmental disorders
- With radiation, the main risks for child health include:
  - Childhood malignancy

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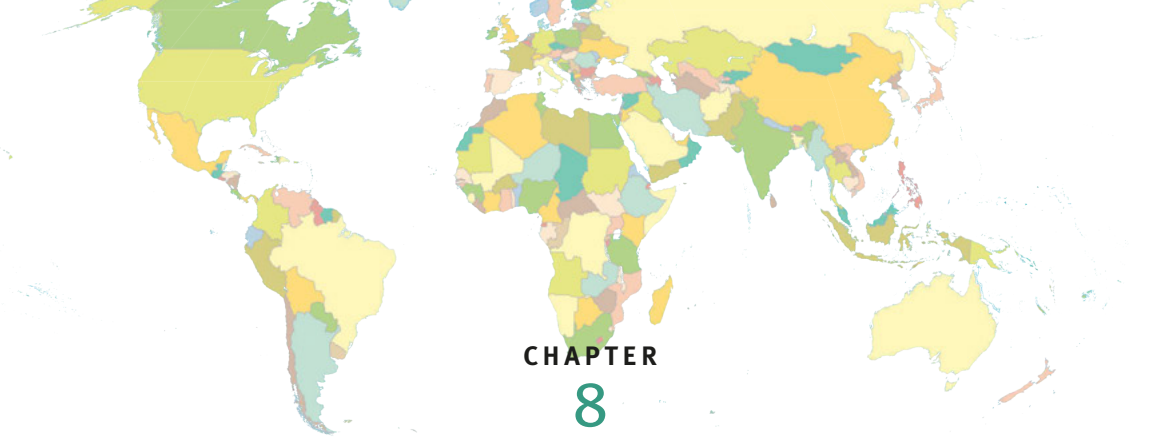

CHAPTER
8

Medical Work in Resource-Limited Countries

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THE YEARNING TO HELP

It is without a doubt that truly incredible needs exist for children around the world—in the more affluent higher-income countries and in economically and developmentally emerging nations. In fact, most of the globe's children and their families live in challenging situations where food, shelter, security, and access to medical and educational services are scant.[1,2]

It is also true that more people of all backgrounds in developed nations are aware of these disparities and wish to help rectify the situation. There is a growing tangible yearning to reach out and help, respond to the images bombarding us, and participate in some meaningful way. Unfortunately, it can become difficult, even for those in the medical profession, to determine the best way to do that.

The Reality That Drives the Yearning to Respond

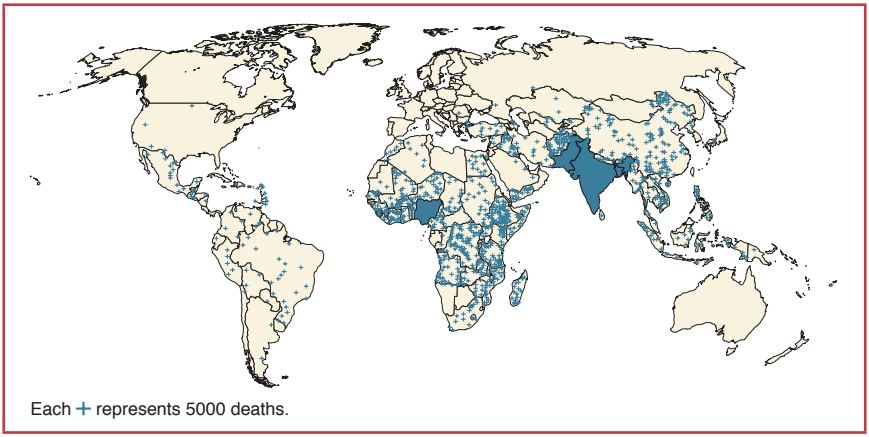
Every few seconds a child younger than 5 years dies despite the fact that most of these deaths could reasonably be averted through evidence-based interventions at the family, community, and regional level. The World Health Organization (WHO) reports that every day, 800 women die in pregnancy or childbirth, leaving their families worse off than before. The disparity in wealth, life expectancy, and access to services such as health, education, and water is growing ever wider among and within countries.[3] The burden of living in miserable conditions and

suffering inordinate childhood mortality is increasingly concentrated in fewer regions, all of which are far from our higher-income realities and attention. This is powerfully demonstrated in Figure 8-1, in which each plus symbol represents the death of 5,000 children younger than 5 years in 2003. Progress has been made, but there is still much to do: 12.7 million children younger than 5 years died in 1990, while only 6.3 million died in 2013.

A hypothetical random sampling of the general US population will reveal that there is an awareness that horrible situations exist "over there" and organizations and individuals are responding. Many are at least vaguely aware of some of the efforts to improve the health and well-being of our global neighbors—Bono's concerts and his (RED) program; the US President's Emergency Plan for AIDS Relief; the Clinton Global Initiative; the Bill & Melinda Gates Foundation; Dr Paul Farmer's work in Haiti, detailed in Tracy Kidder's book *Mountains Beyond Mountains;* and the United Nations Children's Fund (UNICEF). A very few may have heard of the Millennium Development Goals (MDGs).

On further questioning, our respondents would be able to list some of the situations that pose dire threats to children: hunger, HIV/AIDS, malaria, and cleft palates. These answers reflect the images portrayed in advertisements from organizations looking for donations and from episodic reports in the news. It is rare that internal military conflicts, child trafficking, access to services, corruption, family and national debt burden, neglected diseases, and even tuberculosis are mentioned.

Figure 8-1. Worldwide Distribution of Child Deaths



From Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet.* 2003;361(9376):2226–2234. Copyright 2003, with permission from Elsevier.

Many in the health field would respond similarly to those in the general population, but over the last decade there has been a remarkable increase in a deeper awareness of the realities—and the desire to respond—led in no small part by our younger colleagues. A defining moment in the accessibility of lucid information was the *Lancet* child survival series in the summer of 2003,[4] which crystallized the state of the globe's neediest in terms of mortality, etiologies, evidence-based health interventions, and economic and political responses. This was followed by similar series on maternal[5] and neonatal[6] situations and needs and the newborn series, which was updated in 2014.[7]

Clarifying the crushing needs in such a pithy manner has paralleled the frequency of presentations at conferences and discussions in academic centers, leading to increased interest among health professionals to respond. Furthermore, the recognition that health as a component of general well-being is a fundamental human right, based on the UN Convention on the Rights of the Child,[8] means that participation in global health efforts becomes a logical means to aid the global family in attaining realization of this philosophy.

Yearning to Help: The Response

Historically, the response to medical needs around the world originated through a combination of religious, political, and military influences. The Order of Malta formed around 1048 during the crusades when the first knights built a hospital in Jerusalem. Over the centuries, a variety of Catholic orders dedicated themselves to service of the sick; after the Reformation, other Christian religions began ministries to the sick at home and abroad, often following in the footsteps of explorers and colonization.

Presently, a considerable proportion of the medical aid provided, especially in Africa and the Americas, is through faith-based organizations. Jewish and Islamic medical aid organizations are becoming increasingly active throughout the world. It is only relatively recently that medical aid organizations have been created without a religious underpinning. Henry Dunant's efforts in response to the atrocities of war led to the adoption of the Geneva Conventions as well as the formation of the International Committee of the Red Cross in 1863, and Doctors Without Borders came into being in 1971, ostensibly as an areligious and apolitical entity; these are 2 of the most recognizable organizations. However, until recently, relatively few people undertook these efforts. Albert Schweitzer's 1931 book, *On the Edge of the Primeval Forest*, was perhaps the first book to popularize the work of those rare health care workers in developing regions.

Presently, there appear to be 3 populations in health fields with a burgeoning interest to respond to the needs of families in challenging situations. The first and fastest growing population is the learners—undergraduates, health science students, and residents. The second population is those in the workforce, and the third population is the retired.

Surveys conducted over the last quarter century reflect this growing interest. Very few physicians, a paltry 0.32%, were involved with global health activities in 1984.[9] Assuming that offering residency training and electives reflects expressed interest, one can see the remarkable increase in programs offering international health courses or special programs; the proportion of US medical students who took international electives rose from 6% in 1984 to 26% in 2007.[10]

Pediatric residencies offering global health electives mirrored that trend by increasing from 25% of surveyed US and Canadian programs in 1996[11] to 52% in the most recent survey of residencies in the United States, Puerto Rico, and the Caribbean in 2007.[12] The 2008 American Academy of Pediatrics (AAP) survey of graduating residents contained illuminating responses; training in global health topics was available to 59% of respondents, and 21% participated in such training. Moreover, the opportunity to participate in global health training was an essential or very important factor in selecting a residency program for 22% of respondents. Remarkably, about one-third of respondents were definitely or very likely planning to work or volunteer in a developing country after residency.[13]

The only time that international health interest and activities were assessed in practicing pediatricians occurred with the ninth AAP Periodic Survey of Fellows in late 1989. With a response rate of 71% from 1,000 surveys, 38% of respondents said they would serve or may be interested in serving in some capacity in a developing country within the next 3 years. Even then, 20 years ago,

> *Sixteen pediatricians (about 2% of all respondents) said they participate in overseas health programs, and have devoted an average of 122.3 hours in those activities during the past year. Among these pediatricians, 69% volunteered their time, 19% participated for a reduced fee, and 12% participated for a full fee. The pediatricians were equally divided on how they participated in the overseas health programs: 33% each said they did direct patient care, participated as an advocate/consultant, and did both direct patient care and advocacy/consultation.*[14]

Medical academies and societies are also responding to the interests and needs of their membership by dedicating staff and programs to support global health activities. Examples include the American Academy of Family Physicians (AAFP) Center for Global Health Initiatives, created in 2000; the American Congress of Obstetricians and Gynecologists Department of International Activities; and the American College of Physicians International Activities Coordinating Committee. The Canadian Paediatric Society and Royal College of Paediatrics and Child Health in Britain have international health sections, while the AAP has a dedicated office of International Affairs as well as the member-driven Section on International Child Health. The Academic Pediatric Association had a board-created task force on global health integrated into its Global Health Special Interest Group. The Association of Pediatric Program Directors created a Global Health Program Directors group in response to the obvious need brought by faculty and programs. The American Board of Pediatrics created a Global Health Task Force and was instrumental in creating the Global Pediatric Education Consortium (www.globalpediatrics.org) and its product, the Global Pediatric Curriculum.

The number of organizations dedicated to working on issues in developing regions has increased dramatically over recent years. Of the 5,400 larger nongovernmental organizations (NGOs) that Charity Navigator[15] tracks, 500 are involved in international activities. GuideStar[16] currently tracks 9,505 nonprofits under the category of international health. Even this does not reflect the multitude of small grassroots groups that exist within developing countries or the small 501(c)(3) nonprofits that community groups or individuals create for their specific projects. Furthermore, it is difficult to estimate the total number and types of health-related organizations because one might argue that groups involved in agriculture, land rights, microenterprise, and human rights can improve general health and should be included.

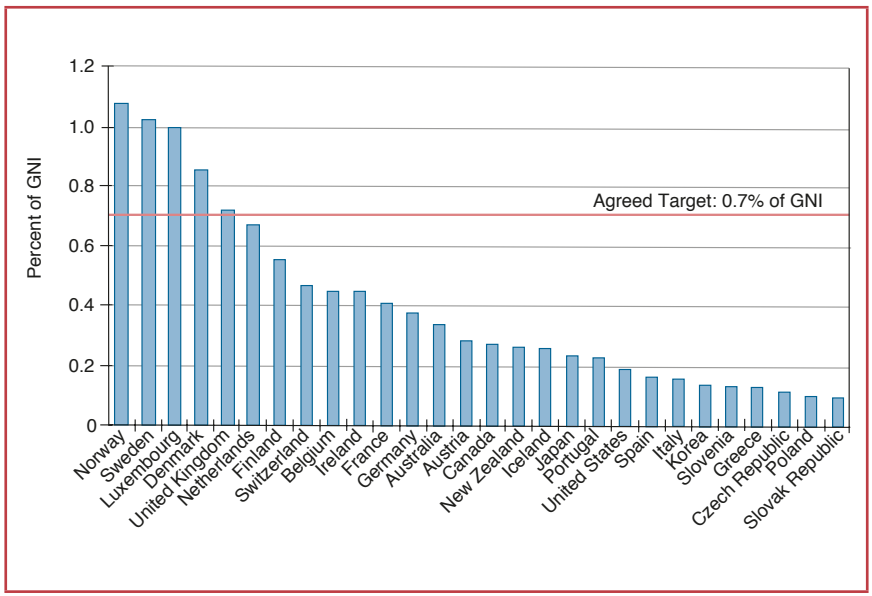
Pediatric-related NGOs within the NGO Committee on UNICEF increased from 13 in 1949 (when it first began) to 80 presently, with 191 NGOs having consultative status with UNICEF in 2006. Nongovernmental organizations having a relationship with WHO increased from around 10 in 1948 to 190 in official consultative status as of January 2014.[17]

Governments and intergovernmental organizations increasingly involve themselves in responding to needs in poorer regions. Younger-than-5 mortality trends are good proxy measures of national health status and intervention efforts; the rate decreased substantially from

1960 to 1990 because of enormous efforts after the Declaration of Alma-Ata. However, since then, the rate of decline in childhood mortality has slowed from 2.5% to 1.1% per year. This reality led to a renewed and coordinated response through the September 2000 UN MDGs,[18] whose signatories represent all 189 UN member states. Tracking from 1990 through 2008 produced a worldwide average reduction rate of 1.8%, which translates into 3.7 million fewer children dying each year, a commendable achievement.[19] However, for the 8.8 million children who do die yearly (as of 2008), there remains an urgent call to more intense action.

The governments of the 20-some wealthy nations that comprise the Development Co-operation Directorate of the Organisation for Economic Co-operation and Development recently reaffirmed their promise to increase economic aid to 0.7% of gross national income (GNI) (formally GNP or GDP). Unfortunately, they have a dismal record of complying with the agreement, which was first made in 1970 with the goal of reaching that level by the mid-1970s.[20] Currently, they voice intent to reach the goal in the MDG 2015 time frame—45 years late. The United States is well below its commitment at 0.2% GNI (Figure 8-2). At this time, only 5 countries meet the goal.[21]

Figure 8-2. Net Official Development Assistance in 2013 as Percent of Gross National Income



From Organisation for Economic Co-operation and Development. http://www.oecd.org/dac/stats/documentupload/ODA%202013%20Tables%20and%20Charts%20En.pdf. Accessed June 1, 2015.

How to Operationalize the Yearning to Help

The previous section's brief overview of the magnitude and generalized responses to global need is a necessary prelude to this section. How might any one individual who is responding to the yearning to help consider proceeding? This section is based on my experience advising a variety of students, physicians, and other health professionals during the working part of their lives, as well as retirees, over the past 15 years. It is wonderful to see such enthusiasm and altruism in those who are gifted with intelligence and skills. It is sad to see the idealism fade as the pressures of study, family, loan repayment, and work pry many of them away from their dreams as they failed to find a way to channel their energies during the period in their lives when they were open to making the difficult decisions that might set them on a road less traveled.

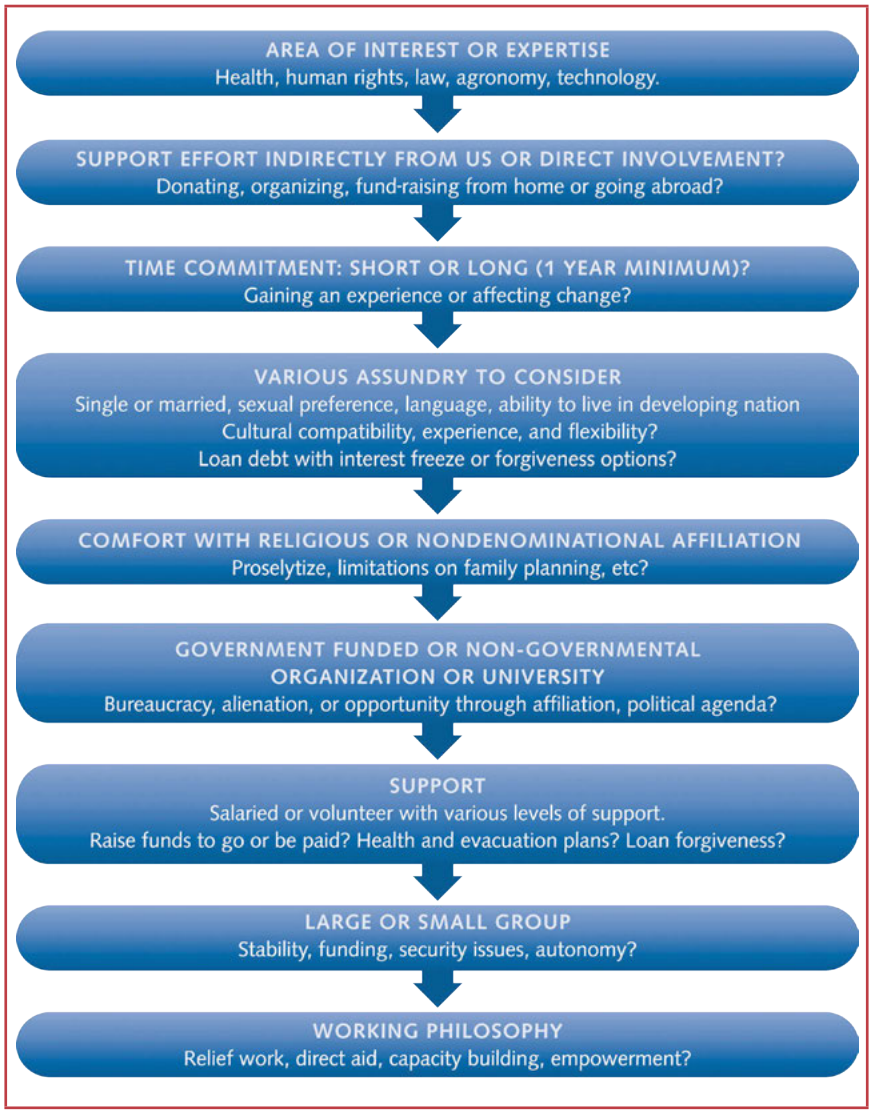
The desire to respond to the yearning is powerful. To actualize that dream, it is imperative to go through a process of self-discernment to determine a realistic path. One must be open to a variety of options and truthful about the limitations that exist. It can be helpful to lead people through a simple discernment process.

Figure 8-3 presents a generalized decision tree for those early in their career decision-making process, often at the undergraduate level, when determining an area of concentration. It is fairly self-explanatory, but volumes could be written about each step. Despite the fact that the second level asks whether one will actually go abroad to be involved in global issues or do so from his or her developed nation, most learners do not understand how critical that step is until the other parameters are considered, and they often end up back at that point. The sequence of decision steps is not necessarily fixed and must sometimes be rearranged based on the unique priorities of the individual.

Following the same logic, Figure 8-4 illustrates a more specific pathway for those in the medical field. It is not exhaustive, and there are most likely unique life choices not covered. Its aim is to paint broad swaths of choices to help learners determine what they are certain of and what they are equivocal about and, therefore, what they still need to research.

For the purposes of this chapter, it will be assumed that the reader is following the path in Figure 8-4 down to working abroad for a long-term block of time with an organization. However, someone who only gets partway down the decision tree should not be dissuaded from becoming involved in work abroad. There are innumerable examples of physicians from private, health maintenance organization, community clinic, and Indian Health Service settings who travel abroad episodically and

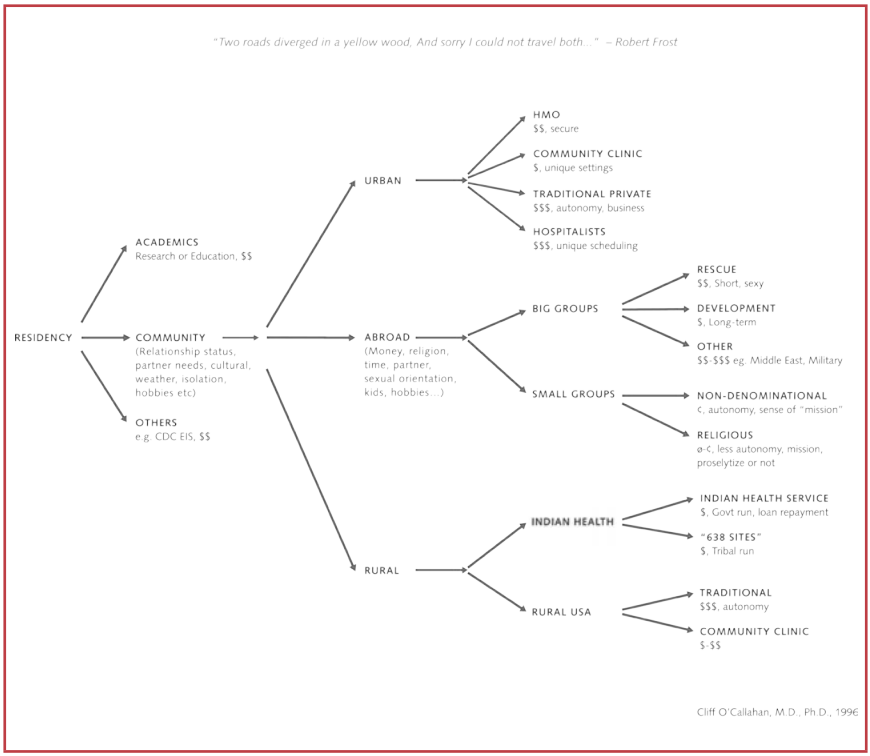
Figure 8-3. Generalized Logic Decision Tree



support efforts from home. There is a growing body of pediatricians, especially hospitalists and emergency physicians, who are becoming adept at negotiating unique job schedules. Many pediatricians contract to work in blocks or job share to amass time for work abroad.

Alternatively, another route to involvement with global health improvement is through academic institutions. Collaborative

Figure 8-4. Medical Jobs Off the Beaten Path



partnerships created between academic centers and communities or institutions in other countries can be extremely powerful catalysts for change for the learners and academicians of both parties. Table 8-1 lists a few examples of such partnerships.

For those pediatricians, regardless of their primary work environment, who truly feel they can go abroad for episodic short-term or longer tours, ongoing discussions are warranted with mentors who can help them filter the choices found in the many aid agency listings.

Perhaps the most critical step in the self-discernment process is to determine the capacity in which one wishes to work. Is one drawn to disaster relief, refugee aid, education, direct patient care in hospitals or clinics, community organizing, public health, or research on a particular disease entity? Once this becomes clear, it is easier to negotiate the daunting lists.

Obvious next issues to address and research are whether one is comfortable working within an organization with religious overtones

Table 8-1. Academic Centers and Community Partnerships

NAME	ACADEMIC PARTNER	HOST PARTNER
Shoulder to Shoulder[22]	10 US academic medical centers	Honduras
The Canadian Neonatal Network[23]	11 Canadian universities	China
Welbodi Partnership[24]	Welsh ABM University Health Board	Sierra Leone
Human Resources for Health[25]	19 US academic centers	Rwanda

Abbreviation: ABM, Abertawe Bro Morgannwg.

or a mission to proselytize; it becomes immediately clear that the vast majority of organizations listed are, to some degree, religiously affiliated. However, affiliation with a denomination does not automatically indicate religious overtones in the provision of care and demonstrates the need to research each option carefully.

The ability to search for opportunities is much easier in the digital age, but there are also some superb printed resources. The AAP Section on International Child Health maintains an up-to-date catalog of groups who use pediatricians in its book *Working in International Child Health,* 2nd Edition,[26] and on its Web site.[27] Other texts are useful from a general medicine perspective, such as the accessible *Finding Work in Global Health*[28] and the quite extensive *Awakening Hippocrates: A Primer on Health, Poverty, and Global Service*.[29] The latter's companion volume, *A Practical Guide to Global Health Service,* contains an extensive list titled, "The Omni Med database of international health service opportunities."[30] Particular positions of a wider spectrum that would include public health, consulting, administrative, and managerial work with agencies and universities can be found in other sources, such as the Global Health Council job board.[31]

Evaluating an organization for which one might consider working or donating is also more easily accomplished now. A variety of resources are available and can be found in Box 8-1. However, it can still be difficult to research background on small nonprofit organizations with budgets below US $1 million per year.

BARRIERS TO BECOMING INVOLVED

The algorithms for self-discernment allude to barriers that might preclude working in certain categories. It is important to take time and examine these honestly with oneself, family, and mentors.

Box 8-1. Resources for Evaluating Organizations

American Institute of Philanthropy at www.charitywatch.org critically evaluates more than 500 groups.

Charity Navigator at www.charitynavigator.org rates more than 5,000 groups using Form 990.

Ministry Watch at www.ministrywatch.com rates more than 500 evangelical groups.

Evangelical Council for Financial Accountability at www.ecfa.org rates 1,400 groups.

GuideStar at www.guidestar.org facilitates access to the Form 990 that nongovernmental organizations submit to the Internal Revenue Service for 700,000 charities.

Great Nonprofits at www.greatnonprofits.org is a blog-like review site.

Transparency International at www.transparency.org tracks corruption.

Burden of Debt

One of the most common and insurmountable barriers is the burden of debt when finishing residency. The Association of American Medical Colleges estimates that more than 86% of graduating medical students have educational debt. In 2012, the average US medical school graduate carried a debt burden of more than $160,000 from public medical schools and $190,000 from private medical schools.[32]

European medical students incur less debt burden because very few pay tuition. Their situation may be slowly changing. Britain is now charging students from more affluent families. However, on the positive side, some British physicians in training can take up to 3 years and work abroad in an out-of-program experience with the ability to return to the program and stage they left.

Very few loan programs offer the option to freeze interest accruement and defer principle payments while working in volunteer positions. Sporadic groups on an individual basis have covered the interest accruement as part of their support package for volunteers during their service. The Baylor International Pediatric AIDS Initiative, for example, offers a competitive salary and significant loan repayment. The MedSend model of covering a volunteer's monthly loan payment is a powerful example of what is possible but is limited to those who are comfortable with an overtly Christian agenda. As an alternative to working abroad, many choose to work in Indian Health Service sites where loan repayment can be up to $24,000 per year. Others pursue the Centers for Disease Control and Prevention Epidemic Intelligence Service, in which they earn a domestic salary and are often able to work abroad.

There is a glimmer of hope for the future. Legislative initiatives, such as the Global Health Expansion, Access to Labor, Transparency, and Harmonization Act of 2010 (HR 4933), planned to make moneys available for professionals expanding the health workforce abroad. Significant changes to loan repayment programs became effective through the College Cost Reduction and Access Act of 2007; section 203 creates a new income-based repayment program that can result in substantially lower monthly payments for those with a high-debt/low-income ratio, even if not involved in public service activities. In this program, remaining debt is forgiven after 25 years. For those who seriously consider full-time work in a public service setting or for a nonprofit 501(c)(3) and have a similar high-debt/low-income ratio, section 401 provides forgiveness of remaining debt after just 10 years (which does not have to be continuous). While this legislation was written and designed to aid law graduates working in public service settings, the law is broadly applicable. A superb description of the background to and explanation of this legislation can be found on the Georgetown Web site.[33] The Association of American Medical Colleges recently expanded its Web-based Financial Aid Survival Kit, which has detailed information on many of the income- and service-based means to reduce debt.[34]

Time

The ability to affect change and improve the lives of children and their families depends on many factors; the time we can dedicate to the task is certainly one of the most important. However, the reality for many in the health field is that there are forces pulling us to remain on more typical paths—the weight of building a career in academics or practice, finding a life partner, raising a family, paying off loans, fearing the unknown. The great majority of health professionals who involve themselves with global volunteerism or work do so in short stints of a week to a month at a time. Some find ways to make their short interventions productive and nondisruptive. However, if the MDGs are to be met, it will require more health professionals dedicating longer periods working in nontraditional settings.

The NGOs engaged in long-term work generally recognize that one must commit to at least 1 to 2 years of service to realistically contribute to the program. This time frame likely reflects summiting the steep learning curve that leads to a better understanding of the particular program philosophy, the local security and social norms, the different clinical environment and treatment stratagems, and the comfort of living in another milieu that can be potentially challenging, such as rural or urban poverty, linguistic and sociocultural isolation, physical separation

from friends and family, weather patterns, work ethics, availability of social outlets, and others. It is quite similar to the well-recognized temporal improvement in physician efficacy and comfort when transitioning from residency to work life in a new area but compounded by a multitude of more unique variables.

The length of this transitional phase that brings one from novice to contributing participant is realistically affected by the number and length of prior experiences and the quality and depth of prior training and orientation, both of which are consciously modifiable. On the other hand, the unique combination of resiliency, flexibility, fortitude, and gumption that any individual possesses, and which allows that person to not only survive in challenging environments but thrive, is less modifiable. It must be determined through experiences and followed by reflection and truthful introspection before embarking on further or more extensive endeavors.

Calculating one's unique comfort level in a lower-income country setting is a critical part of the discernment process to know whether one should follow the short-term or long-term experience pathway. For this reason, educational institutions sending learners abroad must provide good preparatory education, as well as create excellent opportunities where a learner can be challenged and supported, and have sensitive mentors or faculty on site to facilitate the reflection process.

Family and Relationships

One very real barrier for many idealistic learners finishing residency and wishing to pursue their dream of working in global health is relationships. For some, the barrier to going abroad is concern for the safety of their spouse, parents, or other family members. For others, it is the time pressure to encounter a compatible life partner. This is potentially more complicated depending on one's gender, race, religion, and sexual orientation in relation to the contemplated region or culture. Furthermore, a greater proportion of women are entering the health profession and expressing an interest in global and community health activities. The pressure to start a family, safety concerns about where to be pregnant and deliver children, and issues surrounding raising and schooling dependents abroad are all valid preoccupations and potential barriers to short- and long-term involvement.

Fear

Fear of working in the developing world is a very real barrier that must be honestly recognized. There is a substantial increase in risk to self, depending on the length of time abroad, including illnesses, stress

resulting in mental health issues, and work-related hazards such as blood-borne pathogens.[35] The rates of road and travel injuries are rising exponentially in lower-income countries even as they decrease in the industrialized world.[36] Fortunately, there remain many opportunities for those who discern that they are not suited to living in an emerging nation or even visiting for short-term collaborations. All organizations and institutions can benefit from volunteers who work on the home front teaching, mentoring, organizing, and fund-raising.

ETHICAL CONSIDERATIONS WHEN INTERVENING IN OTHERS' LIVES

Health professionals channel their efforts to address the needs of those less fortunate in a variety of ways; many choose a long-term commitment of more than a year to work and live in developing nations providing direct care, public health assistance, or community development, or teaching or conducting research. Many more professionals and almost all learners choose a shorter time frame because of time restraints, loans, family commitments, fear of the unknown, and the inability to break away from a comfortable existence.

These shorter experiences may be offered through government or university affiliations, NGOs with a religious or secular bent, or small private groups that are often church based. Many argue that these short visits are helpful,[37] while others contend that they offer little beyond immediate respite, provide substandard care, and squander millions of dollars.[38–42] Regardless, short visits will continue. Those visiting from the educational realm can be a valuable means of raising consciousness and skills in our future medical professionals.[43,44]

The fact that we have the wealth and political advantage to travel abroad and visit a developing country where the vast majority of our hosts will never have such an opportunity creates an immediate and inevitable power imbalance that gives us pause and could prompt reflective discussion among participants before embarking on a journey.

From the collective experience of many colleagues, Sue Hammerton, with whom I worked in Guatemala for many years, and I developed a set of ethical principles that I now offer as a discussion piece and framework for visiting medical groups so they might effectively and ethically work with local health structures in the communities they visit, with the hope that the intervention will affect recipients and visitors in a positive manner.

The principles that guide medical education in our developed country's institutions, such as the Accreditation Council for Graduate Medical Education (ACGME) competencies in the United States, need not be different than the principles that guide medical work in developing

country settings. Professionalism, medical knowledge pertinent to the area, appropriate system-based practice and care, particular emphasis on cultural and linguistic sensitivity in patient care and interpersonal skills, and the goal of continuous learning and improvement from the experience are necessary components for planning a medical visit or long-term stay—as necessary as a passport and plane ticket. Appropriately, there is now an internationally directed part of ACGME called the ACGME-International.[45] Various countries, such as India, Nepal, El Salvador, Jamaica, and Rwanda, place restrictions and oversight on visiting groups.[46] It is reasonable to suggest that it is even more important that a group aims for the highest standards when it is a guest in regions where there is no explicit oversight or accountability, realizing the challenges of monitoring outcomes and providing follow-up in a vulnerable population.[47]

The overarching goal of these recommendations is that the host community and visiting group have a *mutually beneficial ethical relationship*. Professionals come with good will and energetic plans for intervention, but often, these visitors may be misguided or influenced by a naive personal agenda. Therefore, it is not surprising that the resulting effort does not affect the community through positive health improvements and programs.

Guidelines for how a traveler might optimally behave while abroad have been developed. The International Society of Travel Medicine created a guide for "the responsible traveler" that is applicable to anyone going abroad.[48]

A 1997 editorial in *BMJ* led to a conference in Cambridge, MA, in 2000 with the theme "Shared Statement of Ethical Principles for Everyone in Health Care." The published report[49] nicely summarizes the discussions around the 6 major principles proposed.

1. Health care is a human right.
2. The care of the individual is at the center of health care, but the whole system needs to work to improve the health of populations.
3. The health care system must treat illness, alleviate suffering and disability, and promote health.
4. Cooperation with each other, those served, and those in other sectors is essential for all who work in health care.
5. All who provide health care must work to improve it.
6. Do no harm.

These principles, though quite broad, can certainly be used when designing or examining a global health program.

Guidelines that are more directed at medical professionals interested in short-term medical work abroad have been postulated.[47] The most

recent and excellent is the product of the Working Group on Ethics Guidelines for Global Health Training, which elucidates a broad array of guidelines broken down into categories under "Sending and host institutions," "Trainees," and "Sponsors" that are particularly pertinent to global health training programs.[50]

The framework that Sue Hammerton and I first created in 2004 (Box 8-2) proposes 7 principles that we felt were imperative to incorporate into a visit conducted by *any* medical group that claims it is there to contribute to the improvement of global health at the community level.

Discernment of Self and Visiting Group

One of the most important but often overlooked steps in the process of arranging for a medical visit abroad is *intention,* the process of discernment and planning whereby the individual and group reflect on the impetus to make such a visit and explicitly clarify their goals. Many of us would, on serious reflection, acknowledge the wish to journey abroad for reasons that might include altruism, adventure, compassion, proselytizing, guilt, learning, escape, and personal gain. The last might include admiration from others, professional advancement, and research and project completion. All may be valid if realized in a thoughtful way.

The importance of this first principle is that the discerning process can dictate every aspect of the visit, ultimately determining whether the great effort in getting to a community resulted in a mutually positive experience or, alternatively, a few stories in the local paper about the visitors and plastic bags of out-of-date sample medicine for nebulous ills in the hands of confused locals.

Expressed Felt Need of Host Community

For the relationship to be mutually beneficial, the visiting group must determine the expressed felt needs of the host community.[51] This implies creating a space of time, commitment, and effort whereby the visiting

Box 8-2. Framework for a Mutually Beneficial Ethical Relationship

Discernment of self and visiting group
Expressed felt need of host community
Cultural and linguistic competency
Benefit to host community
Benefit to visiting group
Ethically acceptable material benefits
Ethical relationship

institution, because of its discernment process and resultant goal setting, meets with a community to learn with them and provide services perceived to be vital by the host community. This is in contrast to medical visits that seldom have an effect beyond the immediate distribution of services and medicine. The glaring need that initially inspired the effort to visit rarely results in a change in the overall state of well-being for the hosts. However, by incorporating the most basic rural public health initial assessment tools[52] into a first step, the visiting group could meet with established leaders, elders, and elected and medical representatives. Additionally, it should also make it a point to meet with local women's groups to get an accurate reflection of maternal and child health needs. This process takes time and may seem to delay the intentions of the visitors. We trust that embracing this kind of relationship will eventually result in a richer experience. Demonstrating thoughtful planning and implementation is especially important for our learners and colleagues.

The importance of this principle is the acknowledgment that local people know their own needs and visiting medical guests can respect their host's dignity and intelligence by helping them to address necessary issues. There are a growing number of examples of such collaboration.[53–55]

Cultural and Linguistic Competency

This principle reflects how we act and interact with the host community. For a visiting group to accurately assess and clarify a mutually expressed felt need with a host community, it must proceed with cultural and linguistic competence. Medical institutions in the United States are expected to provide patients with access to translation services. We hold our medical learners and practitioners to a high standard of cultural integrity through regulations, despite the challenge of actually meeting those expectations.[56] For example, in the United States, these regulations originate with the ACGME and The Joint Commission, while in Britain, it is with the General Medical Council. It is equally vital to strive toward those expectations of language and cultural competency while working as guests among vulnerable populations. Visiting preceptors of medical learners bear an even greater responsibility to acquire linguistic skills or quality translators and model cultural awareness and sensitivity. In many cases, it is possible to find local organizations and individuals who can help with this process of acculturation.

Benefit to Host Community

Most visiting medical professionals would claim that sharing the wealth of knowledge and skills they possess, with the goal of improving health for the chosen host community, is one of the most important

motivating factors for traveling on a medical delegation or living and working abroad. Providing ambulatory care to long lines of villagers might give the perception that needs are being addressed. However, most resulting interventions have exceedingly short-term results because of a lack of continuing care and medicine. Moreover, the presence of foreign doctors can often undermine the confidence that hosts have with their local providers. Conversely, by working in conjunction with local physicians, rural nurses, health promoters, and midwives, visitors create the opportunity to play a critical role in improving health system capacity and quality.[57] It is necessary that a visiting group acts in ways that reflect a conscious choice to put the good of their hosts above its own needs.

One of the simplest, yet profound, benefits that host communities express is the joy they feel in knowing that others from more powerful nations know and care about them as they work together in solidarity.

Benefit to Visiting Group

The purpose of this principle is to optimize the benefit to visitor and host while minimizing harm to the host community. One of the most powerful transformative aspects of working in economically, environmentally, or politically challenged resource-poor areas is to be exposed to the reality of life beyond a developed country. Physicians attracted to this work know they will gain much more than they could ever hope to give and will benefit tremendously from the experience.[58] Being forced to diagnose using clinical skills and bearing witness to advanced stages of disease with little recourse for cure crystallizes the effect of public and interventional health, economics, policy, and geography on the well-being of our neighbors in lower-income settings. Coupled with built-in time for reflection and directed instruction, the lessons learned in such settings can improve our provision of care to large immigrant and indigent populations in developed regions and can be the catalyst for novel and ongoing collaborations.[59,60] Such partnerships between higher-income and lower-income areas are critical if there is to be an improvement in global health to meet the MDGs.[61–64]

There are unique situations that bear continued scrutiny and reflection, such as the experiences surgical trainees gain from performing surgeries abroad that are rarely, if ever, performed in their home institutions.

Ethically Acceptable Material Benefits

Health systems in the developed world generate an enormous amount of medical waste, and some of it can certainly be used in less well-supplied regions. Many examples exist at the local and regional level for collecting medicines, supplies, and equipment for donation.[65] The challenge

behind this sixth principle is that the recipient must be provided some choice in what is brought, often at great expense, and that the material is appropriate. Durable medical equipment should be in good working order and accompanied by spare parts and instructions in the recipient's language. Reference material and journals are best in the local language, although English is moderately universal as a medical language, and should be less than 5 to 10 years old, depending on the type, as stated by AAP and AAFP book repositories. Patient-directed educational material should be language and culture appropriate. Medicines should be appropriate in type, quantity, and expiration date.[66]

It is worth considering whether collecting monetary donations and buying materials and medicines in country might benefit the community on a larger scale.

The Shelf-Life Extension Program that the US Food and Drug Administration administers for the US military demonstrates that many drugs can be used beyond their expiration date,[67] but donating expired medicines can be offensive to our hosts and illegal for many countries' ministry of health to accept. If a decision is made to use expired medicines, the visiting group must take responsibility to communicate this decision with the host, repackage, and explain the change of expiration dates. Samples of medicines rarely used and of amplified spectrum should be avoided. A guiding principle could be to bring only high-quality generics from WHO lists, general and pediatric, of essential medicines[68] that have a remaining 12-month shelf life.

Ethical Relationship

Both words in this principle are important; everything that a visiting or collaborating group does should be based on ethical standards of practice and conducted within a relationship *with* the host community. Mutual respect and shared goals achieved over an extended period have much more likelihood of fostering good will and positive outcomes for all involved. Eliciting the perceptions of the host community can be extremely valuable and remarkably revealing.[69,70]

Group leaders, those involved in research projects, and all health professionals who teach, bear an enormous responsibility. They are the ambassadors of the institution they represent and the country from which they originate. These health ambassadors have a tremendous effect on their learners and colleagues as well as on host participants and patients. Their attention to details such as providing quality orientation and daily feedback, ensuring good patient documentation and follow-up, and maintaining communication with host representatives

can ensure a positive ongoing relationship. The lack of such detail can be devastating.[71]

All short- and long-term visitors and the institutions, NGOs, and churches they represent need to take responsibility in maintaining the highest standards of medical care. Significant insightful work published on ethical principles for students needs to be adopted and incorporated.[72,73]

The guiding principles outlined here are merely a framework, leaving more to be discussed and built. Based on discussions during various international health conferences, it is probable that many would support proposing the development of a similar set of expanded principles to evaluate the work of NGOs because they work with the most marginalized populations and expend enormous amounts of resources in the name of improving global health.

GLOBAL WORK FROM HOME

If the process of engaging in quality experiences and reflection with trusted and thoughtful mentors results in a discernment that precludes living or working abroad, that is a positive outcome. It prevents disappointment and stress in the individuals trying to force themselves to live a dream in a manner to which they are not suited and saves time and resources for the organization.

It is true that some barriers, such as debt or raising young children, are temporary and that when life circumstances change, other paths may open up. For example, a significant number of senior and retired physicians are exploring opportunities to work or teach in underserved settings.

For many, the simplest route to getting involved is through charitable giving. If one feels he or she does not have the skills, time, or interest in actually working abroad at the global level, that person can certainly donate monetarily. Investing wisely by researching a recipient organization is now much easier by using the tools in Box 8-1. Consciously choosing to donate the equivalent of one's most common visit level or procedure, or a block of time, on a regular basis (eg, deciding to donate the equivalent of what one earns from the most common US clinic visit billed, such as **99213,** or a 30-minute salary equivalent for someone in the National Health Service Corps, every 2-week pay period) is a concrete way of donating skills and energy toward meeting the MDGs, albeit through another's actions.

Some professionals might consciously choose not to go abroad on a short-term intervention so that they might divert the money otherwise used in lost productivity at home, travel, and lodging toward engaging

and paying for more local involvement in the host community. For example, the money that a plastic surgeon loses by taking a week of vacation, flying to South America, and staying in a hotel to perform a couple dozen operations could otherwise employ a local physician for months. That locally trained equivalent would perform many times that number of operations and would be there to provide follow-up and respond to complications. A powerful means to increase local capacity through donations is by sponsoring promising high school, university, and medical students through reputable organizations.[74]

GOING MEANS RETURNING: REENTRY PHENOMENON

Returning to a home country after a short stay away can be jolting, but there is often profound and ongoing psychological anguish after an extended period abroad. This is certainly recognized and described among returning missionaries, diplomatic corps members, military, students, and even businesspeople. Various religious groups have programs to address this, as does the US Department of State and military. The business community recognizes it as a potential threat to employee satisfaction and longevity among its most experienced managers.

Literature is sparse on this subject, but some commonalities emerge: individuals who indicate a change toward a more global identity experience high satisfaction with life. However, it is also found that those who embrace a more global cultural identity tend to feel more estranged from their original identity and exhibit much higher distress during repatriation.[75]

There is a brief practical learning module on medical worker reverse culture shock available on the Web[76]; each institution and organization should consciously develop and incorporate such a program into its structure. The existence of proactive reentry training can be an important method of evaluating groups and academic institutions on comprehensive support.

KEY POINTS

People tend to be happier when they are involved in activities beyond their usual work life that are for the benefit of others. *Global* implies more than simply abroad or international and may mean becoming involved in our own communities. Further richness can be attained by learning how our neighbors in more challenging settings live and work by spending time with them and determining, together, how to affect lasting change. However, the further one's dream takes him or her from the typical medical trajectory, the deeper one needs to contemplate the journey and its perils and rewards.

- Interest in global health activities is increasing among learners, those in practice, and retirees.
- Governmental and nongovernmental involvement in global health issues has proliferated over the past century.
- A process of discernment can be critical for the individual or organization contemplating involvement in global health activities.
- Significant barriers exist that must be considered and surmounted before embarking on any long-term global health activities.
- A set of ethical principles or guidelines is presented to stimulate discussion and reflection in those contemplating spending time in developing regions and those already engaged in activities.
- Anyone can be actively involved in global health improvements without even leaving home.

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CHAPTER

9

Natural Disasters

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INTRODUCTION

> *Disaster: "[A] sudden, calamitous event that seriously disrupts the functioning of a community or society and causes human, material, and economic or environmental losses that exceed the community's or society's ability to cope using its own resources."*[1]

The modern disaster relief movement finds its origins during the Johnston, PA, floods of 1889. In the span of a few weeks, torrential storms caused the failure of the South Fork Dam on the Little Conemaugh River, unleashing floods that killed at least 2,000 people. Clara Barton, who started the American Red Cross to alleviate the suffering of victims of conflict after the American Civil War, successfully pushed to assist the victims of the Johnston floods. From there, the idea of relief for natural disasters blossomed and evolved drastically over the past century.[2] The last 10 years have seen dramatic examples of natural disasters, including the 2004 Indian Ocean earthquake and tsunami (>220,000 deaths[3]), Cyclone Nargis in Myanmar in 2008 (>84,000 deaths[4]), and the Haiti earthquake in 2010 (>316,000 deaths caused by the earthquake,[3] not including the >7,000 subsequent deaths from the post-earthquake cholera outbreak[5]). Similarly, after a slight decrease in the number of persons worldwide who live in conflict zones, there has been a sharp increase in recent years owing to ongoing or flaring wars

in Syria, Iraq, Afghanistan, South Sudan, and Central African Republic. However, since the days of Clara Barton, while medical relief efforts in natural disasters are still closely related to patient care in conflict zones, there are sufficient divergences such that the health care of children after natural disasters deserves its own chapter.

This evolution is partly driven by the exponential growth in the number and type of organizations providing medical relief during natural disasters. Coordinating responsibilities belong to public health departments and other statutorily created bodies, such as the Federal Emergency Management Agency in the United States and the UN Office for the Coordination of Humanitarian Affairs (OCHA) internationally. Meanwhile, implementing organizations range from the International Federation of Red Cross and Red Crescent Societies to local nongovernmental organizations (NGOs), international NGOs, non-secular relief agencies, and academic university–based groups.

Recent natural disasters, such as the 2004 tsunami in Asia, the 2010 earthquake in Haiti, and the 2013 typhoon in the Philippines, demonstrate how disaster relief is increasingly provided by a complex mixture of local and international medical professionals.[6] Unfortunately, the advances in disaster responses have not resulted in sufficient reductions in mortality rates and human suffering, demanding increased scrutiny by the international community and health practitioners.[7] Part of the problem is the gravitation of inexperienced and poorly qualified relief workers to disaster zones, such as after the 2010 earthquake in Haiti, "where most responders were younger than 30 years of age and had no previous disaster-response experience."[6] Another significant aspect is the difficulty of coordinating among all these groups, whether by national ministries of health or the UN cluster system.[8] A final, separate temporal problem is that all too often, the catastrophe dealt to the affected geographic region is forgotten in subsequent weeks as the rest of the world returns to its own concerns.[9] Largely, it is the post-event effect on infrastructure (eg, roads, communication, transportation) that potentiates the surrounding challenge of immediate disaster relief. These difficulties make it imperative that well-intentioned pediatricians who would like to assist in disasters ensure they have the minimum skills necessary for disaster-related care and work with a reputable organization that adds value to the relief effort rather than depletes valuable resources.

This is especially important because there has been a marked increase in the scale and scope of natural disasters, which have affected more than 200 million people each year since 1990.[10] With a rapid growth of urban centers, the developing world is projected to be the home of 80%

of the world's population by 2025,[11] with much of this growth in areas of high population density,[12] poverty, and limited infrastructure support. This confluence forms the perfect storm, placing the least-developed countries at the highest risk for enduring mass casualties. Properly trained pediatricians are in need more than ever given the particular vulnerability of infants and children in these crises.

SPECIAL NEEDS OF CHILDREN

Disasters disproportionally affect children for medical and nonmedical reasons. Children, particularly infants, differ anatomically and physiologically from adults, which markedly affects how they should be medically managed in disasters.[13] They have a relatively immature immune system and a higher basal metabolic need due to growth demands. They also have a much higher surface area to volume ratio than adults, which increases their risk of dehydration, hypothermia, and exposure-related toxicities. Increased respiratory rates place children at elevated risk from aerosol exposures. Children may not be able to sense and avoid dangers associated with the disaster. Age and developmental stages markedly influence how children will respond psychologically to disasters and the events surrounding them. Combined, these factors put children at risk for the 5 main causes of mortality following a disaster: acute respiratory illnesses, diarrheal diseases, measles, malnutrition, and, where relevant, malaria (Box 9-1).[13] For all of these reasons, pediatric health professionals are essential to disaster response efforts.

Even experienced clinicians need to be reminded of the particular nonmedical vulnerabilities of children after disasters. The medical risks in Box 9-1 can be compounded by prevailing poverty, which results in lower baseline nutritional status, decreased immunization rates, higher loads of intestinal parasites, and limited access to health care.[14] Splitting up of families and death of caregivers can occur as a result of severe disasters. Unaccompanied orphans can be found roaming the streets in the initial weeks after the destruction. Disasters often create an even

Box 9-1. Top 5 Causes of Post-disaster Mortality in Developing Nations

1. Malaria
2. Malnutrition
3. Diarrhea/dehydration
4. Measles
5. Acute respiratory illnesses

greater socioeconomic burden on countries already struggling with poor governance and impoverished residents. The economic effect can be devastating; an initial rise in food prices can lead to worse malnutrition rates and overcrowding of urban centers, further exacerbating the effect of poverty in severe emergencies. Delayed recovery can worsen acute and chronic adverse psychological sequelae of the disaster.[15]

Increased attention is also being focused on the significant psychological trauma children experience in these settings, as evidenced by physical violence, exposure to drugs, and forced separation from their families. Poverty and political instability coexist in many instances. The tragedy of natural disasters is further complicated by human-driven conflict. As many as 300,000 children younger than 18 years were involved in some combat role in more than 50 countries in 2001.[14] Management strategies of childhood psychological emergencies include active intervention versus removing children from these harmful exposures and restoring normalcy as quickly as possible through family reunification.[16,17] A high proportion of children exposed to disasters experience some degree of post-traumatic stress disorder (PTSD), depression, or anxiety.[15]

NEEDS ASSESSMENTS OF HUMANITARIAN CRISES

The process of intervening after a disaster starts with the initial assessment. The effects of disasters are often a consequence of population displacement and the subsequent breakdown of health care systems and supply chains. This degrades essential programs directed toward vaccination, maternal care, and nutrition. If the pre-disaster public health infrastructure functioned well, there may already be a local contingency plan or one emulating the World Health Organization (WHO) recommended Early Warning Alert and Response Network.[18] However, despite the best preparatory measures, local resources may not have sufficient resilience to manage the problems, which is one of the definitions of a disaster.[1] In these cases, rapid epidemiologic surveys may be necessary. In early post-disaster stages, they need not be excruciatingly thorough, as the most vulnerable populations (children and pregnant or lactating women) and major causes of morbidity and mortality can be inferred from previous epidemics.

However, rapid surveys must be systematic, able to set health priorities, and relevant for programmatic implementation (Table 9-1).[19] Ideally, if possible, they should be continued longitudinally to evaluate trends and predict epidemics. Surveys can be active, with surveillance teams going out to collect data, or passive, with information collected as patients come to health structures.[20] Of course, these approaches

Table 9-1. Minimum Standards in Humanitarian Response	
INDICATOR	**THRESHOLD**
Mortality rates (should be adjusted to baseline)	Crude mortality rate <1/10,000/d and under-5 mortality rate <2/10,000/d
Basic health coverage	1 primary health center/10,000 persons
Health personnel coverage	1 doctor/50,000 persons, 1 nurse/10,000 persons, 1 midwife/10,000 persons, and 1 community health worker/1,000 persons
Water availability	>15 L/person/d
Water quality	0 fecal coliforms/100 mL of water at point of delivery
Toilets	Maximum 1 toilet/20 persons
Shelter	Minimum 3.5 m^2/person covered floor

can be combined to get more accurate and timely information, such as the surveillances done in the aftermath of the 2010 Haiti earthquake.[21] Community health workers are a growing component of active surveillance teams so that issues of language and culture are mitigated but also as a way to maintain longer-term surveyors.

The surveys themselves should relay the most relevant health information, including the crude mortality rate (CMR) and the under-5 mortality rate (U5MR), both of which are expressed in number of deaths per 10,000 people. Generally accepted thresholds for declaring an emergency is a CMR greater than 1 per 10,000 or a U5MR greater than 2 per 10,000.[22] Working to improve equity and the needs-based response, effective assessment tools using randomized rapid cluster methods have been developed to provide sound estimates of mortality and malnutrition, aiding to facilitate.[23] Surveys should also relay information on incidence rates of the 5 main morbidities in children (see Box 9-1). In addition, following some disasters, measles vaccination coverage rates and incidence should be sought, given that measles can cause significant morbidity and mortality in high-density populations, such as those in refugee camps. Finally, new online tools (Table 9-2) have been made freely available to assist clinicians in carrying out post-disaster surveillance and interpreting the data, including the Sphere handbook,[19] which lists the universal minimum standards of a humanitarian response, and SMART (Standardized Monitoring and Assessment of Relief and

Table 9-2. Helpful Online Resources

- **Software for emergency nutrition assessment**
  www.nutrisurvey.de/ena2011
- **Famine Early Warning Systems Network**
  www.fews.net
- **Sphere Handbook**
  www.sphereproject.org/resources/download-publications/?search=1&keywords=&language=English&category=22
- **Médecins Sans Frontières/Doctors Without Borders reference books**
  www.refbooks.msf.org/msf_docs/en/MSFdocMenu_en.htm
- **The Johns Hopkins and International Federation of Red Cross and Red Crescent Public Health Guide for Emergencies**
  www.jhsph.edu/research/centers-and-institutes/center-for-refugee-and-disaster-response/publications_tools/publications/_CRDR_ICRC_Public_Health_Guide_Book/Public_Health_Guide_for_Emergencies

Transitions), which helps with epidemiologic calculations, including the Early Nutrition Assessment for malnutrition screening.[24]

MEDICAL CONSIDERATIONS

Simultaneous with undertaking a rapid survey, contingency plans should be made to treat the most common medical conditions children face after a disaster (see Box 9-1).[13] In addition, recent literature seeks to include psychological care of children as a top priority, given its effect on the overall well-being of each child.[25]

Acute Respiratory Illness

Depending on the disaster context, clinicians may not have access to laboratory or x-ray diagnostics. In these cases, it may be necessary to use a simplified clinical diagnosis, dividing respiratory illnesses into severe pneumonia, pneumonia, and upper respiratory illness (ie, cough/cold without pneumonia). Pneumonia can present with or without fever and should be suspected in children who present with cough, difficulty breathing, or tachypnea. Infants who are younger than 2 months or malnourished are the highest risk of severe disease. Signs of severe pneumonia include grunting, flaring, retractions, cyanosis, and signs of serious illness (eg, lethargy, stridor) (Table 9-3).[26] These children require hospitalization for parenteral antibiotics (eg, ampicillin ± gentamicin, ceftriaxone) and respiratory support.[27] Children with tachypnea but without

Table 9-3. Guide to Respiratory Rates in Children of Different Ages		
AGE	**NORMAL RESPIRATORY RATE/MIN**	**SEVERE RESPIRATORY DISTRESS**
Infants <2 mo	30–40	>60
2–12 mo	30–40	>50
12 mo–5 y	25–30	>40
>5 y	20–25	>30

signs of serious illness may be diagnosed with pneumonia and treated in an ambulatory setting with oral antibiotics (eg, amoxicillin). Finally, those children without tachypnea but with cough can be treated conservatively. If the cough persists for longer than 3 weeks, tuberculosis, asthma, and pertussis should be included in the differential diagnosis.[28]

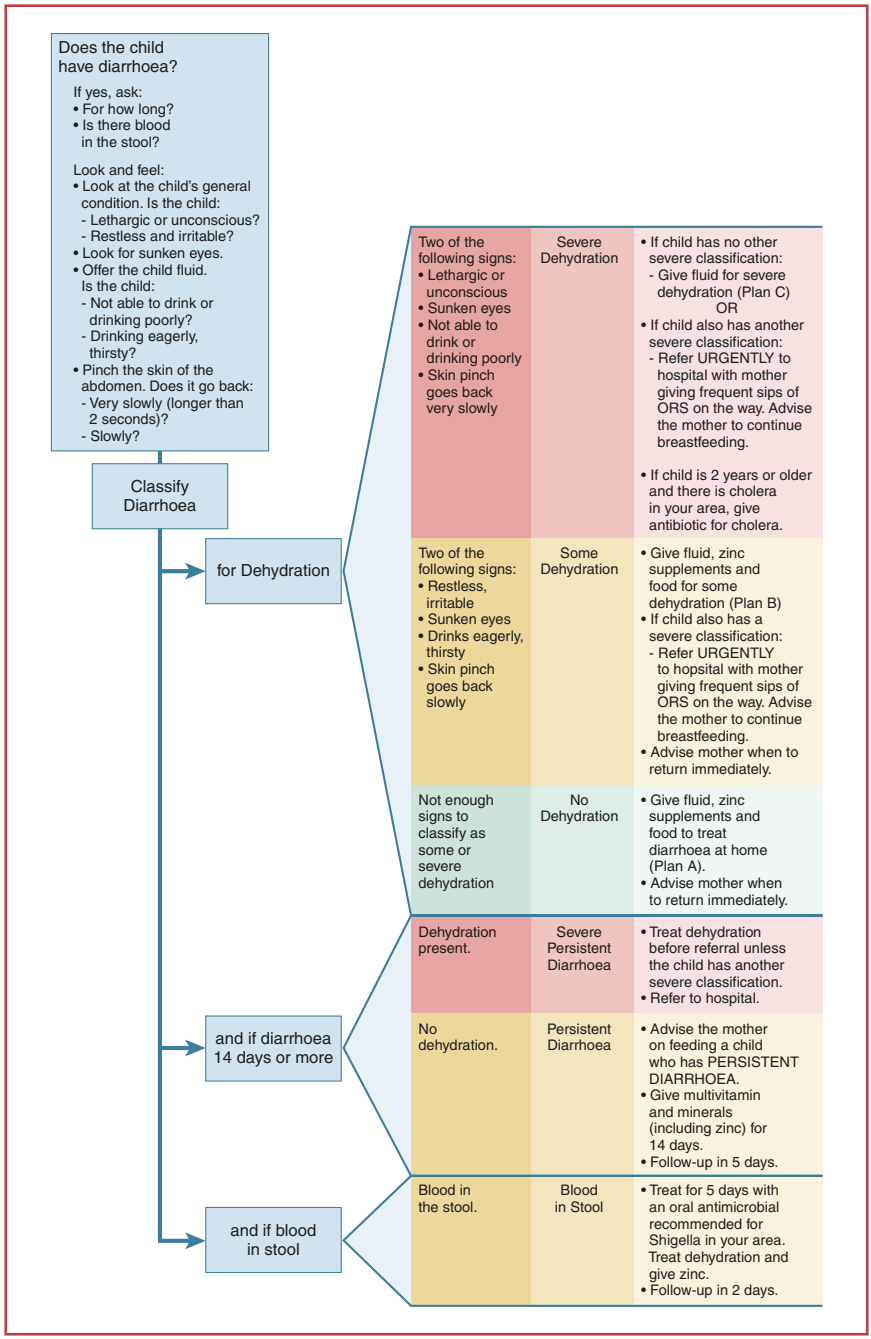
Diarrheal Diseases and Dehydration

Diarrheal illnesses commonly lead to dehydration, making an urgent evaluation of each child necessary. The main historical questions should be, "Is the diarrhea bloody?" and "Is the child dehydrated?" Most diarrheas are not bloody and do not require antibiotics. However, bloody diarrhea may indicate shigellosis dysentery, which is treated with a fluoroquinolone or third-generation cephalosporin.[27] Vigilance should also be taken to screen for cholera, which is usually seen as profuse watery diarrhea in children older than 5 years but which can affect young children too. Clinical signs can classify a child as having no, some, or severe dehydration. Corresponding rehydration therapies (WHO plans A, B, and C) can guide a clinician on whether the patient can be treated at home with oral rehydration solution or whether the patient will need intravenous resuscitation (Figure 9-1).[29] Children with diarrhea leading to dehydration should receive zinc supplementation, especially those younger than 5 years, because they are at highest risk for severe disease and receive the greatest benefit.[30]

Malnutrition

Severe acute malnutrition (SAM) and moderate acute malnutrition (MAM) are diagnosed in reference to WHO weight-to-height standards for children between the ages of 6 and 59 months. Severe acute malnutrition and MAM are diagnosed when the weight to height ratio is less than 3 and less than 2 standard deviations below normal, respectively, or if there is bilateral pedal edema (ie, kwashiorkor [a form of

Figure 9-1. Treatment Plans for Diarrhea



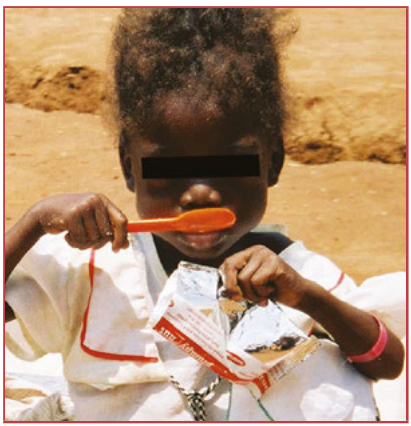
Adapted from World Health Organization. *The Treatment of Diarrhoea. A Manual for Physicians and Other Senior Health Workers.* 4th rev ed. Geneva, Switzerland: World Health Organization; 2005. http://www.who.int/maternal_child_adolescent/documents/9241593180/en. Accessed June 1, 2015.

SAM]). Clinically, the use of a mid–upper arm circumference (MUAC) (Figure 9-2) has made screenings much faster, with SAM diagnosed when the MUAC is 115 mm or less and MAM is 116 to 125 mm.[31] Ideally, treatment of malnutrition will be done in an ambulatory setting, although some severely affected patients will require a brief inpatient stay. Main treatment consists of feedings with ready-to-use therapeutic food (eg, Plumpy'Nut) (Figure 9-3) and antibiotics, deworming tablets, vitamins, and vaccinations to prevent comorbidities.[28]

Figure 9-2. Measurement of the Mid–Upper Arm Circumference of a Young Child for Indication of Malnutrition

From American Academy of Pediatrics. *Atlas of Pediatrics in the Tropics and Resource-Limited Settings.* Spector JM, Gibson TE, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Figure 9-3. Child Eating Ready-to-Use Therapeutic Food



From American Academy of Pediatrics. *Atlas of Pediatrics in the Tropics and Resource-Limited Settings.* Spector JM, Gibson TE, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Measles

Measles is a highly contagious viral infection that is spread by respiratory droplets. After disasters, children are specifically vulnerable if they live in crowded camps and if the overall population vaccination rate falls below 90%. Once infected, a child is susceptible to dangerous sequelae, including secondary pneumonias and diarrhea. Between 5% and 20% of infected persons die due to complications of measles, with the highest risk occurring in malnourished children younger than 5 years.[32,33] Measles can be detected clinically, including typical patterns of cough, coryza, conjunctivitis, fever, and rash. However, laboratory confirmation must be performed at the onset of a suspected outbreak. Outbreak response includes supportive care and vitamin A for all infected children, the treatment of bacterial superinfections, and consideration an immediate measles mass vaccination campaign.[34]

Malaria

Malaria is a mosquito vector-borne disease that is endemic in many developing countries. The incidence rate of malaria can increase substantially after a disaster, especially in flooded areas. The most common presenting sign in a child is fever. Rapid tests that use capillary blood simplify the diagnosis, although thin and thick blood smears may sometimes still be needed. Because of the spread of chloroquine resistance, the most common medicine used is an artemisinin derivative orally or parenterally. Adjunct treatments may include benzodiazepines for seizures and transfusions for symptomatic anemia.[28] Distribution of insecticide-treated mosquito nets to families should be done to facilitate malaria prevention.[35]

Mental Health

Children may be more susceptible to PTSD than adults following a disaster. However, children may not have the cognitive capacity to express their feelings and emotions, making a proper diagnosis difficult. Moreover, the signs of PTSD in children are subtle, can involve different levels of anxiety and depression, and can often be mixed with other childhood mental health disorders. Systematic screening should be considered, and treatment programs using local volunteers to maintain cultural competence are encouraged.

CRITICAL PUBLIC HEALTH INTERVENTIONS

Good health outcomes are highly dependent on the rapidity of appropriate medical and surgical responses because the probability of survival from serious injury decreases substantially 12 to 24 hours after the disaster occurs.[36] Médecins Sans Frontières (Doctors Without Borders) follows a list of top 10 priorities in precarious situations, such as those faced by disaster survivors, to guide its responses (Box 9-2).[36]

Some of the more medical issues in Box 9-2 were previously addressed. Others on this list relate more to public health and organizational efforts but are crucial for the health of children affected by disasters. Particularly, there is an imperative to provide adequate water, sanitation, and hygiene; shelter; and coordination to stave off adverse medical outcomes.

Water, Sanitation, and Hygiene

The Sphere handbook sets out minimum standards during a humanitarian response. These specify that each person has access to at least 15 L of water per day, the maximum distance from any household to a water

Box 9-2. Ten Priorities of Disaster Response

1. Initial assessment
2. Measles immunization
3. Water and sanitation
4. Food and nutrition
5. Shelter and site planning
6. Health care in the emergency phase
7. Control of communicable diseases and epidemics
8. Public health surveillance
9. Human resources and training
10. Coordination

point be 500 m, and the queue for water retrieval at any water point be less than 30 minutes. Further specifications are made for the quality of water and minimum distance away from water sources where waste disposal areas can be located.[19]

Shelter and Site Planning

The Sphere handbook also requires that each individual have at least 3.5 m^2 of covered floor area in which to live. The shelter should be culturally appropriate, use local construction workers, and have sufficient covered living space, ensuring privacy, safety, and health to allow for essential household activities.

Coordination and Security

Given the array of different actors that arrive at a disaster zone, from governmental agencies to international and local NGOs, coordination must be considered during any disaster response. Depending on the extent of the disaster, local authorities may or may not be able to take the lead in coordination. If they are unable, UN agencies, such as OCHA, may take the lead. Recently, OCHA has been using the cluster approach; however, it has received some criticism, especially in the response to the 2010 Haiti earthquake.[37,38]

The proliferation of cell phone technology and geographic information systems has allowed more decentralized coordination. In addition, the use of crowd-sourced platforms like Ushahidi allow user-generated profiles, which are changing surveillance methodologies.[39]

UNIQUE CIRCUMSTANCES ASSOCIATED WITH SPECIFIC NATURAL DISASTERS

While the previous discussions about the most common medical and public health issues can be appropriate generalizations for most disasters, each type of disaster has unique challenges. From tsunamis to tropical storms and volcanic eruptions to floods, there exist patterns of health-related issues for each type of disaster. In addition, the effect of global climate change is potentially exacerbating the frequency and devastation of certain disasters.

Earthquakes

Earthquakes are one of the deadliest and most destructive natural events, responsible for more than 1 million deaths and injuries in the past 2 decades.[40] Building collapse and entrapment pose the greatest risks. The most successful rescues take place within the first 24 hours, and most lives are saved by immediate actions of survivors.[41] Health concerns following an earthquake are related to entrapment, including hypoxia, inhalation injury, hypothermia, dehydration, drowning, crush syndrome, and infected wounds.[42]

Tsunami

A tsunami is a very large wave or series of waves resulting from an underwater earthquake or volcano. This can result in immediate building destruction and death secondary to drowning and crushing. Infectious sequelae following seawater aspiration lead to pneumonias and soft tissue infections, as was observed in the South Asian tsunami in December 2004.[43]

Floods

Floods are the most common natural disaster worldwide, affecting the most people and causing the greatest number of fatalities among all calamities.[44] Seventy percent of all deaths from floods occur in India or Bangladesh, although they exist in almost every country.[41] Injury occurs due to fast-flowing debris and boulders as well as fallen trees. While the main cause of death is drowning, damage to community agriculture and housing can result in food shortages and homelessness. Contaminated water supplies can lead to infections, especially cholera.

Tropical Storms

Tropical rotating storm systems are called cyclones, hurricanes, or typhoons, depending on in which region of the globe they occur. These

events primarily affect coastal areas, with a recent increase in injuries and death as a result of population growth in these locales.[45] Together with strong damaging winds, secondary effects can include tornadoes and flooding. Drowning is the leading cause of death, although other causes include trauma from flying or fast-flowing objects as well as entrapment.

Tornados

Tornados consist of violently strong winds with a vacuum vortex that is often responsible for extensive damage to non-reinforced buildings in their path. High-velocity winds can throw debris, causing fatal injuries and high rates of secondary infected lacerations.

Volcanic Eruptions

Areas surrounding volcanoes are often well populated because volcanic ash provides highly fertile soil. The greatest immediate risks of a volcanic eruption include suffocation and respiratory ailments from ash inhalation and possibly lethal gas.[46,47] Pyroclastic flows are fast currents of extremely hot gases (>1,000°C) that can move at several hundred kilometers per hour, posing a considerable risk to life because they are hard to escape.

Climate Change

There is growing consensus that the effects of global climate change will result in extreme weather events, sea-level changes, and ecologic disturbances. Direct effects of global warming are possibly already related to increased heat waves, floods, and fires. Indirect future consequences may be related to adverse effects on food yields and water sources, leading to malnutrition and premature deaths, respectively.[48]

Natural and artificial disasters directly affect the morbidity, mortality, and well-being of large populations, with children being disproportionately affected due to numerous innate vulnerabilities. There are encouraging signs of progress underway in a collaborative effort to continually improve emergency response operations. However, it remains crucial to address ongoing challenges to coordinate health needs assessment activities, minimize the use of additional parallel health systems on top of existing community public health structures, and employ appropriate exit strategies to ensure the best possible transition of care. Although relief will always be required in immediate disaster response, continued emphasis on preparatation, disaster readiness, and prevention are vital to further advance the humanitarian response.

KEY POINTS

- Children are particularly vulnerable in a crisis and at high risk for mortality caused by acute respiratory illnesses, diarrheal diseases, measles, malnutrition, and malaria.
- Critical services requiring immediate reestablishment include adequate clean water, sanitation, nutrition, shelter, immunizations, infection control measures, surveillance, training, and coordination between partners.
- All disasters have unique aspects, but recognizing common features permits rapid and orderly facilitation of much-needed health care services.
- Continued efforts to improve the collaborative model of emergency responses are integral to future success of enhanced disaster care and strengthened resilience of local systems.

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SECTION 2

Caring for Pediatric Travelers and Immigrants

CHAPTER

10

Travel Clinics

John C. Christenson, MD, FAAP

INTRODUCTION

Every year, more than 1 billion people travel across international boundaries. More than 50 million people travel to countries with limited resources. Ten percent of international travelers are children.[1] Countries within sub-Saharan Africa, Asia, and Latin America are frequently visited by children.[2] Many of these countries are endemic for malaria, typhoid, dengue, and yellow fever. In addition, traveler's diarrhea is one of the most common diseases acquired while traveling in these regions. These diseases are preventable. Individuals should seek pretravel medical advice with the goal of preventing travel-related illnesses. In addition, administering specific vaccinations and prescribing prophylactic medications against malaria are important means of preventing disease. While some clinicians are comfortable providing this type of medical care to their patients, many seek the assistance of experts in travel medicine. Vaccines specific to international travel, such as those for yellow fever and typhoid, are not available in most primary care practices. Web sites and printed materials can help clinicians prepare their patients for travel. Travelers can also easily access these sources; however, they may be too basic or too difficult for some to assess the precise risk in a given region, thus necessitating an expert in travel medicine to provide needed advice. Travel clinics are the most reliable assets in these circumstances. Education, risk assessment, medical advice, vaccinations, and prescriptions for chemoprophylaxis can all be obtained in a single place.[3]

Pediatric travelers pose a great challenge because they require different considerations for recommended antimalarial chemoprophylaxis agents, with dosing according to body weight and possible contraindications for certain vaccines in younger children. Infants whose families want to take them to areas of the world at risk for high-altitude illness require specialized attention, family education, and chemoprophylaxis. Many travelers, especially those visiting friends and relatives, frequently do not visit travel clinics or receive preventive medical advice, vaccines, or chemoprophylaxis.[4] It is imperative that clinicians become more knowledgeable in most aspects of travel medicine and learn how to access pertinent sources of information.[5] In some primary care settings, clinicians with travel medicine expertise successfully integrate travel medicine consultation into their practice.[6,7]

This chapter specifically discusses the multiple aspects needing consideration when developing a travel clinic, whether as a freestanding practice or an integrated component of a large medical practice. Emphasis is given to pediatric travelers and their families.

SOURCES FOR TRAVEL ADVICE, VACCINES, AND CHEMOPROPHYLAXIS

Parents of traveling children need accessible sources of reliable information to educate themselves and their children on the most appropriate means of disease prevention. Travel magazine articles and books are reasonable initial sources, but some do not contain the most up-to-date information. At times, information in travel brochures or from tour operators is not accurate. Frequently accessed Internet sites are the Centers for Disease Control and Prevention (CDC) Travelers' Health (www.cdc.gov/travel) and World Health Organization International Travel and Health (www.who.int/ith/en/index.html). While these sites contain useful information, navigating through them may be cumbersome for many nonmedically trained individuals.

Pediatric travelers visiting an at-risk country may be referred to a travel clinic by their primary care physician; others are self-referred. Unfortunately, travel clinics may not be available locally for some. In these cases, the primary care physician may be asked to provide the necessary advice. Multiple review articles on travel medicine have been published,[5,8] which clinicians may find useful.

Travel clinics are frequently affiliated with large medical centers. Some are contained within clinical infectious disease programs. Many clinics are self-sustaining private clinics or part of a primary care medical practice. Travel vaccines are now available through many local pharmacies and nurse-based immunization services. In addition, city- or

county-based health departments may provide vaccination services for travelers. There are few travel clinics that exclusively cater to the pediatric age group and their families. Within travel clinics, the level of comfort in providing services to infants and children varies.

WHERE CAN ONE FIND A TRAVEL CLINIC?

Two easily accessible Internet sites provide a list of clinics: the American Society of Tropical Medicine and Hygiene (www.astmh.org/source/ClinicalDirectory) and the International Society of Travel Medicine (www.istm.org). These Web sites contain a list of travel clinics within the United States and other countries and provide information on travel medicine practitioners with special certifications in travel health. Church, humanitarian, and study groups with prior travel experiences usually know where to obtain vaccines, prescriptions, and advice and frequently refer friends, relatives, and members to these sources. Unfortunately, at times, travelers with "good" past travel experiences may dissuade a "novice" traveler (frequently a friend or family member) from receiving necessary vaccines and chemoprophylaxis, placing the novice traveler at risk for malaria, typhoid, and yellow fever. Community centers of various ethnic groups will refer members to specific clinics for vaccinations. In some communities, travelers planning to visit friends and family will only visit a travel clinic or immunization center if a yellow fever vaccine is required to enter a country.

VISITING A TRAVEL CLINIC

Travelers' medical history, past travel experience, and immunization history influence their needs. For a travel medicine practitioner to be able to offer the best advice, various components of a travel clinic consultation need to be assessed. In most cases, travelers or their parents or guardians will complete a clinic visit questionnaire in which this information will be recorded. The form should allow space for the travel clinic practitioner to record useful information about the visit.

Travel Destinations

Travel advice, vaccines, and need for antimalarial chemoprophylaxis are based on a traveler's expected risk. Travelers must identify countries or regions they plan to visit. Detailed maps should be available for research. A comprehensive, detailed world atlas is an essential tool for all travel clinics. Risks may vary within a country. For example, travelers visiting Guatemala and spending time exclusively in the capital will not be exposed to malaria. However, if visiting Mayan ruins in the Petén, they will need antimalarial chemoprophylaxis. Most of South Africa is malaria

free and travelers will not require antimalarial prophylaxis. However, visits to Kruger National Park in the northeastern region will require it.

Travel Activities

The type of activities planned may affect risk. The risk of acquiring certain infections, such as hepatitis A, typhoid, and diarrhea, vary greatly. A careful businessperson staying with family in a 5-star hotel will have a lower risk than a student backpacking in rural areas of the same country. Knowing these plans beforehand allows the practitioner an opportunity to give specific recommendations. For example, travelers wanting to participate in white-water rafting may place themselves at risk for leptospirosis, necessitating a discussion about doxycycline chemoprophylaxis, while travel with young infants may trigger discussions about safe travel practices during flight and on land.

Building an Educational Handout

Starting with this information, an individualized educational handout for travelers can be built. The handout will include general recommendations addressing travel, required and recommended vaccines, and need for antimalarial chemoprophylaxis. Information about the country (eg, culture, crime, embassy contact information) and regions can be included. Web sites such as www.cdc.gov and www.who.int/en can be used. Global TravEpiNet, a consortium of many clinical sites throughout the United States, including primary care clinics, academic travel medicine practices, pharmacy-based practices, public health clinics, and occupational health clinics that provide pretravel advice, care, and vaccinations (www.healthful.travel), has created Web-based tools based on CDC recommendations that may be useful when preparing families for international travel. In addition, commercial sites such as Travax (www.travax.com) and Tropimed (www.tropimed.com) can be used to obtain up-to-date information, including maps. These commercial sites require an annual subscription fee. Advice on food and beverage precautions, swimming, sexual activity, animal bites, altitude illness, and safety can be provided. The information provided to the traveler should be documented on clinic visit forms. During the visit, the travel medicine specialist can decide which items should be discussed in person. Depending on the number of travelers, complexity of the trip, number of vaccines to be administered, and past travel experiences, a clinic visit may take up to 1 hour or more. Because it would be impossible to cover all aspects of travel and provide vaccines, most of the needed information can be provided through a printed handout, allowing travelers to review and read it at home before their trip. Social media, digital imaging, and slide

presentations are used by some to share useful travel-related information before and during travel.

Topics that may require discussion during a clinic visit include

- Immunizations (benefits and potential side effects)
- Antimalarial chemoprophylaxis
- Insect bite prevention
- Accident and injury prevention
- Food and beverage precautions
- Food preparation
- Treatment of traveler's diarrhea (eg, rehydration, antibiotics)
- Country-specific access to health care
- Jet lag
- Motion sickness
- Travel-related thrombosis
- Altitude illness
- Traveling with young children
- Animal bites
- Crime
- Travel and medical evacuation insurance
- Swimming

Travel Dates and Duration

Departure dates and travel duration also influence risk. In some countries, certain periods are associated with a higher risk of disease, such as the rainy season (malaria) and dry season (meningococcal disease). Prolonged stays increase the risk of acquiring most travel-related illnesses, such as traveler's diarrhea, malaria, typhoid fever, and Japanese encephalitis virus (JEV) infection.

Medical History

Most travelers are healthy, but many have chronic medical problems. A current list of medications and past illnesses is important. A list of allergies, especially severe allergies to egg products, vaccines, and medications, should be obtained and the following questions asked:

- Is the traveler currently immunosuppressed?
- Does the traveler suffer from gastrointestinal disorders such as inflammatory bowel disease?

Many disorders may increase the risk of illness while traveling and adverse reactions resulting from medications or vaccines or pose contraindications for receiving a given vaccine or medication. Examples include a history of depression, which would contraindicate the use of mefloquine as antimalarial chemoprophylaxis, and immunosuppressed

individuals, who should not receive live vaccines such as yellow fever, oral typhoid Ty21a, or measles, mumps, and rubella.

Immunization Record

Past immunizations must be recorded. Travelers are encouraged to bring their vaccine records to the travel clinic visit. Vaccines should not be repeated unnecessarily. In some states and countries, online vaccine registries are available; they provide invaluable information on the vaccine history of the traveler. At the completion of the travel clinic visit, administered vaccines should be entered into the database. While hepatitis A vaccine is frequently recommended for travel to developing countries, in the United States, most children will routinely receive it at 1 year of age. Eleven- to 12-year-olds and adolescents routinely receive the quadrivalent meningococcal conjugate vaccine, which is recommended for travel to countries in the sub-Saharan Africa meningitis belt during the dry season and when planning pilgrimage (hajj) trips to Saudi Arabia. Clinics in the United States usually take advantage of the CDC Vaccine Information Statements (VISs) and provide them to travelers for each vaccine they receive. Vaccine Information Statements can be obtained from the CDC Web site (www.cdc.gov/vaccines/hcp/vis/index.html). Administered vaccines must be recorded in the traveler's clinic visit form, including injection site, dose, log numbers, and expiration dates. It should also be documented that potential vaccine side effects were discussed and VISs provided.

Prescribed Medications

Medications prescribed for antimalarial chemoprophylaxis, self-treatment of traveler's diarrhea, and prevention of altitude illness should be recorded. It should be documented that their potential side effects were discussed. The dosage and number of doses prescribed should also be recorded. Preprinted prescription pads may be useful for some practitioners.

Patient/Parent Acknowledgment

The clinic visit form should include a general acknowledgment or disclosure paragraph stating that potential benefits, side effects, and costs of vaccines and chemoprophylactic medicines were discussed with travelers and their families. The traveler or parent should sign a statement affirming this. The form should state which information was provided, including antimalarial agent adverse reactions, insect bite prevention, safety, sexual activity, altitude illness, animal bites, and jet lag. The educational handout will usually contain much of this information.

Costs and Billing

Because of the potential costs of vaccines and medications, a visit to a travel clinic can be concerning. To avoid unnecessary expenses and potential side effects, the travel medicine specialist should have a good understanding of the traveler's needs. Most private and public insurers will not offer coverage for travel-related clinic visits, vaccines, or medications. To avoid collection delays or lack of compensation, most travel clinics require payment at time of service. Forms and receipts can be provided to travelers so they can bill insurers if they would like.

Billing forms containing appropriate coding information may facilitate payment to the traveler (if available). In the United States, *Current Procedural Terminology*® codes are available for travel-related counseling and vaccines (please refer to the most recent *Current Procedural Terminology* manual published by the American Medical Association).

Vaccines

Travel clinics stock a variety of vaccines. Vaccines against typhoid, rabies, JEV, and yellow fever require special purchasing and are not routinely available in the offices of primary care physicians. Practitioners are required to have prior authorization from state health departments to administer yellow fever vaccine—an official stamp is needed. If a practitioner is expecting a large volume of travelers in the practice, the clinic could purchase and stock necessary vaccines. For most vaccines, storage requirements are similar to those of other vaccines. Like other vaccines, practitioners must be familiar with administration routes and potential side effects. Clinics belonging to local health departments or larger medical centers (who can negotiate better contracts based on volumes) can offer many travel vaccines at a lower cost to the traveler. The primary care physician could administer some recommended vaccines. Good examples are tetanus-diphtheria boosters (including tetanus, diphtheria, and acellular pertussis vaccine), meningococcal vaccines, and hepatitis A vaccine. These are frequently covered by the traveler's primary insurance and would not require out-of-pocket payment (other than a co-payment).

TIMING OF VISIT TO TRAVEL CLINIC

Depending on the type of travel, duration, destination, and prior vaccination experiences, travelers should plan for sufficient time to complete all necessary vaccinations and initiate antimalarial chemoprophylaxis if necessary. Two to 4 weeks is usually sufficient for most pediatric travelers whose routine immunizations are up-to-date. Adults with limited

travel experience may require multiple visits and months to complete a vaccine series, such as parents traveling to adopt a child and who require hepatitis B vaccination (which may require 6 months to complete). Depending on the antimalarial agent selected, initiation may be required up to 2 weeks prior to travel. For some vaccines, accelerated schedules may be available (eg, hepatitis B, hepatitis A and B), but they still require at least 2 to 3 weeks to complete. Vaccines such as rabies and JEV will require up to 4 weeks to complete. Travel medicine practitioners should be familiar with these schedules. Primary care physicians must educate patients and parents to plan ahead and seek travel advice with sufficient time to complete needed vaccinations and other preventive measures.

MEDICAL CARE DURING AND AFTER TRAVEL

A clinician knowledgeable in travel-related illnesses should be available for the returning traveler, if needed. Fevers, skin ailments, and diarrhea are frequent problems. If the individual providing pretravel advice is uncomfortable providing this care, a referral to an infectious disease specialist or an expert in travel medicine (www.istm.org or www.astmh.org) is pertinent. Travelers benefit from having information on how to access health care abroad. US medical insurance plans are not accepted in most lower-income countries; the traveler will be expected to pay for services at the time of the visit. However, the traveler may enroll beforehand in an international medical and evacuation insurance program that provides coverage for the traveler and his or her family while traveling. Many of these may even help coordinate medical care. Individuals with chronic medical problems should have specific information on specialists or hospital centers in areas being traveled. When traveling, travelers should have a list of all medications, by generic name, and doses in case medical care is needed.

Preparation and provision of appropriate pretravel education and needed vaccines and prescriptions are useful tools in the prevention of travel-related illnesses. Where travel clinics are unavailable, a well-prepared and knowledgeable primary care practitioner can be just as efficient as a travel medicine practitioner. The pediatric traveler requires special attention and consideration. The traveler must enjoy the activities surrounding a visit to relatives and friends, humanitarian work, or studying abroad. Staying healthy will help ensure this. Most travel-related illnesses are preventable.

KEY POINTS

- Travel clinics provide necessary medical preventive advice, required and recommended vaccinations, and antimalarial chemoprophylaxis for at-risk travelers.
- Destinations, travel duration, planned activities, and medical and immunization history help determine the degree of risk travelers will experience during a trip.
- A comprehensive educational handout is an integral part of travel clinic visits.
- Most public and private insurers do not pay for pretravel consultations and vaccinations.

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CHAPTER

11

Pretravel Care

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INTRODUCTION

International travel continues to increase. According to the UN World Tourism Organization, there were 1,035 million international arrivals (overnight visitors) in 2012, which is an increase of 40 million (>4%) from 2011.[1] The purposes for international travel can include pleasure, visiting friends and relatives, or business. Children often accompany adults during travel. Traveling with family can be an educational and entertaining experience for children. Unfortunately, information about the incidence of pediatric illnesses associated with international travel is limited because the numbers of children traveling are fewer than adults. Health issues related to pediatric international travel are complex because of variable immunity, different age-related behaviors reflecting varied activities, exposure, and age-specific health risks. The most common reported health problems related to travel include diarrheal illnesses, malaria, and motor vehicle–related and water-related injuries. Children traveling to developing countries are at higher risk for a variety of travel-related infectious health problems, including malaria, intestinal parasite infestations, and tuberculosis. Risk of acquiring illness during travel depends on the geographic area visited and individual factors such as age, baseline health conditions, length of stay, and activities planned.

The consulting pediatric health professional has a key role in preparing the family for prevention of travel-related illnesses and helping reduce health risks so the entire family can enjoy its travel.

PLANNING FOR HEALTHY TRAVEL

Precaution and Prevention

Prior to travel, practitioners should provide the following key advice to traveling families:

- *Child identification documentation.* The child should carry identification and travel destination(s). Long travel times, layovers, and nonfamiliarity with new areas and locations can result in the separation of children and parents.
- *Travel insurance coverage.* Families should purchase health insurance coverage for travel because accidents are the leading cause of mortality in young travelers.[2] If a family's regular health plan does not have coverage for international travel, it should purchase travel and evacuation insurance, as the cost of an evacuation could range from $25,000 to $100,000 per person.
- *Documentation for child traveling with one parent.* Because of increasing incidents of child abduction in disputed custody cases, a letter of authorization giving permission for the travel from the nonaccompanying parent should be obtained. It is advisable to have the letter notarized so its validity will not be questioned. In addition, a notarized copy of the custodial document or death certificate is required if the accompanying parent is divorced or widowed.

MINIMIZING TRAVEL ANXIETY

Stress management techniques should be discussed with families to minimize children's anxiety about traveling to new areas.

- *Planning process.* Parents should include the child in the planning process of the anticipated trip by creating excitement with videos, books, pictures, food, and the Internet. Children can help plan for sites and people they will visit and foods they would like to eat. These activities give children a sense of control and ownership of the travel process.
- *Items of security/familiarity.* Allowing the child to carry a special toy, blanket, or picture helps establish a sense of security and familiarity during travel.
- *Disruption of normal routines.* Children should be made aware that they might encounter situations that could disrupt their normal routines, such as long delays, irregularly scheduled meals, and unusual schedules and nap times.

PRETRAVEL INTERVENTION

Chemoprophylaxis

Malaria

Malaria is endemic throughout the tropical areas of the world. It is caused by 1 of 5 *Plasmodium* species, which are intraerythrocytic protozoa: *P falciparum, P vivax, P ovale, P malariae,* or *P knowlesi. P knowlesi* is a parasite of Old World monkeys but is increasingly reported to cause human disease in Southeast Asia. Malaria is usually acquired from the bite of a nocturnal-feeding female *Anopheles* mosquito. Symptoms of malaria include high-grade fever with chills, rigors, and headache and can be paroxysmal. Anemia and thrombocytopenia are commonly seen. Jaundice can occur because of hemolysis. Infection with *P falciparum* is potentially fatal and can manifest as cerebral edema with varying neurologic manifestations, including seizures, mental confusion, coma, and death.

According to the 2013 World Health Organization malaria report,[3] an estimated 207 million malaria cases occurred among 3.4 billion at-risk people in 2012 with an estimated 627,000 deaths. The majority of deaths occurred in Africa (90%) and in children younger than 5 years (77%).

In the United States and other higher-income countries, the majority of malaria infections occur among persons who traveled to areas with ongoing malaria transmission. Children account for a considerable proportion of total malaria cases imported into non-endemic countries.[4] From 1992 through 2002, more than 17,000 cases of imported malaria in children 18 years and younger were reported in 11 non-endemic countries, including the United States, United Kingdom, and France; most cases (more than 70%) were acquired in Africa.[4] The largest overall percentage of cases occurred among children 15 to 17 years of age.[4] Visiting friends and relatives in the country of origin was a risk factor for acquiring malaria.

All travelers should be counseled about taking appropriate antimalarial chemoprophylaxis, as well as various preventive measures to avoid mosquito bites. It is important to emphasize that no antimalarial agent is 100% effective in protecting against the risk of contracting malaria. The appropriate antimalarial agent must be combined with personal protective measures, such as insect repellent, long sleeves, and pants. An insecticide-treated bed net is essential to protect against mosquito bites when accommodations are not adequately screened or air-conditioned.

A recommendation for appropriate antimalarial chemoprophylaxis is determined by the risk of acquiring malaria and the prevalence of

antimalarial drug resistance in the destination. The possibility of drug interaction and drug allergies should also be considered.

Resistance to antimalarial agents has developed in many areas of the world. Currently, *P falciparum* resistance to chloroquine was confirmed in all areas with *P falciparum* malaria except in the Caribbean, Central America west of the Panama Canal, and some countries in the Middle East.[5] Resistance to mefloquine was reported on the borders of Thailand along Burma (Myanmar) and Cambodia, in the western provinces of Cambodia, in the eastern states of Burma on the border between Burma and China, in Laos along the borders of Laos and Burma, and the adjacent parts of the Thailand-Cambodia border, as well as in southern Vietnam.[5] For up-to-date information on antimalarial-resistant patterns, health care professionals should consult the Centers for Disease Control and Prevention Travelers' Health Web site at www.cdc.gov/travel.

Indications for prophylaxis in children are the same as those in adults except for doxycycline, which should not be given to children younger than 8 years because of the risk of dental staining. In addition, the use of atovaquone and proguanil (Malarone) is not established in children weighing less than 5 kg. Drug dosages in children should be calculated based on their current weight and should not exceed adult dosages. Drug doses for malaria chemoprophylaxis are provided in Table 11-1. In the United States, mefloquine and chloroquine phosphate are available only in adult tablet forms, while atovaquone and proguanil is available in pediatric tablet form. These drugs have bitter tastes. Pharmacists can pulverize the tablets and prepare gelatin capsules according to calculated pediatric doses. Gelatin capsules can then be opened and mixed in a small amount of food or drink to administer to children.

Because antimalarial chemoprophylaxis is not completely effective and some may elect not to take prophylaxis, travelers should be aware of the signs and symptoms of malaria (eg, fever, chills, flu-like symptoms) and seek medical attention immediately if these signs and symptoms develop. If prompt medical attention is not available, self-treatment with atovaquone and proguanil (Malarone), if not already taking for prophylaxis, should be initiated immediately because malaria can be fatal if treatment is delayed. For patients already taking atovaquone and proguanil (Malarone) for prophylaxis, the use of the same drug at therapeutic doses is not recommended; artemether-lumefantrine (Coartem) can be an option for presumptive self-treatment for malaria. Despite self-treatment for possible malaria, travelers still need to seek urgent medical attention—this is only a temporary measure. Doses of atovaquone and proguanil (Malarone) and artemether-lumefantrine (Coartem) for self-treatment are provided in Table 11-2.

Table 11-1. Drugs Used in the Prophylaxis of Malaria				
DRUG	**USAGE**	**ADULT DOSE**	**PEDIATRIC DOSE**	**COMMENTS**
Atovaquone and proguanil (Malarone)	Prophylaxis in all areas	Adult tablets contain 250-mg atovaquone and 100-mg proguanil hydrochloride. One adult tablet orally, daily.	Pediatric tablets contain 62.5-mg atovaquone and 25-mg proguanil hydrochloride. 5–8 kg: ½ pediatric tablet daily >8–10 kg: ¾ pediatric tablet daily >10–20 kg: 1 pediatric tablet daily >20–30 kg: 2 pediatric tablets daily >30–40 kg: 3 pediatric tablets daily >40 kg: 1 adult tablet daily	Begin 1 to 2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in persons with severe renal impairment (creatinine clearance <30 mL/min). Atovaquone and proguanil should be taken with food or a milky drink. Not recommended for prophylaxis for children weighing <5 kg, pregnant women, and women breastfeeding infants weighing <5 kg. Partial tablet dosages may need to be prepared by a pharmacist and dispensed in individual capsules.
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive malaria	300 mg base (500 mg salt) orally, once per week	5 mg/kg base (8.3 mg/kg salt) orally, once per week, up to maximum adult dose of 300 mg base	Begin 1 to 2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. May exacerbate psoriasis.
Doxycycline (Many brand names and generic)	Prophylaxis in all areas	100 mg orally, daily	8 years and older: 2.2 mg/kg up to adult dose of 100 mg/day	Begin 1 to 2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in children younger than 8 years and pregnant women.

Table 11-1. Drugs Used in the Prophylaxis of Malaria, continued

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for prophylaxis only in areas with chloroquine-sensitive *Plasmodium falciparum*	310 mg base (400 mg salt) orally, once per week	5 mg/kg base (6.5 mg/kg salt) orally, once per week, up to maximum adult dose of 310 mg base	Begin 1 to 2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas.
Mefloquine (Lariam and generic)	Prophylaxis in areas with chloroquine-sensitive malaria	228 mg base (250 mg salt) orally, once per week	≤9 kg: 4.6 mg/kg base (5 mg/kg salt) orally, once per week 10–19 kg: ¼ tablet once per week 20–30 kg: ½ tablet once per week 31–45 kg: ¾ tablet once per week >46 kg: 1 tablet once per week	Begin at least 2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 weeks after leaving such areas. Contraindicated in persons allergic to mefloquine or related compounds (eg, quinine, quinidine) and with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a previous history of depression. Not recommended for persons with cardiac conduction abnormalities.

Table 11-1. Drugs Used in the Prophylaxis of Malaria, continued				
DRUG	**USAGE**	**ADULT DOSE**	**PEDIATRIC DOSE**	**COMMENTS**
Primaquine[a]	Prophylaxis for short-duration travel to areas with principally *P vivax*	30 mg base (52.6 mg salt) orally, daily	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, daily	Begin 1 to 2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level.
	Used for presumptive anti-relapse therapy (terminal prophylaxis) to decrease the risk of relapses of *P vivax* and *P ovale*	30 mg base (52.6 mg salt) orally, once per day for 14 days after departure from the malarious area	0.5 mg/kg base (0.8 mg/kg salt) up to adult dose orally, once per day for 14 days after departure from the malarious area	Indicated for persons who have had prolonged exposure to *P vivax, P ovale,* or both. Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level.

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

[a] All persons who take primaquine should have a documented normal G6PD level prior to starting the medication.

Adapted from Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2014*. Atlanta, GA: US Department of Health and Human Services, Public Health Service; 2014. http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria#3936. Accessed June 1, 2015

Table 11-2. Presumptive Self-treatment[a] of Malaria

DRUG	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Atovaquone and proguanil[a] (Malarone) The adult tablet contains 250 mg atovaquone and 100 mg proguanil. The pediatric tablet contains 62.5-mg atovaquone and 25-mg proguanil.	4 tablets orally as a single daily dose for 3 consecutive days	Daily dose to be taken for 3 consecutive days 5–8 kg: 2 pediatric tablets 9–10 kg: 3 pediatric tablets 11–20 kg: 1 adult tablet 21–30 kg: 2 adult tablets 31–40 kg: 3 adult tablets >41 kg: 4 adult tablets	Contraindicated in persons with severe renal impairment (creatinine clearance <30 mL/min). Not recommended for self-treatment in persons on atovaquone and proguanil prophylaxis. Not currently recommended for children weighing <5 kg, pregnant women, and women breastfeeding infants weighing <5 kg.
Artemether-lumefantrine (Coartem) One tablet contains 20-mg artemether and 120-mg lumefantrine.	1 tablet = 20-mg artemether and 120-mg lumefantrine	A 3-day treatment schedule with a total of 6 oral doses is recommended for adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose orally twice a day for the following 2 days.	5–<15 kg: 1 tablet per dose 15–<25 kg: 2 tablets per dose 25–<35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose

[a] Self-treatment drug to be used if professional medical care is not available within 24 hours. Medical care should be sought immediately after treatment.

Adapted from Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2014*. Atlanta, GA: US Department of Health and Human Services, Public Health Service; 2014. http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria#3936. Accessed June 1, 2015.

Traveler's Diarrhea

Traveler's diarrhea (TD) is common among infants and children, and signs and symptoms tend to be more prolonged and more severe.[6] Leading etiologies[7] of TD in children are the same as adults, including bacterial causes: *Escherichia coli* (enterotoxigenic, enteroaggregative), *Campylobacter, Salmonella,* and *Shigella*. Other causes of TD include viruses (ie, rotavirus, norovirus) and protozoa (eg, *Giardia, Cryptosporidium*, *Cyclospora*).

To prevent TD, families should be counseled not to consume unsafe foods; the "cook it, boil it, peel it, or forget it" rule should be followed; families should practice water and food safety measures; and anticipatory guidance on diarrhea treatment should be given. Use of an oral rehydration solution to prevent dehydration should diarrhea develop should be emphasized. While prophylaxis with nonantibiotic agents, such as bismuth subsalicylate (BSS), as well as antibiotics is used in adults to prevent TD, it is not recommended in children because of the lack of data on its efficacy. Furthermore, the BSS dose for prevention of TD in children is currently unknown. Frequent and prolonged use of BSS can potentially cause salicylate intoxication from salicylate absorption[8] as well as increase the risk of developing Reye syndrome in patients with influenza or chickenpox.

Antimicrobial prophylaxis for TD can lead to the development of resistant enteric pathogens, allergic reactions, and antibiotic-associated enterocolitis. Antimicrobial prophylaxis for TD is not recommended in children because the potential risks outweigh the benefits. Similarly, antibiotic prophylaxis is generally not recommended in adults.[9] However, fluoroquinolones are usually the antibiotics of choice when considering chemoprophylaxis for TD.[9] Recently, fluoroquinolone use has been associated with predisposition to infection with hypervirulent strains of *Clostridium difficile* associated with increased morbidity and mortality.[10] Fluoroquinolone use in children is limited because of the concern of cartilage damage in weight-bearing joints among beagle pups seen in animal toxicology studies.[11] Reported fluoroquinolone-associated musculoskeletal events in children were none[12] or transient and reversible.[13]

Presently, quinolones that are approved by the US Food and Drug Administration for use in children are nalidixic acid for urinary tract infections, ciprofloxacin for inhalational anthrax and complicated urinary tract infections, and pyelonephritis and levofloxacin for inhalational anthrax.[14] Although some probiotics appear to prevent TD in adults,[15] data showing effectiveness in children are still limited.

AIR TRAVEL

Air travel has become a convenient and accessible form of transportation; more families, including children, travel by air. Illness associated with air travel is usually related to changes in air pressure and oxygen concentration, immobility during flights, or transmission of communicable diseases caused by close proximity to other passenger with infectious diseases.

Age

For healthy children, including newborns and infants, air travel is generally safe.[16] However, it is advisable to delay travel 1 to 2 weeks after birth to ensure that the newborn is indeed healthy and free of congenital defects or cardiovascular and pulmonary disease. Most commercial airlines reach cruising altitudes of 11,000 to 13,000 m (36,000 to 40,000 feet), and this would lead to hypoxia if uncompensated. The aircraft cabin is therefore pressurized to atmospheric pressure of 1,500 to 2,400 m (5,000 to 8,000 feet). At this altitude, the barometric pressure in the aircraft cabin is around 560 mm Hg, which is equivalent to 15% oxygen and is lower compared with the normal value of 760 mm Hg and oxygen pressure of 21% at sea level.

While healthy children may be asymptomatic from lower oxygen concentrations, children with preexisting medical conditions, such as cardiopulmonary diseases, anemia, and sickle cell, as well as upper or lower respiratory symptoms at the time of travel, may be at risk for hypoxia and increased risk of exacerbation of their disease during the flight. Consultation with a physician should be done before the scheduled flight so arrangements can be made with the airline to provide oxygen and monitoring equipment if needed.

Otolaryngological Conditions

Barotitis Media

To equalize cabin air pressure, air in the middle ear and sinuses expands during ascent and contracts during descent. Middle ear barotrauma is characterized by otalgia and is secondary to the inability to equilibrate tympanic cavity and atmospheric pressures because of eustachian tube obstruction.[17] Barotitis media is an acute or chronic inflammation of the middle ear caused by barotrauma[17] and characterized by an acute onset of ear pain, hearing loss, or vertigo. The prevalence of barotitis in young children is 25% compared with 5% in adults[18]; ear pain is reported in 55% of children and 20% of adults during descent.[18] Equalization of pressure in the middle ear can be facilitated by swallowing motions,

such as breastfeeding or bottle-feeding babies. Older children can chew gum, blow up a balloon, or close their nose with their thumb and index finger and exhale gently with the mouth closed (Valsalva maneuver).[19]

Otitis Media

Otitis media is not thought to preclude flight if appropriate antibiotics are administered for at least 48 hours and the eustachian tube is patent. While limited to expert opinion, it has been recommended that children wait 2 weeks after treatment for acute otitis media before flying.[15] Recent surgical procedures involving structures of the inner or middle ear may be affected by pressure changes and are a contraindication to flight. Children who underwent recent procedures, such as tympanomastoidectomy, stapedectomy, labyrinthectomy or acoustic neurectomy, mastoidectomy, or other otologic surgeries, should not fly until cleared by their otolaryngologist.[16] Myringotomy or ear tube placement is not a contraindication to flying because they actually protect against middle ear barotraumas by minimizing pressure changes.[16] Children with chronic otitis media rarely suffer from barotraumas; it is not a contraindication to air travel.[20]

Thromboembolic Disease

Healthy children are not known to be at risk for developing deep vein thrombosis during a prolonged flight.[17] However, children with hypercoagulable states, as well as those with a history of thromboembolic events, major surgery within 6 weeks, or a malignancy, may be at increased risk of developing deep venous thrombosis as a result of immobility. They should consult their own physicians, who may advise prophylaxis with low molecular weight heparin or acetylsalicylic acid.

In-flight Transmission of Communicable Diseases

The enclosed environment of the aircraft cabin, including limited ventilation, recirculated air, and close proximity to fellow passengers, has the potential for disease transmission.[21] Within this confined environment, the risk of disease transmission is not well known. The most studied in-flight transmission of an airborne pathogen is *Mycobacterium tuberculosis* (TB).

The risk of TB transmission aboard commercial aircraft remains low. Several studies of potential transmission of TB infection during air travel were reported in the mid-1990s. Subsequently, contact investigations revealed a probable link of transmission of infection in 2 investigations by conversion to a positive tuberculin skin test, but active TB disease was

not found in any of the infected individuals. Limited data suggest the risk of disease transmission to other passengers is associated with sitting within 2 rows of a contagious passenger for more than 8 hours.[22] Other airborne diseases, including measles, meningococcal disease, severe acute respiratory syndrome, and influenza, are rarely implicated in aircraft transmission. Transmission of norovirus gastroenteritis on airplanes has also been reported rarely. Mode of transmission of norovirus gastroenteritis is generally by person-to-person spread via the fecal-oral route or through contaminated food or water. However, on an aircraft with high incidence of vomiting among infected individuals, airborne transmission may occur with subsequent ingestion of viral particles.[23]

Despite these cases, the chance of contracting a respiratory infection during air travel is quite small; the quality of aircraft cabin air is well controlled.[24] Most commercial aircraft recirculate 50% of the air in the cabin in an effort to conserve fuel. The recirculated air in the cabin passes through a series of high-efficiency particulate air (HEPA) filters; the same type of HEPA filters are also used in hospitals and can remove 99.97% of dusts, bacteria viruses, and fungi at a size of 0.3 μm. In addition, air exchanges in the aircraft cabin range from 20 to 30 times per hour compared with 12 air exchanges per hour in most office buildings. To minimize the risk of transmission of communicable diseases, passengers who are unwell should postpone travel until they are recovered. Furthermore, passengers who appear to have a communicable disease may be denied boarding by the airline.

Use of Restraining Devices

According to the US Federal Aviation Administration (FAA), the safest place for a child on an airplane during turbulence or an emergency is in an approved child restraint system (CRS) or a child safety device—not on a parent's lap.[25] The FAA strongly encourages the use of a CRS or an FAA-approved child safety device. However, the FAA does not mandate CRS use, as it requires families to purchase an extra airline ticket. Some families may even decide to drive, which is statistically more dangerous than flying.[26]

A CRS is a hard-backed safety seat approved by the government for use in aircraft and motor vehicles. Each CRS contains the wording, "This restraint is certified for use in motor vehicles and aircraft." The FAA recommends that children weighing less than 20 pounds use a rear-facing CRS. Children weighing 20 to 40 pounds should use a forward-facing CRS. Children between 22 to 44 pounds have the option of using the FAA-approved Child Aviation Restraint System (CARES), which is a harness-type restraint. The FAA approved this child safety

device for use on aircraft only; it contains the wording, "FAA Approved in Accordance with 14CFR 21.305(d), Approved for Aircraft Use Only."[25] Children weighing more than 40 pounds can be secured with an airplane seat belt.[25]

While other vehicular restraint systems (eg, booster seats, harness vests) enhance safety in vehicles, the FAA prohibits their use on airplanes during takeoff, taxiing, and landing. These restraints should not be brought into the cabin but rather checked as baggage. In addition, "belly belts" or supplemental lap restraints are not approved for use in airplanes or vehicles in the United States.

Jet Lag

Jet lag is a group of symptoms associated with rapid, long-haul flights across different time zones. It is characterized by sleeping disturbances, daytime fatigue, irritability, and generalized malaise.[27] It is still not known to what extent children experience jet lag. Travel to different time zones, jet lag, and schedule disruptions can disturb sleep patterns in infants, children, and adults. Parents should help children adapt to new time zones as quickly as possible by encouraging them to stay active and exposing them to natural light during the day. Melatonin has been used to reduce the symptoms of jet lag and improve sleep after travel to multiple time zones.[27] However, it is not recommended because of insufficient evidence to conclude its effectiveness in children with jet lag. Diphenhydramine can be useful for some children but may cause oversedation or paradoxical agitation; a test dose should be administered before travel to determine the effect on the individual child.

Motion Sickness

Motion sickness is the discomfort experienced when perceived motion disturbs the organs of balance. Nausea, vertigo, pallor, and cold sweats are common manifestations of motion sickness in children.[28] Ataxia and nausea are the most frequent symptoms in children younger than 5 years and in children older than 12 years, respectively. The most common medications used to control motion sickness in children are dimenhydrinate and diphenhydramine. For symptomatic treatment, dimenhydrinate, 1 to 1.5 mg/kg per dose, or diphenhydramine, 0.5 to 1 mg/kg per dose up to 25 mg, can be given 1 hour before travel and every 6 hours thereafter during the trip. A test dose should be given before departure because some children can have paradoxical reaction to these drugs. Parents should also be advised of sedative side effects.

Safety data on other antiemetic compounds in children are limited. Anti-dopaminergic agents, such as metoclopramide and

prochlorperazine, are not recommended because of their ineffectiveness to control motion sickness and their association with extrapyramidal symptoms in children.[29] Scopolamine is also not recommended due to its known side effects and lack of clinical use in children.[30] Alternatives to medical treatment include directing fresh, cool, ventilated air on the face; avoiding seats toward the rear of the aircraft; focusing on the horizon or a stable object; not reading books or playing video games; limiting head movement; and reclining whenever possible.[28]

OTHER TRAVEL-RELATED HEALTH RECOMMENDATIONS

Food-borne and Waterborne Illness

Using common sense when handling and preparing food is the best way to reduce the risk of food-borne and waterborne illnesses in infants and children. Parents should use purified bottled water for drinking, brushing teeth, preparing food, and mixing infant food. It should be stressed that washing hands with soap and water is the best way to reduce the number of germs prior to touching, preparing, or eating food. If soap and water are not available, an alcohol-based hand sanitizer containing at least 60% alcohol should be used. The family should carry finger foods or snacks when traveling due to the irregularity of mealtimes. Food sold by street vendors should be strictly avoided.

Motor Vehicle Crashes and Drowning

Vehicle-related accidents are the leading cause of death among travelers.[2] The American Academy of Pediatrics provides recommendation in choice of CRS to ensure optimal safety for children of all ages and adolescents during all forms of travel: rear-facing car safety seats for most infants up to 2 years of age; forward-facing car safety seats for most children through 4 years of age; belt-positioning booster seats for most children through 8 years of age; lap-and-shoulder seat belts for all who have outgrown booster seats. In addition, all children younger than 13 years should ride in the rear seats of vehicles.[31] Car seats should be brought from home, as well-maintained and approved seats may not be available at the travel destination.

Drowning is the second-leading cause of death among travelers.[2] Children must be well supervised around water. In addition, parents should closely monitor tides, currents, and warnings.

Sun Exposure

Approximately 23% of a person's lifetime sun exposure reportedly occurs before 18 years of age.[32] Strong evidence exists of a relationship between

cumulative sun exposure and skin cancer. Therefore, infants and children should be kept away from direct sunlight. If in sunlight, appropriate protective clothing, such as hats and long-sleeved, loose-fitting shirts, should be worn to decrease sun exposure. Waterproof sunscreen with a sun protection factor of 15 or higher should be used.[33]

Protection Against Insects and Other Arthropods

Several infections (eg, malaria, yellow fever, dengue) can be transmitted via insect bites; it is important that travelers avoid these insects. Children should wear light-colored, protective clothing (eg, long-sleeved shirts, long trousers, socks).

Insect repellents can help reduce exposure to mosquito bites that may carry viruses. Repellents should be used according to manufacturers' instructions. Products containing the following ingredients provide long-lasting protection: diethyltoluamide (DEET), picaridin (KBR 3023), IR3535 (3-[*N*-butyl-*N*-acetyl]-amino-propionic acid, ethyl ester), or plant-based oil of lemon eucalyptus (p-menthane-3,8-diol).

DEET is safe and effective. A concentration of 30% or less is considered safe and can be used on children 2 months and older.[34] Products with a concentration of 20% provide protection lasting for up to 5 hours.[34] Specifically, a product containing 23.8% DEET provided an average of 5 hours of protection from mosquito bites; 20% DEET provided almost 4 hours of protection; 6.65% DEET provided almost 2 hours of protection; and 4.75% DEET provided approximately 1 hour and 30 minutes of protection. DEET should only be applied to exposed skin. Avoid areas around the eyes and mouth and over cuts, wounds, or irritated skin.

In the United States, picaridin is available in 7%, 15%, and 20% formulations. It has been shown to be as effective as lower concentrations of DEET and provide longer protection with higher concentrations. For long-lasting protection, frequent reapplication is needed.[34]

IR3535 is available in 7.5% to 20% formulations. Estimated protection times range from 2 to 8 hours with the higher concentrations. Oil of lemon eucalyptus (OLE) has similar duration of action as products with lower concentrations of DEET (protection from 30% OLE equivalent to 15% DEET).[34]

Permethrin is a synthetic pyrethroid that is highly effective as an insecticide and repellent.[34] It can be used on clothing, shoes, camping gear, and bed nets. Refer to the product's label for instructions on reapplying the insecticide repellent. Permethrin should not be sprayed onto skin.

Altitude Illness

Like adults, infants and children can suffer from altitude illness, including acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE).[35] Young children may present with nonspecific symptoms of fussiness and alterations in appetite, activity, or sleep patterns during or following recent exposure to altitude.[35] Acute mountain sickness is usually a benign disorder but may progress to HACE or HAPE if not promptly treated. Treatment for AMS depends on the severity of symptoms.[36] For mild AMS, treatment includes halting ascent, hydrating, resting, and taking analgesics.[36] For more severe symptoms, treatment includes descent, steroids (dexamethasone 0.15 mg/kg/dose orally up to 4 mg every 6 hours), acetazolamide (2.5 mg/kg/dose orally every 12 hours, maximum of 250 mg per dose) and oxygen. For prevention of AMS, a slow-graded ascent is recommended to achieve acclimatization.[36] *Acclimatization* refers to physiological changes that allow the body to function at relative hypoxia. When a slow-graded ascent is not possible, the use of acetazolamide to aid in acclimatization may be needed.[36] Acetazolamide extended-release capsules have been used for prophylaxis or amelioration of symptoms of AMS in patients 12 years and older: 500 to 1,000 mg orally extended-release capsule once a day; during rapid ascent, 1,000 mg per day is recommended; initiate 24 to 48 hours before ascent and continue for 48 hours or longer while at high altitude. Acetazolamide is contraindicated in children with a known sulfa allergy.[37]

Parasitic Infestations

Children are more likely than adults to become exposed to various parasites (eg, *Ascaris, Trichuris,* hookworm, *Strongyloides,* cutaneous larva migrans) because they are more likely to come in contact with soil or sand. Children should wear protective footwear and parents should lay down a sheet or towel before placing the child on the ground. In addition, parents should not dry clothes or diapers on the ground. Cutaneous infestations with fly larvae (myiasis) can be prevented by ironing clothes that are dried in open air.

COUNSELING FOR CHILDREN WITH CHRONIC MEDICAL CONDITIONS

Children with preexisting medical conditions pose a different set of challenges. It is important for the parents of such children to consult with a travel medicine specialist prior to traveling. It is essential for parents to carry an adequate supply of medications (eg, seasonal allergy medication) in their carry-on luggage. All medications should be transported

in their original containers. An adequate supply of syringes and needles should be provided, along with a letter justifying their need, for children with insulin-dependent diabetes. An oral or topical steroid burst can be carried for eczema or asthma, while a preloaded epinephrine syringe (EpiPen) should be carried for children with a history of allergic and anaphylactic reactions (eg, bee stings, shellfish or peanut allergies). Pediatric-dose EpiPens are available for children weighing less than 30 kg. Children with more complicated conditions, such as cystic fibrosis, HIV/AIDS, congenital heart disease, and renal disease, should be managed in consultation with their respective specialists.

Parents should be advised to carry a medical kit containing prescription medications and other items (Box 11-1). Parents should also be instructed to seek medical attention at early signs and symptoms of disease. Such symptoms might include high fever, lethargy, unexplained fussiness, crying without tears, dry mouth, high respiratory rate, labored breathing, or a toxic appearance (the child "looks sick").

KEY POINTS

The travel experience is important for families. Health care professionals can help minimize stress related to travel by counseling families and providing medical and commonsense advice. Practitioners can also refer to several electronic resources related to travel listed in Table 11-3 for more information.

Box 11-1. Suggested Items to Carry in a Medical Kit

- Adequate supply of prescription medications in original containers
- Analgesics/antipyretics (eg, ibuprofen, acetaminophen)
- Antihistamine/antipruritic (eg, diphenhydramine)
- Epinephrine auto-injector (especially if there is history of severe allergic reaction)
- Bandages and wound dressings
- DEET-based repellent and permethrin (when appropriate)
- Diaper rash ointment (eg, A+D, zinc oxide, Aquaphor)
- Disinfectant solutions (eg, 10% povidone-iodine, chlorhexidine)
- Oral rehydration solutions or packets
- Sunscreen of greater than 15 SPF and active against UV-A and UV-B
- Thermometer
- Tweezers
- Scissors
- Antibacterial ointment
- Antimalarial drugs (if applicable)

Abbreviations: DEET, diethyltoluamide; SPF, sun protection factor.

Table 11-3. Selected Travel Medicine–Related Web Sites for Practitioners

AUTHORITATIVE TRAVEL MEDICINE RECOMMENDATIONS	
CDC Travelers' Health Includes current travel health notices, disease- and destination-specific health recommendations, and guidance on a variety of topics in travel medicine	www.cdc.gov/travel
CDC Travelers' Health Yellow Book Homepage Includes a searchable version of *CDC Health Information for International Travel 2016* (the Yellow Book) and a list of any updates occurring between print editions	www.cdc.gov/yellowbook
US Department of State Bureau of Consular Affairs	www.travel.state.gov
US Department of State Bureau of Consular Affairs Learn About Your Destination Country-specific information, travel warnings, and travel alerts	http://travel.state.gov/travel/cis_pa_tw/cis/cis_4965.html
WHO international travel and health Includes the current edition of the *International Travel and Health* (Green Book) publication, disease updates for travelers, International Health Regulations documents, and other disease-specific information	www.who.int/ith/en
"The Practice of Travel Medicine: Guidelines by the Infectious Diseases Society of America"	http://cid.oxfordjournals.org/content/43/12/1499.full
US Department of Transportation Aircraft Disinsection Requirements	http://ostpxweb.dot.gov/policy/safetyenergyenv/disinsection.htm
EMERGING DISEASES AND OUTBREAKS	
WHO Global Alert and Response (GAR) Includes current disease outbreak news and outbreaks sorted by country, disease, and year	www.who.int/csr/en
CDC Health Alert Network (HAN) Archive	http://emergency.cdc.gov/HAN/dir.asp
GeoSentinel: The Global Surveillance Network of the International Society of Travel Medicine and CDC	www.geosentinel.org

Table 11-3. Selected Travel Medicine–Related Web Sites for Practitioners, continued	
EMERGING DISEASES AND OUTBREAKS, CONTINUED	
ProMED-mail Includes moderated reporting of global infectious diseases and acute exposure to toxins	www.promedmail.org
HealthMap: Global Disease Alert Map	www.healthmap.org/en
The Henry J. Kaiser Family Foundation Global Health Facts Portal for information on the US role in global health	http://kff.org/globaldata
SURVEILLANCE AND EPIDEMIOLOGIC BULLETINS	
CDC *Morbidity and Mortality Weekly Report (MMWR)*	www.cdc.gov/mmwr
WHO *Weekly Epidemiological Record (WER)*	www.who.int/wer
PAHO National Epidemiological Surveillance Information List of links to national bulletins in the Americas	www.paho.org/English/DD/AIS/vigilancia-en.htm
PAHO Ministries of Health in the Americas	www.paho.org/English/PAHO/MOHs.htm
WHO International travel and health links to national travel and health websites	www.who.int/ith/links/national_links/en/index.html
World Organisation for Animal Health	www.oie.int
Eurosurveillance	www.eurosurveillance.org
ECDC News	www.ecdc.europa.eu/en/press/news/Pages/News.aspx
Caribbean Public Health Agency	http://carpha.org
ReliefWeb Administered by the UN Office for the Coordination of Humanitarian Affairs, includes information on humanitarian emergencies and natural disasters from a variety of UN agencies and other sources	http://reliefweb.int
WHO Humanitarian Health Action Crises Health-related situational updates	www.who.int/hac/crises/en
EpiNorth Network: A Co-operation Project for Communicable Disease Control in Northern Europe	www.epinorth.org

Table 11-3. Selected Travel Medicine–Related Web Sites for Practitioners, continued	
SURVEILLANCE AND EPIDEMIOLOGIC BULLETINS, CONTINUED	
EpiSouth Network for the Control of Public Health Threats in the Mediterranean Region and South East Europe	www.episouthnetwork.org
VACCINE RESOURCES	
CDC ACIP Vaccine Recommendations Recommendations on individual vaccines	www.cdc.gov/vaccines/hcp/acip-recs/index.html
CDC Vaccine Information Statements (VIS) Fact sheets to download	www.cdc.gov/vaccines/hcp/vis/index.html
CDC Current Vaccine Shortages & Delays	www.cdc.gov/vaccines/vac-gen/shortages/default.htm
American Academy of Pediatrics *Red Book Online* Vaccine Status Table Tables on status of licensure and recommendations for new vaccines	http://redbook.solutions.aap.org/vaccine-status.aspx?gbosid=167073
CDC *Epidemiology and Prevention of Vaccine-Preventable Diseases* (Pink Book) Includes an online version of the current edition, updates to the print edition, slide sets, and selected chapters from earlier editions	www.cdc.gov/vaccines/pubs/pinkbook/index.html
Immunization Action Coalition Directory of Immunization Resources	www.immunize.org/resources
Immunization Action Coalition Quick Chart of Vaccine-Preventable Disease Terms in Multiple Languages	www.immunize.org/izpractices/p5122.pdf
Immunization Action Coalition Vaccine Information You Need	www.vaccineinformation.org
WHO Immunization, Vaccines and Biologicals Includes links to national, regional, and international resources providing immunization information	www.who.int/immunization/en
WHO vaccine-preventable diseases: monitoring system. 2015 global summary Country-specific routine immunization schedules	http://apps.who.int/immunization_monitoring/globalsummary/schedules
PATH Vaccine Resource Library	www.path.org/vaccineresources

Table 11-3. Selected Travel Medicine–Related Web Sites for Practitioners, continued	
CONSUMER-ORIENTED TRAVEL HEALTH INFORMATION AND PRODUCTS	
High Altitude Medicine Guide	www.high-altitude-medicine.com
Travel Health Online	www.tripprep.com
MDtravelhealth.com	www.mdtravelhealth.com
Chinook Medical Gear, Inc.	www.chinookmed.com
Magellan's	www.magellans.com
Travel Medicine, Inc.	www.travmed.com
OVERSEAS MEDICAL AND SAFETY ASSISTANCE	
US Passports and International Travel Your Health Abroad	http://travel.state.gov/content/passports/english/go/health.html
International Association for Medical Assistance to Travelers	www.iamat.org
International SOS Medical and security solutions, products, and assistance	www.internationalsos.com
MEDEX Worldwide travel assistance and international medical insurance	www.medexassist.com
MAPS AND COUNTRY INFORMATION	
US Overseas Security Advisory Council Includes current US Department of State travel alerts, travel warnings, embassy warden messages, and safety and security resources	www.osac.gov
US Central Intelligence Agency: The World Factbook	https://www.cia.gov/library/publications/the-world-factbook
US Department of State Bilateral Relations Fact Sheets	www.state.gov/r/pa/ei/bgn
US Federal Aviation Administration International Aviation Safety Assessment (IASA) Program Data on air safety standards in foreign countries	www.faa.gov/about/initiatives/iasa
European Commission Mobility and Transport Air	http://ec.europa.eu/transport/air/index_en.htm

Table 11-3. Selected Travel Medicine–Related Web Sites for Practitioners, continued	
MAPS AND COUNTRY INFORMATION, CONTINUED	
Global Gazetteer Version 2.3	www.fallingrain.com/world
Association for Safe International Road Travel	http://asirt.org
UN Cartographic Section	www.un.org/Depts/Cartographic/english/htmain.htm
University of Texas at Austin Perry-Castañeda Library Map Collection	www.lib.utexas.edu/maps
One World - Nations Online Destination guide to countries and nations	www.nationsonline.org
GeoNames Geographic database	www.geonames.org
Lonely Planet Travel information	www.lonelyplanet.com
DISABILITY INFORMATION	
MossRehab Einstein Healthcare Network	www.mossrehab.com/disability-resources
US Department of Transportation Aviation Consumer Protection and Enforcement	http://airconsumer.ost.dot.gov/publications/disabled.htm
Society for Accessible Travel & Hospitality	www.sath.org
Mobility International USA	www.miusa.org
PROFESSIONAL MEDICAL SOCIETIES WITH A FOCUS ON TRAVELERS' HEALTH	
International Society of Travel Medicine	www.istm.org
American Society of Tropical Medicine and Hygiene	www.astmh.org
Infectious Diseases Society of America	www.idsociety.org
Pediatric Infectious Diseases Society	www.pids.org
Divers Alert Network	www.diversalertnetwork.org
Wilderness Medical Society	www.wms.org
Undersea & Hyperbaric Medical Society	www.uhms.org
American Travel Health Nurses Association	www.athna.org
Christian Medical & Dental Associations	www.cmdahome.org

Table 11-3. Selected Travel Medicine–Related Web Sites for Practitioners, continued	
DISEASE INFORMATION	
CDC Diseases and Conditions A–Z list	www.cdc.gov/DiseasesConditions
WHO Health topics A–Z list	www.who.int/topics/en
PAHO Health Topics A–Z list	www.paho.org/hq/index.php?option=com_joomlabook&Itemid=260
Malaria Atlas Project	www.map.ox.ac.uk
CDC Malaria Map Application	www.cdc.gov/malaria/map/index.html
CDC Influenza (Flu) Includes information about seasonal influenza, avian influenza, and other	www.cdc.gov/flu
The Imaging of Tropical Diseases	www.isradiology.org/tropical_deseases/tmcr/toc.htm
WHO Rabies Bulletin Europe	www.who-rabies-bulletin.org
WHO Water Sanitation and Health (WSH) Progress on sanitation and drinking-water: 2015 update and MDG assessment	www.who.int/water_sanitation_health/en
WHO Global Schistosomiasis Atlas	www.who.int/schistosomiasis/epidemiology/global_atlas/en/index.html
Global Polio Eradication Initiative	www.polioeradication.org
GENERAL TRAVEL AIDS	
US Department of State Foreign Embassy Information & Publications	www.state.gov/s/cpr/rls
Washington, DC, Embassies	www.embassy.org/embassies/index.html
The World Clock—Worldwide	www.timeanddate.com/worldclock
World Tourism Directory	www.worldtourismdirectory.com
Visa Global ATM Locator	www.visa.com/atmlocator/index.jsp#%28page:home%29
MasterCard ATM Locator	www.mastercard.us/en-us/consumers/get-support/locate-an-atm.html

Table 11-3. Selected Travel Medicine–Related Web Sites for Practitioners, continued	
US ORGANIZATIONS OFFERING TRAINING IN TRAVEL MEDICINE	
International Society of Travel Medicine	www.istm.org
American Society of Tropical Medicine and Hygiene	www.astmh.org
University of Alabama at Birmingham School of Medicine Gorgas Courses in Clinical Tropical Medicine	www.gorgas.org
Tulane University School of Public Health and Tropical Medicine Department of Tropical Medicine	www.sph.tulane.edu/tropmed
University of Washington School of Medicine CE Portal	https://uw.cloud-cme.com/Ap2.aspx
University of Minnesota Medical School Department of Medicine Global Health	www.globalhealth.umn.edu

Abbreviations: ACIP, Advisory Committee on Immunization Practices; ATM, automated teller machine; CDC, Centers for Disease Control and Prevention; CE, continuing education; ECDC, European Centre for Disease Prevention and Control; PAHO, Pan American Health Organization; UN, United Nations; WHO, World Health Organization.

Adapted from Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2014*. Atlanta, GA: US Department of Health and Human Services, Public Health Service; 2014.

Summary of Pretravel Physician Visit

- Assess routine childhood immunization.
- Assess the need for any travel-specific vaccines and malaria chemoprophylaxis.
- Provide anticipatory guidance about monitoring children carefully for signs and symptoms of illness.
- Explain that children with fever, unexplained irritability, or signs of dehydration should be evaluated urgently.
- Ensure families know when and where to seek medical attention.
- Provide the family with a list of resources on traveling with infants and children.

Summary of Physician Advice to Traveling Family

- Carry documentation.
- Involve children in the planning process.
- Bring medications to combat jet lag and motion sickness.
- Secure children in appropriate seating device while traveling.

- Wash hands with soap and water before touching, preparing, or eating food.
- Alcohol-based hand sanitizer (at least 60% alcohol) may be used if soap and water are not available.
- Use bottled water for drinking, brushing teeth, and preparing food.
- Avoid disease-causing insects and animals.
- Avoid sun exposure.

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CHAPTER

12

Adolescent Travelers Without Parents

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INTRODUCTION

Adolescence is a time for significantly remodeling the brain's gray and white matter.[1] Risk taking may ensue as adolescents strive to be more independent. As part of the journey to independence, the opportunity for international travel without parental supervision may arise.

Parents may seek the counsel of the pediatrician to determine if their adolescent is mature enough to travel without them. To assess if an adolescent could travel alone responsibly, parents should consider circumstances from the recent past in which the adolescent displayed decision-making skills. The adolescent's reasonable management of past and present difficulties, especially emergency situations, provides some reassurance that the adolescent is capable of coping with unpredictable events that may arise while traveling abroad.

Once the decision for adolescent travel is made, the pediatrician may be consulted for advice on international travel. The pediatrician must keep in mind that the travel's health implications will vary depending on the destination, reason, and length of stay.

EPIDEMIOLOGY

Youth travel represents 20% of the total global travel market.[2] Along with recreation and study, adolescents travel for several purposes (Box 12-1). *Spring break* is typically a 1-week pleasure vacation for

Box 12-1. Reasons for Adolescent Travel

- Adventure travel
- Club activity
- Cultural exploration
- Ecotourism
- Missionary projects
- Performing arts
- Recreation
- Religious pilgrimages
- Sporting events
- Study
- Visitation of friends and relatives
- Volunteerism
- Work

American high school and college students occurring in the months of February through April. This annual jaunt has become synonymous with binge drinking, substance use, and sexual promiscuity,[3] as millions of vacationers visit popular destinations each year.[4] Whether the travel is brief and solely for recreation or lengthier and for more altruistic purposes, health-related issues (Box 12-2) may arise and vary depending on the details of the travel agenda.

Infectious Diseases

Although there are no studies that address the acquisition of infections in adolescent travelers specifically, there are some studies available that include young adults in the surveyed populations.[5–8] The most common health complaints during travel include upper respiratory and gastrointestinal symptoms. Common viral illnesses such as influenza, rather than exotic local pathogens, are more likely to be the cause of respiratory symptoms emerging during travel. Steffen et al reported that teenagers and young adults are at particular risk of acquiring traveler's diarrhea; the risk-taking behavior of this age group and perhaps the tendency to not comply with safe eating practices may explain the increased risk.[9]

In general, longer travel duration is associated with a higher risk of contracting infection in developing countries.[6] Malaria and dengue are often listed in the top 5 infections encountered from travel to developing or tropical destinations.[5–8] Among others, measles,[10] typhoid, and hepatitis B are infections that can spread in travelers. Risk factors for hepatitis B acquisition are more common among younger travelers on longer trips.[11] Hospitalization, sexual activity, or body piercings or

Box 12-2. Health Issues of Adolescent Travel

- Infectious diseases
- Sexual hazards
- Noninfectious diseases
- Trauma
- Substance use
- Crime

tattoos while traveling are some of the reported risk factors for acquiring hepatitis B.[11,12]

Obtaining a tattoo or body piercing may go hand in hand with risk-taking behaviors like alcohol and marijuana use.[13] Along with the acquisition of hepatitis B, some potential infectious complications of body modification include other blood-borne viral and bacterial infections such as hepatitis C, HIV, skin abscesses, and endocarditis.

Sexual Hazards

Adolescents are at risk for sexually transmitted infections (STIs) while traveling. *Chlamydia,* gonorrhea, human papillomavirus (HPV), syphilis, hepatitis, and HIV are some of the infections spread during travel. Shah and colleagues tracked STIs in US citizens post-travel and found a significant peak in March and May, perhaps coinciding to spring break return.[14] During travel, adolescents may be more uninhibited because of freedom from adult supervision. The adolescent's first sexual encounter may occur while vacationing and is often viewed as a negative experience.[15] Being male and younger than 20 years is associated with a high frequency of casual sexual encounters during travel.[16] However, adolescent girls are also very sexually active during travel, and some may use alcohol to justify risky behavior.[17] Casual sex while traveling abroad correlates to casual sex in the home country.[18]

Experiencing multiple sex partners, unprotected sex, and sex while intoxicated are high-risk behaviors for contracting an STI.[19] Common reasons for not using condoms include poor judgment due to alcohol use, lack of condom availability, and lack of consideration of long-term consequences of unsafe sex.[18] One-third of spring break travelers admitted to having sex with a new partner they met at the vacation location. Many of the travelers reported that they rarely or never worried about contracting an STI.[19]

HIV is particularly worrisome because young adults bear the major burden of this infection worldwide. The immaturity of the adolescent cervix makes girls more vulnerable to STIs like herpes simplex, which

increases the susceptibility to HIV.[20] Certain areas of the world have very high infection rates, and the adolescent's destination is a factor in the degree of likely exposure. The risk of acquiring HIV is highest for travel to Africa, followed by South Asia.[21]

A potential noninfectious health consequence of increased and unprotected sexual activity is pregnancy. The risk of an adolescent conceiving while traveling is unknown.[22] Researchers of a survey of adolescent girls reported that 15% of respondents were concerned about the possibility of being pregnant after vacationing for a week with other adolescents and without parental authority.[15]

Noninfectious Diseases

Exposure to the natural elements of the surroundings puts young travelers at risk for heat or cold injuries, animal bites, insect and marine creature stings, and acute mountain or altitude illness (Box 12-3). Acute altitude illness is characterized by headache, dizziness, nausea or vomiting, insomnia, and fatigue, which results from hypobaric hypoxia at altitudes higher than 2,500 m above sea level.[23] Being more physically fit does not prevent one from experiencing altitude illness.[23] Triggers of acute altitude illness include overexertion within 24 hours of ascent, dehydration, hypothermia, smoking, and alcohol or sedative consumption.[23]

Trauma

Injuries are a major potential health concern for the adolescent traveler. Death is more likely to occur during travel due to an accident than secondary to an infectious disease or other physical illness.[24] Motor vehicle crashes (MVCs) and drowning are the main causes of injury

Box 12-3. Potential Health Hazards During Adventure Travel

- Altitude illness
- Bites
  - Animal
  - Arthropod
  - Marine life
- Cold injuries
- Dehydration
- Dermatologic diseases
  - Contact dermatitis
  - Photodermatitis
  - Phytophotodermatitis
  - Sunburn
- Drowning
- Head injury
- Heat illness
- Lacerations
- Musculoskeletal injuries
  - Fractures
  - Sprains

while traveling abroad.[24,25] Travel to developing countries places the adolescent at a particularly high risk compared with developed countries. Characteristics of the young traveler and host country place the young traveler at particular risk for MVCs. High-risk behaviors, such as not using seat belts or driving under the influence of mind-altering substances, increase the odds that the adolescent will be in an MVC. Poor road conditions, poorly functioning vehicles, unfamiliar roads and road rules, and lack of law enforcement of road rules in the host country add to the danger.

Morbidity and mortality associated with bodies of water are mainly caused by drowning. Swimming alone in unfamiliar territory, inexperience with water sports such as diving or snorkeling, or being under the influence of mind-altering substances increase the chances of drowning or near-drowning experiences.

Substance Use

Substance use is more likely to occur in adolescents who vacation in popular locations known for a party atmosphere than those who travel to metropolitan areas, national parks, or small towns.[3] Binge drinking, cigarette and marijuana smoking, and other illicit drug use are common and can escalate during adolescent travel without parental guidance.[15,26] Spring break is a risk factor for heightened alcohol use,[3,27,28] along with traveling with friends.[26] College students vacationing with friends during spring break dramatically increased their alcohol use, as revealed in one study.[26] In a survey of spring break participants, the vast majority of men, some younger than 21 years, and more than three-quarters of women admitted to drinking excessively in the past day.[3] Men are more likely to drink greater amounts, to the point of intoxication and sickness. However, female travelers also engage in more risky substance abuse. Fifteen percent of the respondents in a survey of adolescent female travelers sought medical care after sustaining injuries while under the influence of alcohol or other mind-altering substance.[15] The vast majority who engaged in sexual activity (86%) admitted to doing so while drunk.

The use of illegal drugs also may increase. Josiam reported that approximately half of spring break vacationers were offered an illegal substance while traveling, but less than 5% admitted to trying the new drug.[29] Cigarette smoking doubled in a surveyed group of adolescent girls, and marijuana was smoked for the first time by some of the travelers.[15] Routine users of drugs admit to heightened drug use during spring break travel.[29]

Crime

As the naive traveler may venture into unfamiliar and unsafe areas in the host country, the risk of becoming a victim of rape, thievery, assault and battery, or a terrorist attack is heightened.[24] Rape is not uncommon; 12% of polled female spring break travelers felt forced or pressured into engaging in sexual activity.[17] Popular spring break destinations experience increased rates of crimes such as rape, assault, and arrests during the spring break time frame.[17]

More young men than women are arrested for crimes in other countries.[30] Narcotics and violence are often involved in the unlawful act. Possession of prescription medications, if not properly identified, may be a cause for legal woes in some foreign countries.

PRETRAVEL ADVICE

General

Providing pretravel advice (Box 12-4) reduces morbidity during travel.[31] Parents and adolescents can be referred to helpful resources to ensure that all aspects of health care and travel preparations are considered before traveling from home.[22,32–36] Pretravel advice should focus on issues most likely to arise for the type of travel the adolescent will be taking. Student travelers are strongly urged to register their foreign travel with the US Department of State, which can contact the traveler or family if an emergency arises in the foreign land or at home.[36]

The adolescent with a chronic illness, including psychiatric and physical disorders, is a special circumstance. Before independent travel can occur, the chronically ill adolescent must be in complete control of the disease. The pediatrician can prescribe an adequate supply of emergency medications and enough maintenance medications to last the entire trip. If several months of medication are required, perhaps a local physician should be found before travel in case a medical emergency arises or medical assistance is needed. The safest approach to traveling with medications is for the traveler to carry written information from the physician about the necessity of the prescription to avoid any legal consequences. A concise written review of the adolescent's chronic medical condition(s) should also be taken on the journey. Travel insurance, which covers evacuation, is strongly encouraged, as medical evacuation can cost tens of thousands of US dollars.[34]

Infectious Diseases

The need for vaccinations is the likely impetus for parents to seek pretravel medical advice for their adolescent. Two to 6 months in advance

Box 12-4. Pretravel Advice

GENERAL

- Schedule pretravel appointment months in advance.
- Research the travel destination and proposed travel activities so specific potential health hazards are determined.
- Establish plans for potential health hazards that may arise.
- Invest in travel insurance, including evacuation insurance.
- Register travel plans with US Department of State.

ADOLESCENT WITH CHRONIC DISEASE

- Provide adolescent with strategies and information to control all aspects of daily living with chronic disease.
- Locate a physician in host country who may be called on if expertise is needed.
- Ensure adequate supply of maintenance and emergency medications.
- Provide brief review of pertinent medical records.

PREVENTION OF ACUTE INFECTIOUS DISEASE

- Ensure routine vaccinations required in United States are up-to-date.
- Receive location-specific vaccines.
- Determine need for malaria prophylaxis.
- Discuss proper hygiene practices for food consumption.

PREVENTION OF SEXUALLY TRANSMITTED INFECTIONS AND RELATED HEALTH HAZARDS

- Educate about acquisition and prevention of sexually transmitted infections.
- Encourage safe sex; provide condom samples.
- Provide adolescent with information about the link between alcohol and drug consumption, sexual activity, and date rape.

PREGNANCY PREVENTION

- Discuss proper use of emergency contraception and offer prescription.

PREVENTION OF TRAUMA/SUBSTANCE USE/CRIME-RELATED HEALTH HAZARDS

- Reinforce commonsense behavior and basic safety practices of routine seat belt and helmet use and obeying rules of the road.
- Discuss avoidance of driving, swimming alone, wild animals, excessive alcohol intake, illicit drug use, and potential crimes.
- Avoid walking or socializing alone or in areas with an unsafe reputation.
- Encourage discussion between adolescent and parent about emergency planning in the event of rape and other crimes.
- Remind adolescent that civil rights are not guaranteed outside the United States.
- Determine location of closest consulate (information available at US Department of State Bureau of Consular Affairs [www.travel.state.gov]).

of travel is a reasonable time frame so that most vaccine series can be completed before travel and advice is not forgotten. Even if a vaccine series cannot be completed before travel, some protection will be obtained from vaccines administered. As with any traveler, the destination will determine the need for certain vaccines, and the pediatrician should consult various resources, such as the Centers for Disease Control and Prevention, for the most up-to-date immunization recommendations. The adolescent should receive the full series of vaccines routinely

recommended in the United States, including meningococcal, hepatitis A and B, HPV, and influenza. The meningococcal vaccine is particularly important for hajj pilgrims or visitors to areas of outbreaks such as the sub-Saharan "meningitis belt"—a region stretching across mid-Africa from parts of Senegal to Ethiopia. Adolescents with underlying immune deficiencies (terminal complement deficiency or asplenia) are also at increased risk for meningococcal infection. Parents should ensure that their adolescent receives 2 measles, mumps, and rubella vaccinations a month apart administered after 1 year of age in their lifetime before travel because measles outbreaks still occur worldwide.

A discussion about prevention of acute illness, especially infectious diseases, and avoidance of environmental hazards should be part of pretravel advice. Hand washing is a major preventive measure for most respiratory and gastrointestinal disorders. Packing portable containers of liquid hand sanitizer is a practical tip. Hygienic eating practices are advocated for all travelers. Avoiding raw or undercooked food and drinking from local water supplies, especially in lower-income countries, is strongly recommended. The adolescent traveler should be warned that adherence to proper personal hygiene alone may not prevent traveler's diarrhea due to poor restaurant hygiene in most developing countries.[37]

If the adolescent develops diarrhea, maintaining proper hydration during acute illnesses should be encouraged. Supplying the adolescent with powdered electrolyte solution packets, and education to properly prepare the solutions with bottled water is advised. Empiric use of antibiotic prophylaxis for traveler's diarrhea is not routinely recommended in children, but adolescents may benefit from the administration of azithromycin or a fluoroquinolone if severe diarrhea develops.[38]

Malaria prevention will need to be addressed if the adolescent is traveling to malaria-endemic areas. Malaria prophylaxis recommendations depend on the details of the travel agenda, especially the travel destinations. The specifics of the prescribed antimalarial chemoprophylaxis depend on the presence of resistant strains along the journey's route. Compliance with chemoprophylaxis must be emphasized along with the implementation of steps to minimize mosquito contact and bites.[38] Mosquito avoidance is possible by wearing protective clothing, consistently applying insect repellents, and using appropriate netting around bedding and windows.[38]

Sexual Hazards

Ideally, parents should have already counseled their maturing adolescent about sexual issues in everyday life[39]; if not, the potential consequences of reckless sexual behavior must be discussed openly and completely.

Counseling should be individualized so that high-risk adolescents receive more warning about sexual hazards, but it should be kept in mind that traveling abroad can foster risky behavior in any adolescent who engages in out-of-the ordinary activities.[18] Parents and adolescents can be referred to sexual health resources[40] to become more knowledgeable about potentially life-altering and life-threatening STIs. Condoms and other birth control products should be made available to the traveling adolescent, and consistent use of these products must be emphasized. In one report, taking condoms on the journey and reading information about STIs were predictors of practicing protected sex during travel.[41] Hepatitis B and HPV vaccination are especially important for the sexually active teen. Emergency contraception should be discussed with girls and perhaps a prescription provided so proper use can be discussed in the controlled setting of the familiar pediatrician's office.

Noninfectious Diseases

To avoid adverse environmental health effects, the adolescent should learn about the climate and potential hazards of the travel destination. Appropriate clothing and equipment should be brought for the journey. Avoiding wild animals and properly applying insect repellent will help deter bites. Soft-tissue injury is the main consequence of animal bites, but rabies may be a concern because it exists worldwide and is endemic to many areas, especially in South America and south East Asia. Aggressive application of sunscreen is a basic safety tenet to which an adolescent should adhere, especially if a tropical location is part of the journey. Adolescents should only participate in sporting events and adventure travel activities for which they are adequately trained. The importance of having experienced supervisors or guides present during adventure activities must be emphasized. Trying new hobbies, such as diving or snorkeling, may be very appealing to the young adult but should be discouraged if he or she received little or no training or consumed alcohol beforehand and supervision by trained individuals is not available. The advantages of remaining well hydrated and well rested should be emphasized so the adolescent appreciates that staying healthy will improve the overall quality of his or her travel experience.

Trauma

Because death is more likely to occur secondary to an injury rather than an infectious disease or other illness, providing effective advice about accident prevention is especially important. Because MVCs occur frequently during travel, it is prudent to advise the adolescent against driving in the host country for legal and safety reasons. If available, the

adolescent should use public transportation and avoid driving or being a passenger in a car with a driver who is unfamiliar with the roads. No one should swim or participate in water sports alone, and warning signs at beaches should be obeyed.

Substance Use

Because drug use can escalate while traveling, parents of a known drug user should strongly reconsider the decision to allow solo travel at all. Parents should also be aware of strong advertising campaigns that try to entice young travelers to venture to vacation spots with lenient alcohol laws. Alcohol and illicit substances may be readily available for consumption during a spring break vacation. Using educational brochures as the only tool to counsel about avoiding drug use is not effective in reducing this unwanted behavior; more aggressive counseling is needed for high-risk individuals.[42] References are available to help parents and pediatricians counsel adolescents about avoiding substance use[43,44] and other health-related issues.[45] Parents should seek educational programs that teach strategies to avoid consuming alcohol while on campus and traveling.

Sharing practical information with the adolescent may deter drug use while traveling.[46] The adolescent should be warned that penalties for drug-related offenses in some areas of the world are much more severe than in the United States and may even include the death penalty. All young travelers should be encouraged to obey the laws of the host land, seek non–alcohol-focused activities, and use taxi or shuttle services from their lodging to establishments where alcohol may be consumed.[3]

Crime

Before traveling, the adolescent should know how to contact the closest US embassy or consulate if assistance in legal matters is needed. Basic safety practices, such as not walking alone at night, are an obvious part of crime deterrence. Public transportation and licensed taxicabs should be the preferred mode of traveling around the host country, although adolescents should be warned that they may be targeted as crime victims at places of public transportation in foreign lands. Accepting food or drink from new acquaintances should be discouraged, especially because date rape drugs can be unknowingly slipped into beverages.[22] Young women need to be warned that if rape occurs, authorities (ie, parents and local and US officials) must be informed and medical care sought. The possibility of contracting an STI and becoming pregnant must be addressed after a sexual assault.

The experience of being arrested while abroad can vary depending on the crime and country in which it was committed. Some crimes may involve very serious penalties compared with punishments administered in the United States. The right to legal counsel is not guaranteed in all lands, nor is the right to participate in political demonstrations. Using common sense and obeying local laws will protect the adolescent in most instances.

KEY POINTS

- Millions of American adolescents travel abroad every year, placing themselves at risk for travel-related morbidity.
- Travel-related issues that can adversely affect an adolescent's health include infectious and noninfectious diseases, sexual hazards, trauma, substance use, and crime.
- Pretravel advice should include information about each of the potential travel-related health issues, with emphasis on proper vaccination, sexual and substance use counseling, and safe and law-abiding behavior.
- Parents and adolescents should research travel destinations beforehand so hazards specific to the travel location and agenda can be anticipated.
- Emergency plans should be reviewed for potential crises that may arise during travel.
- Registering with the US Department of State and purchasing evacuation insurance should be strongly encouraged.

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CHAPTER

13

Immunization for Travelers

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PRACTICAL GUIDE FOR IMMUNIZING TRAVELERS

Most international travelers need immunizations that are given routinely in their home country and immunizations required specifically for international travel. Health care professionals need to complete the following 10 steps to provide appropriate immunizations for travelers:

1. *Review the traveler's itinerary.* The health care professional must be aware that the traveler's particular destination (not only the country but particular regions within the country) and the nature and duration of the stay are important factors in determining immunization needs. For example, a volunteer planning to spend 3 months working in a rural village may need different immunizations than a businessperson planning to spend 5 days in an urban area of the same country. The need for specific international travel immunizations should also be based on the destination's disease patterns. The Centers for Disease Control and Prevention (CDC) *CDC Health Information for International Travel* (also known as the Yellow Book) and the CDC Travelers' Health Web site (www.cdc.gov/travel) are 2 sources that provide country-specific information.
2. *Determine the traveler's medical status.* The health care professional should review the traveler's medical history and record to understand his or her health status and eligibility to receive vaccines (especially live vaccines).

3. *Review immunization status.* All routine immunizations should be reviewed and updated. The need for specific international travel immunizations should be based on the traveler's prior immunization status, needs for modifications of routine immunization due to travel, and needs for travel-specific vaccines.
4. *Determine entry requirements.* When itineraries involve travel to Africa or South America, health care professionals should check for yellow fever vaccination status and immunization entry requirements of these countries, as well as all countries that the traveler plans to visit subsequently. This is important because yellow fever vaccination is a regulated international immunization. When itineraries include travel to Saudi Arabia for participation in the annual hajj, special immunization requirements should be checked, as immunization against meningococcal disease, influenza, and polio has been required in recent years.[1]
5. *Complete the international immunization schedule.* Several factors complicate this evaluation.
   a. Number of required or recommended immunizations and their particular schedules
   b. Length of time until departure
   c. Compatibility of certain immunizations with other immunizations, antibiotics, and antimalarials
   d. Traveler's health status, including allergies
   e. Traveler's interest and personal or financial concerns
6. *Educate and inform the traveler about the immunizations recommended and to be administered.* This includes providing Vaccine Information Statements and discussing the indications, effectiveness, and adverse events of each vaccine.
7. *Complete international immunization(s).* Several factors complicate this evaluation.
   a. Number of required or recommended immunizations and their particular schedules
   b. Length of time until departure
   c. Compatibility of certain immunizations with other immunizations, antibiotics, and antimalarials
   d. Traveler's health status, including allergies
8. *Record administered vaccines in the traveler's medical record.*
9. *Complete the International Certificate of Vaccination or Prophylaxis (ICVP), if required.*
10. *Provide a letter documenting the need for exemption, if needed.* The letter may contain items such as exemption from yellow fever vaccination.

TRAVEL-SPECIFIC IMMUNIZATIONS

Hepatitis A Vaccines

General Information About Hepatitis A Infection

Hepatitis A virus is distributed worldwide, although the prevalence of infection varies considerably. In areas with overcrowding, limited access to clean water, and inadequate sewage systems, hepatitis A infection occurs almost universally early in life. Because most young children who acquire hepatitis A are asymptomatic, disease rates in highly endemic areas of the world are reported to be low. Hepatitis A is rarely fatal in children and young adults; however, the case-fatality rate exceeds 2% among those older than 40 years and may be 4% for those aged 60 years or older.

The primary source for hepatitis A transmission is person to person through the fecal-oral route. On rare occasions, hepatitis A infection is transmitted by transfusion of blood or blood products collected from donors during the viremic phase of infection.[2] Since 2002, nucleic acid amplification tests, such as the polymerase chain reaction (PCR) assay, have been applied to the screening of source of plasma used for manufacturing plasma-derived products.[3]

Transmission is generally limited to close contacts, and hepatitis A is rarely spread by casual interactions. Household transmission of hepatitis A is common. Hepatitis A can be acquired through exposure to contaminated water, ice, or shellfish harvested from sewage-contaminated water or from fruits, vegetables, or other foods that are eaten raw and that were contaminated during harvesting or subsequent handling by an infected food handler. Stools from a hepatitis A virus–infected person are most infectious from approximately 14 to 21 days before to approximately 8 days after the onset of jaundice.[4] Hepatitis A RNA has been reported to be detectable in stool by PCR assay for up to 3 months after the acute illness.[5] Children in particular can shed hepatitis A virus for up to 10 weeks after the onset of clinical illness.[5]

The incubation period for hepatitis A averages 28 days (with a range of 15–50 days). Hepatitis A typically has an abrupt onset of symptoms that can include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. The likelihood of having symptoms with the hepatitis A virus is related to the person's age. In children younger than 6 years, most infections (70%) are asymptomatic and the remaining present with mild symptoms. If illness does occur, its duration is usually less than 2 months. Infection is typically symptomatic among older children and adults, with jaundice occurring in more than 70% of

cases. Diagnosis depends primarily on the detection of hepatitis A IgM antibodies, which are detectable 5 to 10 days post-exposure and gradually disappear 6 months post-infection.[6] Although the hepatitis A virus is not excreted chronically, clinical relapses may occur in 10% to 15% of patients over a 6- to 9-month period and may be associated with recurring excretion of the virus in stool.[7]

Hepatitis A is considered the most important vaccine-preventable disease for travelers. The risk of hepatitis A is 4 to 30 cases per 100,000 months of stay in an area that is endemic to hepatitis A for travelers who are not immunized against it.[8] Risk exists even for travelers to urban areas, those who stay in luxury hotels, and those who report having good hygiene and being careful about what they drink and eat. In 2003, international travel was the source of hepatitis A infection for more than 25% of cases among children younger than 15 years. The vaccine should be considered for all travelers to areas with moderate to high risk of infection, and those at high risk of acquiring the disease should be strongly encouraged to be vaccinated regardless of where they travel. Spread of hepatitis A virus in child care settings has occurred from exposure to children who acquired the virus after visiting countries of their parents' birth.

Hepatitis A Vaccine Information

The US Advisory Committee on Immunization Practices (ACIP) recommends routine hepatitis A immunization for all children between the ages of 12 and 23 months.[9] Two monovalent hepatitis A vaccines, Havrix and Vaqta, are currently licensed in the United States for persons at least 12 months of age. Both vaccines are safe and highly effective. Both are made of an inactivated hepatitis A virus adsorbed to aluminum hydroxide as an adjuvant. Havrix is prepared with 2-phenoxyethanol as a preservative, while Vaqta is formulated without a preservative. Both vaccines are available in 2 formulations based on the patient's age. Twinrix is a combined hepatitis A and hepatitis B vaccine licensed for people older than 18 years, containing 720 enzyme-linked immunosorbent assay (ELISA) units of hepatitis A antigen (50% of the Havrix adult dose) and 20 µg of recombinant hepatitis B surface antigen protein (the same as the Engerix-B adult dose).

The different vaccine formulations are similarly immunogenic when given in their respective recommended schedules and doses—one dose of Havrix induced seroconversion by 15 days in 80% to 98% and by 1 month in 96% to 100% of children, adolescents, and adults. One month after a second dose, which was administered 6 months after the first dose, 100% of the children, adolescents, and adults had protective

serum antibody concentrations with high geometric mean titers. One dose of Vaqta induced seroconversion in 69% of adults 2 weeks after the first dose. One month after the first dose of Vaqta, 94% to 97% of children, adolescents, and adults had seroconverted. One month after a second dose, which was administered 6 months after the first dose, 100% had seroconverted. The protective antibody response following primary vaccination in adults and children persists for more than 10 years.[10–12] Results from mathematic models indicate that after completion of the primary series, anti-hepatitis A antibodies probably persist for 30 years or more.[13] Booster doses are not recommended. Given the long incubation period of hepatitis A (average 2–4 weeks), the vaccine is recommended for healthy international travelers aged 40 years or younger regardless of their scheduled dates of departure.[14] One dose of the vaccine administered at any time before departure can provide adequate protection for most healthy people.[14] The use of immunoglobulin is now virtually obsolete for the purposes of travel prophylaxis (see Hepatitis A Vaccine Special Considerations on page 257).

Indications for Hepatitis A Vaccination

Besides routine immunization for all children 12 to 23 months of age, unvaccinated children between 2 and 18 years can be vaccinated at subsequent visits as part of catch-up vaccination. In addition, vaccination is recommended for adolescent and adult males who have sex with men, users of injection and non-injection illicit drugs, people who work with hepatitis A–infected primates or with hepatitis A virus in a research laboratory, people with clotting-factor disorders, and people with chronic liver disease.[9]

People traveling to countries that have high or intermediate hepatitis A endemicity, including Central and South America, Africa, and most of Asia and Eastern Europe, should be vaccinated before departure. The risk of hepatitis A for people traveling to certain areas of the Caribbean is unknown, although vaccination should be considered if travel is anticipated to areas with poor sanitation.

Hepatitis A Vaccine Administration

All hepatitis A vaccines should be administered intramuscularly in the deltoid muscle.[9] The immunization schedule is shown in Table 13-1. Havrix and Vaqta are given in 2 doses. Twinrix requires 3 or 4 doses. The US Food and Drug Administration approved an accelerated schedule of Twinrix (ie, doses at days 0, 7, and 21) for travelers, with a booster dose to be given at 1 year. Even one dose of the vaccine can be administered up to the day of departure and still protect travelers.[14]

Table 13-1. Recommended Doses and Schedules for Inactivated Hepatitis A Vaccines[a]

AGE	VACCINE	HEPATITIS A ANTIGEN DOSE	VOLUME PER DOSE, mL	NO. OF DOSES	SCHEDULE
12 mo–18 y	Havrix	720 ELISA U	0.5	2	Initial and 6–12 mo later
12 mo–18 y	Vaqta	25 antigen U[b]	0.5	2	Initial and 6–18 mo later
≥19 y	Havrix	1,440 ELISA U	1.0	2	Initial and 6–12 mo later
≥19 y	Vaqta	50 antigen U[b]	1.0	2	Initial and 6–18 mo later
≥18 y	Twinrix[c]	720 ELISA U	1.0	3 or 4	Initial, 1 mo, and 6 mo later **OR** Initial, 7 d, and 21–30 d, followed by a dose at 12 mo

Abbreviation: ELISA, enzyme-linked immunosorbent assay.

[a] Havrix and Twinrix are manufactured by GlaxoSmithKline; Vaqta is manufactured and distributed by Merck & Co, Inc.

[b] Each unit is equivalent to approximately 1 µg of viral protein.

[c] A combination of hepatitis B (Engerix-B, 20 µg) and hepatitis A (Havrix, 720 ELISA U) vaccine (Twinrix) is licensed for use in people 18 years and older in 3- and 4-dose schedules.

Adapted from American Academy of Pediatrics. Hepatitis A. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:391–399.

Hepatitis A Vaccine Side Effects

Adverse reactions are mild and include local pain and, less commonly, induration at the injection site. No serious adverse events attributed definitively to hepatitis A vaccine have been reported.

Hepatitis A Vaccine Precautions and Contraindications

The vaccine should not be administered to people with hypersensitivity to any of the vaccine components. Safety data in pregnant women are not available, but the risk is considered to be low or nonexistent because the vaccine contains inactivated, purified viral proteins. Limited data indicate that hepatitis A vaccine may be administered simultaneously with other vaccines. Vaccines should be given in a separate syringe and at a separate injection site. The immune response in people who are immunocompromised, including people with HIV infection, may be suboptimal.

Hepatitis A Vaccine Special Considerations

Vaqta and Havrix, when given as recommended, seem to be similarly effective. Studies among adults have found no difference in the immunogenicity when 2 currently available vaccines are used for primary series, compared with using the same vaccine for primary series. Therefore, although completion of the immunization regimen with the same product is preferable, immunization with different products in primary series is acceptable.

Preimmunization testing for anti-hepatitis A antibodies generally is not recommended for children. Testing may be cost-effective for people who have a high likelihood of immunity from previous infection, including people whose childhood was spent in an area of high endemicity, people with a history of jaundice potentially caused by hepatitis A, and people older than 50 years. Postimmunization testing for anti-hepatitis A antibodies is not indicated because of high seroconversion rates in adults and children. In addition, some commercially available anti-hepatitis A antibody tests may not detect low but protective concentrations of antibody induced by the first dose of vaccine.

For optimal protection, adults older than 40 years, immunocompromised persons, and those with chronic liver disease or other chronic medical conditions planning to travel to an area in less than 2 weeks should receive the initial dose of the vaccine along with immunoglobulin (0.02 mL/kg intramuscularly) at a separate anatomic injection site.[14] The second dose of the vaccine should be completed subsequently at the scheduled interval (see Table 13-1) because completion of vaccine series is necessary for long-term protection. There is no need to restart the vaccine series if the vaccine interval has lapsed more than the recommended schedule interval. Travelers who are younger than 12 months, are allergic to a vaccine component, or otherwise elect not to receive vaccine should receive a single dose of immunoglobulin (0.02 mL/kg), which provides effective protection against hepatitis A for up to 3 months. Those who do not receive vaccination and plan to travel for longer than 3 months should receive an immunoglobulin dose of 0.06 mL/kg, which must be repeated if the duration of travel is longer than 5 months. It should be noted that although hepatitis A vaccine is not recommended for newborns and infants younger than 12 months due to the presence of passive maternal antibody interference effect, some experts recommend that the vaccine be considered in newborns and infants of this age group when benefits are deemed to be greater or when the risk of exposure to the pathogen is high, especially if the mother had neither hepatitis A disease nor vaccine before the infant's birth.[15]

Japanese Encephalitis Vaccine

General Information About Japanese Encephalitis Infection

Japanese encephalitis (JE) is a considerable public health problem in most Asian regions, particularly in South Asia, Southeast Asia, East Asia, and the Pacific. The disease can cause irreversible neurologic damage. The JE virus is mainly transmitted by the mosquito *Culex tritaeniorhyncus,* which prefers to breed in irrigated rice paddies. This mosquito species and members of the *C gelidus* complex are zoophilic. Wading ardeid waterbirds (eg, herons, egrets) serve as virus reservoirs, but the virus regularly spills over into pigs, members of the *Equidae* family (eg, horses, donkeys), and humans. Japanese encephalitis is often confused with other forms of encephalitis. Differential diagnosis should, therefore, include other encephalitides (eg, infections caused by other arboviruses and herpesviruses) and infections that involve the central nervous system (eg, bacterial meningitis, tuberculosis, cerebral malaria).

Because infected pigs act as amplifying hosts, domestic pig rearing is an important risk factor in transmission to humans. Two distinct epidemiologic patterns of JE have been described. In temperate zones, such as the northern part of the Korean peninsula, Japan, China, Nepal, and northern India, large epidemics occur in the summer months; in tropical areas of southern Vietnam, southern Thailand, Indonesia, Malaysia, the Philippines, and Sri Lanka, cases occur more sporadically and peaks are usually observed during the rainy season.

Japanese Encephalitis Vaccine Information

Currently, the only vaccine available in the United States is the inactivated Vero cell culture–derived vaccine (JE-VC) (Ixiaro).[16] This vaccine is derived from the attenuated SA14-14-2 virus strain propagated in Vero cells. The product does not include gelatin stabilizers, antibiotics, or thimerosal. It is currently approved for use in people aged 2 months or older.[17] It should be given as 2 doses intramuscularly 28 days apart. Each dose is 0.25 mL for children 2 months to 2 years and 0.5 mL for children 3 years and older, and adults. Administration of JE-VC for only 1 dose is not recommended due to suboptimal protective antibodies in up to 75% of vaccine recipients.[18]

Protective immune response was demonstrated in 97% of adults after 2 doses of JE-VC, and the protective antibodies can be detected as early as 7 days after receiving the second dose.[18] Up to 80% of recipients have protective antibodies for up to 12 months after vaccination.[19] Among children aged 2 months to 17 years, protective immune response was

demonstrated in 100% of recipients at 28 days after the second dose of JE-VC. At 6 months after vaccination, 88% of children aged 2 months to 2 years and 95% of those aged 3 to 17 years continued to maintain protective immunity.[20] For persons aged 17 years and older, ACIP recommends that if the primary series of JE-VC was given more than 1 year previously, a booster dose may be administered before potential JE virus exposure.[17] The rates of seroprotection remain almost 100% up to 12 months after the booster dose.[21] For persons aged 17 years and older who previously received the mouse brain–derived JE vaccines (JE-MB) and require further vaccination against JE virus, ACIP recommends that a 2-dose series of JE-VC should be administered. However, several studies showed that a single dose of JE-VC can effectively boost immunity in adults who previously received JE-MB, with protective immune response of 89% to 100% up to 2 years after the booster dose.[22–24] Currently, there is no recommendation on the administration of a booster dose following a primary series of JE-VC in children.[17]

It should be noted that licensed JE vaccines available in Asia include an inactivated JE-MB; a live-attenuated, primary hamster kidney cell–based SA14-14-2 vaccine manufactured in China; and a live-attenuated recombinant chimeric SA14-14-2 vaccine.[25] Each of these vaccines is licensed for routine pediatric use in several Asian countries.[26] Considering the current existence of safe and effective JE vaccines at a relatively low cost for wide-scale use globally, the World Health Organization (WHO) continues to advise integrating JE vaccine, either JE-MB or a live-attenuated vaccine, into the WHO immunization initiative in regions where the disease constitutes a public health risk.[27]

Indications for Japanese Encephalitis Vaccination

For most travelers to Asia, the risk for JE is very low but varies based on itinerary, season, and activities. The overall incidence of JE among persons from non-endemic countries traveling to Asia is less than 1 case per 1 million travelers.[28] Estimates suggest that risk of JE in highly endemic areas during transmission season can reach 1 per 5,000 per month of exposure. Risk assessments should be interpreted cautiously because risk can vary within geographic areas and from year to year.

Japanese encephalitis vaccine should be offered to travelers spending a month or longer in endemic areas during the transmission season, especially if traveling to rural areas. Travelers who are uncertain of specific destinations, activities, or duration of travel should also receive the vaccine. Under specific circumstances, vaccine should be considered for people spending less than 30 days in endemic areas (ie, areas

experiencing epidemic transmission) and those whose activities, such as extensive outdoor activities in rural or agricultural areas, place them at high risk for exposure. In all instances, travelers should be advised to take personal precautions to reduce exposure to mosquito bites. The decision to use JE vaccine should balance the risks for exposure to the virus and developing illness, availability and acceptability of repellents and other alternative protective measures, and side effects of vaccination. In general, the vaccine is not recommended for short-term travelers whose visits will be restricted to urban areas outside the JE virus transmission season.[29]

Japanese Encephalitis Vaccine Side Effects

Local and systemic adverse events caused by JE-VC include injection site redness, pain, fever, and myalgia. Compared with first-generation JE vaccines, there have been no serious hypersensitivity reactions or neurologic adverse events reported among JE-VC recipients in clinical trials. Additional post-licensure studies and monitoring of surveillance data are ongoing to evaluate the safety of JE-VC in a larger population.

Japanese Encephalitis Vaccine Precautions and Contraindications

The JE-VC vaccine contains protamine sulfate, a compound known to cause hypersensitivity reactions in some individuals. Severe allergic reaction (eg, anaphylaxis) after a previous dose of JE-VC, any other JE vaccine, or any component of JE-VC, including protamine sulfate, is a contraindication to JE-VC administration. Individuals with a history of severe allergic reaction to another JE vaccine should be referred to an allergist for evaluation if immunization with JE-VC is considered.

Japanese Encephalitis Vaccine Special Considerations

The JE-VC is categorized in pregnancy category B; no specific information is available on the safety of JE vaccine in pregnant women. Therefore, the vaccine should not be routinely administered during pregnancy. Japanese encephalitis acquired during pregnancy carries the potential for intrauterine infection and fetal death. Pregnant women who must travel to an area where risk of exposure is high should be vaccinated when the theoretic risk of immunization is outweighed by risk of infection.

Meningococcal Vaccines

General Information About Meningococcal Disease

Meningococcal disease is characterized by sudden onset of fever, intense headache, nausea, vomiting, stiff neck, rash, and petechiae. The case-fatality ratio may exceed 50%, but early diagnosis and treatment can lower the fatality rate to about 10%. Long-term sequelae among survivors include hearing loss, neurologic disability, or limb loss.[30] Up to 10% of populations in endemic countries carry *Neisseria meningitidis* asymptomatically in the nose and throat.[31]

Five major meningococcal serogroups associated with the disease are A, B, C, Y, and W-135. Meningococci serogroups B and C are responsible for most disease in the Americas and Europe.[31,32] During the past years, serogroup Y emerged as a cause of disease in northern America. Serogroup A meningococci and, to a lesser extent, serogroup C account for most meningococcal disease cases in Africa and some areas in Asia. Serogroup W-135 has been associated with meningococcal disease epidemics in Saudi Arabia and Burkina Faso.[33,34]

Sporadic cases and outbreaks of meningococcal disease occur throughout the world. In the sub-Saharan African "meningitis belt," which stretches from Senegal in the west to Ethiopia in the east, peaks of serogroup A meningococcal disease occur regularly during the dry season (December through June).[35] In addition, major epidemics occur every 8 to 12 years. Travelers to sub-Saharan Africa may be at risk for meningococcal disease. Travelers to the meningitis belt during the dry season should be advised to receive meningococcal vaccine, especially if they will have prolonged contact with local populations. Moreover, large outbreaks of meningococcal disease have occurred in Saudi Arabia in association with the hajj pilgrimage, with almost 80% of cases caused by serogroups W-135 and A.[36]

Meningococcal Vaccine Information

There are 6 meningococcal vaccines currently available in the United States: 3 tetravalent meningococcal polysaccharide–protein conjugate vaccines, 2 meningococococcal group B vaccines, and a tetravalent meningococcal polysaccharide vaccine (MPV4). Conjugate vaccines are expected to be efficacious in young children, confer long-term protection, and provide herd immunity by reducing nasopharyngeal carriage and transmission.

Tetravalent Meningococcal Conjugate Vaccine

There are currently 3 licensed tetravalent meningococcal conjugate vaccines available in the United States: Menactra (meningococcal groups A, C, Y, and W-135 polysaccharide diphtheria toxoid conjugate), Menveo (meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria CRM197 conjugate), and MenHibrix (meningococcal groups C and Y and *Haemophilus influenzae* type b tetanus toxoid conjugate). Menactra was found to be comparable to MPV4 in terms of immunogenicity and safety. Two randomized, controlled trials conducted among people 11 to 18 and 18 to 55 years of age compared immunogenicity of Menactra with MPV4. Percentages of subjects achieving at least a 4-fold rise in serum bactericidal antibody (SBA) titers were similar in Menactra and MPV4 groups. Percentage of subjects with at least a 4-fold rise in SBA was highest for serogroup W-135 and lowest for serogroup Y in both groups. The percentage of subjects achieving an SBA geometric mean titer of 128 or greater was high (greater than 97% for all serogroups) in both groups.[30,37]

Menveo was licensed in 2010. The effectiveness of Menveo in infants and children aged 2 to 23 months was assessed as a 4-dose series given at 2, 4, 6, and 12 to 16 months of age. At 1 month after the third dose, the percentage of infants and children with protective SBA, defined as greater than or equal to 1:8, was 94% to 98% for serogroups C, W-135, and Y and 67% to 89% for serogroup A. At 1 month after the fourth dose, the percentage of infants and children with protective SBA was 95% to 100% for serogroups C, W-135, and Y and 89% to 94% for serogroup A.[38,39] Similar immune response was observed in a study of a 2-dose series given at the age of 7 to 9 and 12 months.[40] In children 2 to 10 years of age, non-inferiority of Menveo to Menactra for the proportion of subjects with a seroresponse was demonstrated for serogroups C, W-135, and Y but not for serogroup A; the proportions with seroresponse to Menveo versus Menactra were 72% versus 77% in children 2 to 5 years of age and 77% versus 83% in children 6 to 10 years of age.[41] Among adolescents and adults 11 to 55 years of age, non-inferiority of Menveo to Menactra was demonstrated for all 4 serogroups with regard to the proportion of subjects with a protective immune response.[41]

The third conjugate vaccine, MenHibrix, was licensed in 2012. It is a combination vaccine of meningococcal serogroup C and Y and *Haemophilus influenzae* type b for infants.[42] A study was conducted to evaluate a 4-dose series of MenHibrix in healthy infants at ages 2, 4, 6, and 12 to 16 months. The percentage of MenHibrix recipients with protective SBA after the third dose was 99% for serogroup C and 96% for

serogroup Y. After the fourth dose, the percentages were 99% and 99%, respectively.[43] The immune response to *Haemophilus influenzae* type b was also excellent.

Meningococcal Group B Vaccines

Two new vaccines to protect against meningococcal serogroup B, which has been spreading through colleges in the United States recently, were approved by the US Food and Drug Administration in 2014 and 2015. Trumenba vaccine requires 3 doses (0.5 mL intramuscularly at 0, 2, and 6 months) and Bexsero vaccine requires 2 doses (0.5 mL intramuscularly at least 1 month apart). Both vaccines are approved for persons 10 to 25 years of age. While there is no routine recommendation for serogroup B meningococcal vaccines at this time, both vaccines will likely play a significant role in controlling meningococcal serogroup B disease outbreaks.[44] However, their roles in international travel health will likely be limited because most outbreaks in sub-Saharan Africa and the Middle East are not due to serogroup B; thus, this chapter will not focus on these 2 vaccines.

Tetravalent Meningococcal Polysaccharide Vaccine

The only licensed meningococcal vaccine for adults aged 56 years and older, MPV4 in general is poorly immunogenic in children, especially those younger than 5 years.[45,46] Moreover, antibody levels decrease substantially during the first 3 years after a single dose of MPV4 in children younger than 5 years. Among adults, antibody levels also decrease but are still detectable 10 years after vaccination.[47]

Indications for Meningococcal Vaccination

Menactra is approved for people 9 months through 55 years of age; Menveo is approved for those 2 months through 55 years of age; and MenHibrix is approved for infants and children 6 weeks through 18 months of age. Menactra and Menveo are approved for routine immunization in all US children 11 to 18 years of age. The vaccines are preferably given at age 11 or 12 years, with a booster dose at age 16 years.[42] The booster dose can be administered any time after the 16th birthday, preferably before college.

Vaccination against meningococcal disease is recommended for travelers visiting the parts of sub-Saharan Africa known as the meningitis belt during the dry season (December through June). Vaccination is also required by the government of Saudi Arabia for all travelers to Mecca during the annual hajj. Only Menactra, Menveo, and MPV4, not MenHibrix, are recommended for travelers because most infections in

Africa are caused by serogroup A and most infections among hajj visitors are caused by serogroups W-135 and A (Table 13-2). Those who have been vaccinated with MenHibrix and are traveling to countries with endemic meningococcal disease should receive a tetravalent meningococcal vaccination appropriate for age prior to travel.[42] It should be addressed that Saudi Arabia requires that hajj visitors have a certificate of vaccination with a tetravalent (conjugate or polysaccharide) meningococcal vaccine within 3 years before entering the country. Advisories for travelers to other countries will be issued when epidemics of meningococcal disease caused by vaccine-preventable serogroups are detected; such up-to-date information is available from international health clinics for travelers and state health departments or from the CDC Travelers' Health Web site at www.cdc.gov/travel, as well as from WHO at www.who.int/csr/disease/meningococcal/en.

Meningococcal vaccination is also recommended for children who have persistent complement component deficiencies (eg, C5-9, properdin, factor H, factor D), with functional or anatomic asplenia, and who are in a defined risk group during a community or institutional meningococcal outbreak.

Table 13-2. Recommended Meningococcal Vaccination for Travelers

TRAVELERS	VACCINE	ADMINISTRATION	BOOSTER
<2 mo	—	No vaccine currently licensed for use in this age	
2–6 mo	Menveo (4 doses)	2, 4, 6, and ≥12 mo	Remains at increased risk and completed the primary dose or series at **2 mo–6 y:** Should receive additional dose at 3 y after primary immunization; boosters should be repeated every 5 y thereafter. **≥7 y:** Should receive booster dose every 5 y.
7–8 mo	Menveo (2 doses)	7–8 mo and ≥12 mo	
9–23 mo	Menveo (2 doses)	Initiate first dose. Second dose at ≥12 mo and ≥3 mo after first dose.	
	Menactra (2 doses)	Initiate first dose. Second dose at ≥8 wk after first dose.	
2–55 y	Menactra or Menveo	1 dose For 11–21 y, routine immunization is recommended, with first dose given at 11–12 y and second dose at ≥16 y.	
≥56 y	MPV4	1 dose	Every 5 y

Abbreviation: MP4, meningococcal polysaccharide vaccine.

Meningococcal Vaccine Administration

All vaccines come as a 0.5-mL dose. Tetravalent meningococcal conjugate vaccines should be given intramuscularly and MPV4 should be given subcutaneously.[48]

Meningococcal Vaccine Side Effects

Adverse reactions to meningococcal vaccines are usually mild; the most frequent reaction is pain, swelling, and redness at the injection site, lasting for 1 to 2 days. Transient fever occurred among 5% or fewer of those vaccinated, more commonly among infants. Allergic reactions (eg, urticaria, wheezing, rash, anaphylaxis) and neurologic reactions (eg, seizures, anesthesia, paresthesia) are rare.

Meningococcal Vaccine Precautions and Contraindications

In 2005, reports suggested a possible association of Guillain-Barré syndrome (GBS) with meningococcal conjugate vaccine, and ACIP initially recommended that people with a past history of GBS not be vaccinated with the vaccine. However, after additional reviews, ACIP voted to remove the vaccine precaution for those with a history of GBS because the benefits outweigh the risk for recurrent GBS. Tetravalent meningococcal polysaccharide vaccine is also an acceptable alternative for those with GBS.

Administration of Menactra, Menveo, MenHibrix, or MPV4 is contraindicated among persons known to have a severe allergic reaction to any component of the vaccine, including diphtheria toxoid, or natural latex rubber. Tetravalent meningococcal polysaccharide-protein conjugate vaccine and MPV4 are inactivated vaccines and may be given to immunosuppressed persons, but this may result in suboptimal immune response. No data are available about safety during pregnancy.

Rabies

General Information About Rabies Infection

Rabies is still a serious public health threat in developing countries. More than 95% of human infections are of canine origin, mainly in Asia and Africa, in areas where dog rabies is endemic and inadequately controlled. Canine rabies virus infection is 100% fatal among humans. Given the increasing amount of international travel, the risk of rabies exposure remains an important public health issue worldwide. Furthermore, the potential for exposure to the virus in higher-income countries still exists via wild animals, including bats, foxes, raccoons, and skunks.

Human rabies encephalitis can take two clinical forms: furious or agitated and dumb or paralytic. The latter is almost always seen in those with bat-transmitted rabies in the Americas of vampire and insectivorous bat origin. Dog-transmitted virus may also cause paralytic rabies. The clinical manifestation may begin with nonspecific prodromal symptoms such as malaise, fever, and anorexia and specific local symptoms such as itchiness, pain, and paresthesia around the healed bite wound. This is followed by the acute neurologic phase with intense anxiety, agitation, confusion, high fever, convulsion, and pharyngeal or laryngeal muscle spasms (hydrophobia). Similar symptoms may also be induced when cool air blows on the face (aerophobia). Subsequently, autonomic instability becomes extreme and hypotension, arrhythmia, hypoventilation, and coma will develop, resulting in death.

Diagnosis of rabies should be considered in any patient with unusual neurologic signs. In children, especially, lack of a history of contact with a mammal should not deter initiation of tests for rabies. It has long been known that children are more vulnerable to exposure to rabies infection, as they fail to recognize the danger or report animal contact. They are unable to run away and are more likely to have severe bites, especially on the head. Diagnosis of rabies could be made by viral isolation from saliva, brain tissues, or cerebrospinal fluid; viral antigen detection from skin biopsy or corneal impression; rabies antibodies in cerebrospinal fluid; or viral gene detection by PCR.

Rabies Vaccine Information

The WHO recommends that the use of nerve tissue rabies vaccines in humans be discontinued and replaced by modern cell culture vaccines because nerve tissue vaccines have low potency and high incidence of serious, even fatal, neurologic complications, such as encephalomyelitis and GBS.[49] However, nerve tissue vaccines are still being used in some developing countries.

Modern cell culture vaccines are safe and immunogenic, with antibody response in more than 99% of vaccines. Currently, human diploid cell vaccine (HDCV), purified chick embryo cell culture vaccine (PCECV), and purified Vero cell vaccine are available internationally. Human diploid cell vaccine and PCECV are licensed in the United States. Purified Vero cell vaccine is easier to produce and therefore cheaper to manufacture—an important factor for developing countries.[50] Rabies vaccination results in high titers of protective rabies virus–neutralizing antibodies as well as long-term immunologic memory. Originally, all vaccines were given intramuscularly; however, the reduced-dose intradermal

vaccination was found efficacious and affordable, especially for developing countries.[49]

Rabies immunoglobulin (RIg) is important in rabies prevention because it provides passive immunity when antibody response to the vaccine is mounting. Human RIg (HRIg) is the preferred product. However, if HRIg is in short supply or not available or affordable, purified equine immunoglobulin (ERIg) should be used. Most new ERIg preparations are potent, highly purified, safe, and less expensive. Rabies immunoglobulin can be administered at the same time as vaccination, in a separate syringe at a distant site, or up to day 7 of vaccination. It is not indicated beyond the seventh day of vaccination because antibody response to the vaccine has likely occurred.

Indications for Rabies Vaccination

Rabies Preexposure Prophylaxis

Preexposure prophylaxis is recommended for anyone at increased risk of exposure to the rabies virus. This includes laboratory staff, veterinarians, animal handlers, wildlife officers, and visitors to areas with a high risk of rabies (Table 13-3). Prophylaxis might offer partial immunity and protection if postexposure prophylaxis is delayed and simplify postexposure management by eliminating the need for RIg, which is unavailable in many countries, and decreasing the number of vaccine doses.

Persons who receive preexposure prophylaxis should have a neutralization antibody test every 6 months or 2 years depending on the risk of exposure. If the neutralizing antibody is less than 0.5 IU/mL or 1:5 serum dilution by the rapid fluorescent focus inhibition test, a single booster dose should be given (see Table 13-3). If antibody testing is not

Table 13-3. Rabies Preexposure Prophylaxis Schedule

VACCINATION	REGIMEN
Primary	HDCV or PCECV 1 mL intramuscularly on day 0, 7, and 28 (or 21 if time is limited)
	WHO also recommends HDCV, PCECV, or PVCV 0.1 mL intradermally on day 0, 7, and 28 (or 21 if time is limited).
Booster	HDCV or PCECV 1 mL intramuscularly on day 0

Abbreviations: HDCV, human diploid cell vaccine; PCECV, purified chick embryo cell culture vaccine; PVCV, purified Vero cell vaccine; WHO, World Health Organization.

Adapted from World Health Organization. Rabies vaccines. WHO position paper. *Wkly Epidemiol Rec.* 2007;82(49-50):425–435; and Manning SE, Rupprecht CE, Fishbein D, et al. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2008;57(RR-3):1–28.

available, booster vaccination every 5 years may be an acceptable alternative. If persons are exposed to rabies in the future, they are considered immunologically primed against rabies and simply require postexposure prophylaxis with vaccination on days 0 and 3 (ie, 2 doses).

Rabies Postexposure Prophylaxis

Prophylaxis after exposure to rabies virus should not await the results of laboratory diagnosis of the animal unless the species is unlikely to be infected with rabies and the test result can be obtained within 48 hours. Prophylaxis can also be postponed if the animal can be observed and rabies in the animal is not suspected. Prophylaxis should include prompt and thorough wound cleansing, passive immunization with RIg, and vaccination with cell culture rabies vaccines (tables 13-4 and 13-5). It should be noted that the postexposure prophylaxis regimen in the United States is different from those recommended by WHO. Nevertheless, prompt postexposure prophylaxis is nearly 100% effective in preventing rabies, even following high-risk exposure.[49]

Recommendations addressing rabies postexposure prophylaxis depend on associated risks, including

1. *Type of exposure*. Bite exposure is more at risk for rabies than non-bite exposure. Prophylaxis is not indicated for non-bite exposure unless saliva or other potentially infected animal material is introduced into fresh, open cuts in skin or onto mucous membranes.

Table 13-4. Rabies Postexposure Prophylaxis Schedule, United States

TREATMENT	REGIMEN
Wound cleansing	Thorough cleansing with soap and water. If available, povidone-iodine solution should be used to irrigate the wound.
HRIg	20 IU/kg. If feasible, full dose should be infiltrated around wounds and any remaining volume should be given intramuscularly distant from vaccine administration.
Vaccine	HDCV or PCECV 1 mL intramuscularly (deltoid area if >2 y, anterolateral thigh if <2 y) on day 0, 3, 7, and 14
If a person previously completed preexposure or postexposure vaccination, HRIg is not needed and the vaccine can be given only on day 0 and 3.	

Abbreviations: HDCV, human diploid cell vaccine; HRIg, human rabies immunoglobulin; PCECV, purified chick embryo cell culture vaccine.

Adapted from Manning SE, Rupprecht CE, Fishbein D, et al. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2008;57(RR-3):1–28.

Table 13-5. Rabies Postexposure Prophylaxis Schedule, World Health Organization

TREATMENT	REGIMEN
Wound cleansing	Thorough cleansing with soap and water. If available, disinfect the wound with iodine solution or 70% alcohol. Postpone suturing if possible.
RIg	Indicated for transdermal bites, scratches, contamination of mucous membrane with saliva (ie, lick), or suspected exposure to bats. *Not* indicated for minor scratches or abrasions without bleeding or nibbling of uncovered skin. 20 IU/kg for HRIg or 40 IU/kg for ERIg If feasible, full dose should be infiltrated around wounds and any remaining volume should be given intramuscularly distant from vaccine administration.
Vaccine	HDCV, PCECV, and PVCV *Intramuscular route* 1 mL intramuscularly (deltoid area or anterior lateral thigh) on day 0, 3, 7, 14, and 28 or Two doses (1 mL each on left and right deltoid) on day 0, then 1 dose on day 7 and 21 *Intradermal route* *8-site regimen for HDCV and PCECV (8-0-4-0-1-1)* Eight 0.1-mL injections on day 0; 4 injections on day 7; 1 on day 30 and 90 *2-site regimen for PVCV and PCECV (2-2-2-0-1-1 or 2-2-2-0-2)* Two 0.1-mL injections on day 0, 3, 7, and 1 injection on day 30 and 90 or Two 0.1-mL injections on day 0, 3, 7, and 28
If a person previously completed preexposure or postexposure vaccination, RIg is not needed and the vaccine can be given intramuscularly or intradermally only on day 0 and 3 or as a 4-site intradermal injection on day 0 only.	

Abbreviations: ERIg, equine rabies immunoglobulin; HDCV, human diploid cell vaccine; HRIg, human rabies immunoglobulin; PCECV, purified chick embryo cell culture vaccine; PVCV, purified Vero cell vaccine; RIg, rabies immunoglobulin.

Adapted from World Health Organization. Rabies vaccines. WHO position paper. *Wkly Epidemiol Rec.* 2007;82(49-50):425–435; and World Health Organization. WHO guide for rabies pre and post-exposure prophylaxis in humans (revised June 15, 2010). http://www.who.int/rabies/PEP_prophylaxis_guidelines_June10.pdf. Accessed June 1, 2015.

2. *Epidemiology of animal rabies and animal species in the area where the contact occurred.*
3. *Circumstance of the exposure incident.* An unprovoked attack might be more likely than a provoked attack to indicate that the animal is rabid. Bites as a result of feeding or handling an apparently healthy animal should generally be regarded as provoked.
4. *Availability of the animal for observation or rabies testing.*

The risk of rabies resulting from an encounter with a bat might be difficult to determine because of the minor injury usually inflicted and because some bat-related rabies viruses might likely result in infection after inoculation into a superficial epidermal layer. Although rare, human cases of rabies as a result of airborne transmission of the rabies virus have been reported[51]; this might be clinically important in view of bat cave exposures. If the person can be reasonably certain that a bite, scratch, or mucous membrane exposure did not occur or if test results on the bat are negative for the virus, postexposure prophylaxis is not needed. Other situations that might qualify for prophylaxis include finding a bat in the same room with a person who might be unaware that contact occurred (eg, a sleeping person awakens to find a bat in the room; an adult witnesses a bat in the room with an unattended child or person with mental illness or who is intoxicated). However, prophylaxis is not needed in those situations if test results on the bat are negative for rabies. Clinicians should seek assistance from public health officials for evaluating exposures or determining the need for postexposure management in situations that are not routine.

Rabies Vaccine Side Effects

Cell Culture Rabies Vaccine

Local reactions, such as pain at the injection site, redness, and swelling, are common. Mild systemic reactions, such as fever, headache, and dizziness, have been reported. Systemic hypersensitivity reactions, including urticaria, pruritic rash, and angioedema, have been reported in up to 6% of people receiving booster vaccination with HDCV.[52]

Rabies Immunoglobulin

Local reactions, such as pain, redness, and induration, are common. Headache is the most common systemic reaction. No serious adverse events, including hypersensitivity from HRIg, have been reported. There is a small risk of hypersensitivity reactions from ERIg. However, there are no scientific grounds for performing a skin test prior to administration of ERIg because the test is not predictive.

Rabies Vaccine Precautions and Contraindications

Contraindications to postexposure prophylaxis following high-risk exposure do not exist because rabies is a lethal disease. This also pertains to postexposure prophylaxis in infants and pregnant women. For preexposure prophylaxis, previous severe reaction to any of the vaccine components is a contraindication for further use of the same vaccine.

For individuals with immune suppression, including HIV, neutralizing antibody testing may be considered at 2 to 4 weeks after completing the preexposure series, and an additional dose of vaccination should be considered if the antibody response is not adequate. Immunosuppressive agents should not be given during postexposure prophylaxis unless essential. Neutralizing antibody testing 2 to 4 weeks after completing the postexposure series should be considered in immunosuppressed hosts. If the antibody response is not adequate, a specialist or public health official should be consulted.

Typhoid Fever

General Information About Typhoid Fever

Enteric (typhoid or paratyphoid) fever is a systemic illness caused by *Salmonella enterica* subspecies *enterica* serovar *Typhimurium, S enterica* subspecies *enterica* serovar *Typhi,* and *S enterica* subspecies *enterica* serovar *Paratyphi*. The organisms are highly adapted to humans and have no animal or environmental reservoirs. It is transmitted by the fecal-oral route. Excretion of the organisms by asymptomatic carriers or individuals who recently recovered from enteric fever is a major source of spread for an epidemic. Most cases are confined to lower-income countries, with the greatest burden in the Indian subcontinent and Southeast Asia. Travelers visiting friends and relatives in endemic areas appear to be at increased risk for enteric fever compared with other travelers.[53] These travelers may have less control over their diet and be more likely to drink untreated water and eat uncooked foods while staying with friends or relatives.

Most people with enteric fever present with a nonspecific febrile illness, often with an insidious onset, after an incubation period of 1 to 2 weeks. Headache, malaise, myalgia, and dry cough are common. There are sudden episodes of shaking chills. Constipation and relative bradycardia are common but not necessary for the diagnosis. Rose spots (2- to 3-mm pink-red macules) on the chest and abdomen may appear. A variety of neuropsychiatric features may occur. Complications include gastrointestinal bleeding, intestinal perforation, and typhoidal encephalopathy. The case-fatality rate is highest among young children and elderly persons. Fewer than 5% will become long-term, asymptomatic carriers who may shed the organism in urine or stool for more than 1 year.[54]

Typhoid Fever Vaccine Information

All available vaccines are effective only against *S Typhi*. None seem to provide any protection against *S Paratyphi*, particularly *S Paratyphi A,* which is increasing in the Indian subcontinent and other parts of the world.[55]

Vi Capsular Polysaccharide Typhoid Vaccine

This vaccine was developed by purifying Vi capsular polysaccharide from wild-type *S Typhi* strain Ty2. The vaccine also contains phenol as a preservative. Previous exposure to *S Typhi* does not seem to influence the immune response to vaccination. The protective efficacy of Vi polysaccharide vaccine in endemic areas was 72% over 17 months,[56] 64% over 21 months,[57] and 55% over 3 years.[58] A drawback of the parenteral Vi polysaccharide vaccine lies in its inability to stimulate mucosal immunity. In addition, revaccination does not elicit a booster effect because the immune response to the vaccine does not involve T cells; therefore, immunologic memory cannot be established. Covalent binding of Vi polysaccharide to recombinant *Pseudomonas aeruginosa* exotoxin A results in the induction of higher and more sustained antibody responses in comparison with pure Vi polysaccharide.[59] It also stimulates a booster response. A field trial in Vietnam showed a 2-dose immunization schedule resulted in 92% protection in children 2 to 5 years of age.[60]

Live, Attenuated Oral Typhoid Vaccine

The live oral vaccine is an attenuated *S Typhi* strain, Ty21a, which is a mutant of the Ty2 strain. The strain lacks Vi antigen and is thus avirulent but contains immunogenic cell wall polysaccharides. The vaccine induces mucosal immunity (mucosal IgA) and serum antibodies, as well as cell-mediated immunity. An overall protective efficacy (as an enteric-coated capsule or liquid formulation) of 67% to 80% was demonstrated for up to 7 years.[61–63] Herd immunity or indirect protection to non-immunized people is also evidenced. Vaccinated individuals will be less likely to excrete virulent *S Typhi,* and there will be fewer temporary carriers in the community; these could result in reduction of infectious cases and transmission within a community.

Inactivated Whole-Cell Typhoid Vaccines

Although protective against typhoid fever, the global use of parenteral whole-cell vaccines for routine vaccination was undermined by their high reactogenicity, including fever, headache, and severe local pain. Consequently, whole-cell vaccines were replaced by the well-tolerated Vi capsular polysaccharide vaccine and oral live attenuated Ty21a vaccine.

Indications for Typhoid Fever Vaccination

The CDC and WHO recommend typhoid vaccination for those traveling to countries where enteric fever is endemic, particularly the Indian subcontinent and Southeast Asia.[64] These vaccines need to be given at least 2 weeks before departure. A unique phenomenon of typhoid vaccine immunity is that it can be overcome by a high inoculum dose (ie, ingestion of a large number of the organism). Thus, other protective measures, including drinking boiled or bottled water, eating thoroughly cooked food, and peeling fruits, must be followed despite vaccination. People with intimate exposure to a documented typhoid fever carrier, such as a household contact, a laboratory worker who has frequent contact with the organism, or those living in the endemic area of typhoid fever, should be vaccinated as well. Currently, there are no commercially available vaccines for children younger than 2 years.

Typhoid Fever Vaccine Administration

Selection of the vaccine largely depends on the recipient's age, desired route of administration (oral versus intramuscular), desired duration of protection (5 years for the oral vaccine versus 2 years for the injectable vaccine), and ability to swallow oral capsules (Table 13-6).

Table 13-6. Administration of Vaccines Against Typhoid Fever

VACCINES	AGE OF RECIPIENTS, y	REGIMEN	COMMENT
Oral live, attenuated Ty21a	≥6	Enteric coated capsule 1 capsule by mouth every other day for 4 doses; booster given every 5 years. In Europe, it is available as a 3-dose vaccine.	Must be refrigerated before use. Taken with cool liquid on an empty stomach (2 hours after last eating) and do not eat anything for 1 hour after ingesting. Concurrent use of antibiotics or antimalarials may interfere with antibody response.
Parenteral Vi capsular polysaccharide	≥2	0.5 mL intramuscularly for 1 dose; booster given every 2 years	

Typhoid Fever Vaccine Side Effects

Adverse systemic reactions from Vi capsular polysaccharide vaccine are estimated to be less than 7%.[65] These include fever and headache. Adverse local reactions at the injection site are mostly mild and may occur in 10% to 40% of vaccines.[66] Adverse effects of oral live, attenuated vaccine, including abdominal pain, nausea, and vomiting, are uncommon (less than 5%). Neither person-to-person transmission nor invasion of the bloodstream has been observed with the use of oral typhoid vaccine.

Typhoid Fever Vaccine Precautions and Contraindications

A contraindication to vaccination is a history of severe local or systemic reactions after a previous dose. No safety data are available for typhoid vaccines in pregnant women. Parenteral vaccine should not be given during an acute febrile illness. The oral live, attenuated vaccine should not be given to those who are immunocompromised; the parenteral Vi polysaccharide vaccine may be an alternative. The oral vaccine requires replication in the gastrointestinal tract for effectiveness; it should not be given during gastrointestinal illness. The theoretic possibility for decreased immunogenicity when oral Ty21a vaccine is administered concurrently with antimicrobials has caused concern. Mefloquine can inhibit the growth of the live Ty21a strain in vitro; if this antimalarial is administered, vaccination with Ty21a should be delayed for 24 hours. The vaccine manufacturer advises that oral Ty21a vaccine should not be administered to persons receiving sulfonamides or other antimicrobial agents; therefore, Ty21a should be administered 24 hours or longer after an antimicrobial dose.

Yellow Fever

General Information About Yellow Fever

Yellow fever is a viral hemorrhagic fever caused by the yellow fever virus in the genus *Flavivirus*. It is endemic in tropical Africa and South America, principally in the Amazon region and contiguous grasslands. Several species of the *Aedes* and *Haemagogus* (South America only) mosquitoes transmit the virus. These mosquitoes are domestic (ie, they breed around houses), wild (ie, they breed in the jungle), or semi-domestic (ie, they display a mixture of habits). Yellow fever has a wide spectrum of illness, from mild nonspecific febrile symptoms to severe multiorgan failure and death.

The disease has 2 stages. The first stage, acute, is characterized by abrupt onset of fever, muscle pain, backache, headache, shivers, loss

of appetite, nausea, and vomiting. The fever is paradoxically associated with a slow pulse. After 3 to 4 days, most patients improve and their symptoms disappear. However, 15% of patients will enter a toxic stage. Fever reappears and several organ systems are affected. Jaundice and abdominal pain may develop rapidly. Bleeding can occur from the mouth, nose, eyes, rectum, and stomach. Myocardial injury and shock may occur. Renal involvement ranges from asymptomatic proteinuria to renal failure. Case-fatality rate is as high as 50%. Definitive diagnosis is made by a viral culture of blood or tissue specimens or by identifying a viral antigen or nucleic acid in tissues using immunohistochemistry, ELISA, or PCR. Detection of yellow fever IgM antibody with confirmation of 4-fold rise in neutralizing antibody titers between acute and convalescent serum samples is also diagnostic.

Yellow Fever Vaccine Information

A live, attenuated vaccine (17D) was developed in 1936 by means of serial passage of the wild-type virus in chicken-embryo tissue. The 17D vaccine induces long-lasting neutralizing antibodies in about 99% of those who are vaccinated.[67] A single dose of vaccination provides protection for 10 years and probably for life.[68] The primary vaccine failure rate is approximately 1%.[69] It is part of a routine immunization program for children 9 months and older in endemic countries as recommended by WHO; however, vaccination coverage in many countries remains suboptimal.

Indications for Yellow Fever Vaccination

Persons 9 months and older who are traveling to or living in areas of tropical Africa and South America where the disease is endemic should be vaccinated.[70] These areas are listed on the WHO Web site (www.who.int) and the CDC Travelers' Health Web site (www.cdc.gov/travel). Vaccination is also recommended for travel to countries that do not officially report the disease but lie in the yellow fever endemic zone. To prevent importing yellow fever into a country where it was never reported, certain countries require that people, even if only in transit, have a valid ICVP if they were in countries known or thought to have yellow fever. Such requirements might be strictly enforced for persons traveling from Africa or South America to Asia, where yellow fever does not exist but *Aedes* mosquito vectors for yellow fever are present.

Although this vaccine is not recommended for infants younger than 9 months, vaccination for infants 6 to 8 months of age may be considered if exposure to yellow fever is unavoidable. Due to the risk of vaccine-associated encephalitis, infants younger than 6 months should

not receive yellow fever vaccine. Laboratory workers who might be exposed to yellow fever virus should be vaccinated.

Yellow Fever Vaccine Administration

Yellow fever vaccine is given subcutaneously at a dose of 0.5 mL. The International Health Regulations, as well as the US CDC, recommend revaccination every 10 years; however, yellow fever vaccine immunity may persist up to 35 years and probably for life.[71] It should be noted that the WHO Strategic Advisory Group of Experts on Immunization endorses that a single dose of yellow fever vaccine is sufficient to confer sustained immunity and lifelong protection and a booster dose is not needed (see International Certificate of Vaccination or Prophylaxis).[72]

Yellow Fever Vaccine Side Effects

Side effects to 17D yellow fever vaccine are usually mild, including headache, myalgia, low-grade fever, or other minor symptoms for 5 to 10 days. Immediate hypersensitivity reactions, characterized by urticaria or wheezing, are very uncommon (1 per 55,000 persons) and occur principally among people with a history of allergies to eggs. Gelatin in yellow fever vaccine has been implicated as a cause of allergic reaction to the vaccine.

Yellow fever vaccine–associated neurotropic disease among children has been the most common serious adverse event associated with yellow fever vaccines. The presentation is similar to viral encephalitis. Most occur among infants younger than 6 months. However, the occurrence of vaccine-associated neurotropic disease does not appear to be confined to infants. More recent reports have been among people of all ages, particularly those 60 years and older.[29] The overall risk for vaccine-associated neurotropic disease has been estimated at 1 per 125,000 persons.

In 2001, yellow fever vaccine–associated viscerotropic disease was described among recipients of 17DD and 17D-204 yellow fever vaccines.[73,74] It manifests with fever, hypotension, respiratory failure, elevated hepatocellular enzymes, hyperbilirubinemia, lymphocytopenia, thrombocytopenia, and death. This serious adverse reaction probably occurs as a clinical spectrum of disease severity, from moderate illness with focal organ dysfunction to severe disease with overt multiple organ system failure and death. Vaccine-type yellow fever virus was isolated from the blood of these patients. Vaccine-associated viscerotropic disease occurs mainly after the first dose, with no cases noted in subsequent doses. Accurately measuring the incidence of this rare vaccine-associated viscerotropic disease is impossible because adequate prospective data

are unavailable; however, crude estimates of the reported frequency are around 0.4 cases per 100,000 doses of vaccine administered.[29] Those older than 60 years seem to have the highest risk of serious adverse events from vaccination.[75] To provide a safer alternative, a purified inactivated cell culture vaccine was developed, and the results indicate good immunogenicity and tolerability in a phase 1 study.[76] Because of the reports of yellow fever deaths among unvaccinated travelers to areas endemic for yellow fever and of vaccine-associated viscerotropic disease, physicians should be careful to administer yellow fever vaccine only to persons truly at risk for exposure to yellow fever.

Yellow Fever Vaccine Precautions and Contraindications

Vaccinating infants younger than 9 months should be avoided because of the risk of vaccine-associated neurotropic disease. In addition, travel to countries in yellow fever endemic zones or experiencing an epidemic should be avoided. However, ACIP and WHO recognize that situations occur in which vaccination of an infant 6 to 8 months might be considered, such as residence in or unavoidable travel to a yellow fever endemic or epidemic area. The decision to immunize must balance the infant's risk for exposure with the risk for vaccine-associated encephalitis. Physicians who consider vaccinating infants younger than 9 months should contact their state health department or the CDC for further advice. Yellow fever vaccine should never be administered to infants younger than 6 months.

Persons 60 years and older might be at increased risk for systemic adverse events after vaccination compared with younger persons. Nevertheless, yellow fever remains a key cause of illness and death in South America and Africa, where potential yellow fever transmission zones have expanded to urban areas with substantial populations of susceptible humans and the *Aedes* vector mosquito. In addition, unvaccinated travelers to endemic areas have contracted fatal yellow fever. Consequently, despite these rare adverse events, yellow fever vaccination of travelers to high-risk areas should be encouraged as a key prevention strategy.

The safety of yellow fever vaccination during pregnancy has not been established, and the vaccine should be administered only if travel to an endemic area is unavoidable and if an increased risk for exposure exists. If vaccination of a pregnant woman is deemed necessary, serologic testing through the state health department or CDC to document an immune response to the vaccine can be considered because the seroconversion rate for pregnant women has been reported to be lower than

observed for other adults.[77] Vaccination of nursing mothers should be avoided because of the theoretic risk for transmitting the vaccine virus to the breastfed infant. Three cases of vaccine-associated neurotropic disease have been reported in exclusively breastfed infants (all were <2 months of age) whose mothers were vaccinated with yellow fever vaccine.[78–80] Nursing mothers can be vaccinated if travel to high-risk yellow fever endemic areas cannot be avoided or postponed.

Infection with yellow fever vaccine virus poses a theoretical risk for encephalitis to patients with malignancy and those whose immunologic responses are suppressed by corticosteroids, chemotherapy, or radiation; these patients should not be vaccinated. If travel to a yellow fever–infected zone is necessary, patients should be instructed in methods for avoiding vector mosquitoes. In addition, their physician should provide them with vaccination waiver letters.

Yellow fever vaccine is contraindicated for people with AIDS, children with HIV infection, and adults with severe immune suppression (CD4 cells less than 200/mm^3 or less than 15% for children) because of a theoretic increased risk of encephalitis in this population. If travel to a yellow fever–endemic area cannot be avoided, a medical waiver should be provided and counseling on protective measures against mosquito bites should be emphasized.

Two studies in HIV-infected adults showed that higher neutralizing antibodies after vaccination were associated with undetectable HIV RNA levels and increasing CD4 cell count, and there were no serious adverse events in this population.[81,82] A study in 364 HIV-infected adults showed antibody response to the yellow fever vaccine in 93% after a mean duration of 8.4 years after vaccination.[83] The key determinant of antibody response was HIV RNA level at the time of vaccination; lower neutralizing antibody titers were associated with shorter duration of undetectable HIV RNA and higher HIV RNA level at immunization, with no correlation observed between CD4 cell count and antibody response. The US CDC currently recommends yellow fever vaccination to HIV-infected travelers with CD4 cell counts above 200/mm^3 or above 15%.[29] Vaccinated persons should be monitored for evidence of adverse events. As vaccine response may be suboptimal, measuring the neutralizing antibody response 1 month after vaccination through the CDC Arboviral Diseases Branch should be considered before travel.

Yellow fever vaccine is produced in chick embryos and should not be administered to those hypersensitive to eggs; typically, people who are able to eat eggs or egg products can receive the vaccine. If vaccination is considered essential because of a high risk of exposure, an intradermal

test dose can be administered under close medical supervision for those with a questionable history of egg hypersensitivity.

No data exist on possible interference between yellow fever vaccine and other vaccines. Because yellow fever vaccine is live, it should be given simultaneously or at least 1 month apart from other live vaccines. Oral Ty21a typhoid vaccine can be given simultaneously or at any interval before or after yellow fever vaccine.[70] No alteration of the immunologic response to yellow fever vaccine was detected when given simultaneously with intramuscular immunoglobulin. Although chloroquine inhibits replication of yellow fever virus in vitro, it does not adversely affect antibody responses to yellow fever vaccine among those receiving chloroquine prophylaxis for malaria.[84]

International Certificate of Vaccination or Prophylaxis

To prevent importation and indigenous transmission of yellow fever, the International Health Regulations allow a number of countries to require an ICVP from travelers arriving from endemic areas, even if only in transit.[85] Travelers arriving without a completed ICVP may be quarantined for up to 6 days or refused entry unless they submit to on-site vaccination. Such requirements may be strictly enforced, particularly for persons traveling from Africa or South America to Asia. Some countries in Africa require evidence of yellow fever vaccination from all entering travelers; others may waive the requirements for travelers coming from non-endemic areas who are staying in the country fewer than 2 weeks.

For purposes of international travel, yellow fever vaccine produced by different manufacturers worldwide must be approved by WHO and administered at a certified center in possession of an official Uniform Stamp that can be used to validate the ICVP. State health departments are responsible for designating nonfederal yellow fever vaccination centers and issuing Uniform Stamps to health care professionals. The ICVP must be validated only by the center that administers the vaccine.

Most city, county, and state health department immunization or travel clinics, as well as private travel clinics or individual health care professionals, are designated sites for yellow fever vaccination. Information about the location and hours of operation of yellow fever vaccination centers may be obtained by contacting local or state health departments or visiting the CDC Travelers' Health Web site (www.cdc.gov/travel). Vaccines should receive a completed ICVP, signed and validated with the official Uniform Stamp of the center where the vaccine was administered. Only the most recent ICVP (form CDC 731) complies with the revised 2005 International Health Regulations and should be

used for any vaccine administered on or after December 15, 2007. This certificate is valid 10 days after vaccination and for a subsequent period of 10 years. Previously issued certificates remain valid, provided that the vaccination was given within 10 years. The ICVP should be kept with the traveler's passport. Failure to secure validations can cause a traveler to be revaccinated, quarantined, or denied entry. In 2014, the WHO World Health Assembly adopted an amendment to the International Health Regulations that the term of validity of ICVP will change from 10 years to the duration of the life of the person vaccinated. This change is anticipated to take effect in June 2016.[86]

Some countries do not require an ICVP for infants younger than 6 or 9 months or 1 year. Travelers should be advised to check the individual country's requirements through the embassies or consulates or the CDC Travelers' Health Web site (www.cdc.gov/travel). If a physician concludes that a yellow fever vaccine should not be administered for medical reasons, the physician should complete and sign the Medical Contraindication to Vaccination section of the ICVP. The traveler should also be given a signed-and-dated waiver letter on the physician's letterhead stationery stating the contraindication to vaccination. Ideally, the letter should bear the stamp used by the health department or the official vaccination center to validate the ICVP.

When planning to use a waiver letter, the traveler should also obtain specific and authoritative advice from the embassy or consulate of the country or countries he or she plans to visit. Waivers of requirements obtained from embassies or consulates should be documented by appropriate letters and retained for presentation along with the completed ICVP. Reasons other than medical contraindications are not acceptable for exemption from vaccination. The traveler should be advised that issuance of a waiver does not guarantee that the destination country will accept it; on arrival at the destination, the traveler may be faced with quarantine, refusal of entry, or vaccination on site.

In May 2014, WHO declared a public health emergency of international spread of polio and issued temporary vaccination recommendations for travelers *from* countries with active polio transmission to prevent further spread of the disease. These countries include Afghanistan, Cameroon, Equatorial Guinea, Ethiopia, Iraq, Israel, Nigeria, Pakistan, Somalia, and Syria. In June 2014, the CDC issued guidance for US residents traveling to the affected countries to ensure that they have evidence of administration of polio vaccine within 12 months of travel, as this may be required when they depart from countries with active poliovirus transmission.[87] If implemented by a country, these

requirements could be mandatory and are intended to prevent exportation of polio.

Infants and children traveling to areas where there has been wild-type poliovirus circulation in the last 12 months should be vaccinated according to the routine schedule. If the routine series cannot be given within the recommended intervals, an accelerated schedule can be used as follows: the first dose should be given to infants 6 weeks or older, the second and third doses should be given 4 weeks or longer after the previous doses, and the minimum interval between the third and fourth doses is 6 months.

Adolescents and adults who are unvaccinated or incompletely vaccinated or whose vaccination status is unknown should receive a series of 3 doses: 2 doses of inactivated poliovirus vaccine (IPV) administered at an interval of 4 to 8 weeks, and a third dose administered 6 months or longer after the second. If 3 doses of IPV cannot be completed within the recommended intervals before travel, the following alternatives are recommended:

- If more than 8 weeks are available before travel, 3 doses of IPV should be administered 4 weeks or longer apart.
- If fewer than 8 weeks but more than 4 weeks are available before travel, 2 doses of IPV should be administered 4 weeks or longer apart.
- If fewer than 4 weeks are available before travel, a single dose of IPV is recommended.

If the vaccine series cannot be completed before departure, the remaining IPV doses to complete the series should be administered when feasible, at the intervals recommended previously, if the traveler remains at increased risk for poliovirus exposure. If doses are needed while residing in the affected country, the polio vaccine that is available (IPV or live oral poliovirus vaccine) may be administered.

Those who have completed a routine series of polio vaccine are considered to have lifelong immunity to poliovirus, but data are lacking.[29] As a precaution, travelers aged 18 years or older who are traveling to areas where there has been polio circulation in the last 12 months should receive another dose of IPV before departure. For adults, available data do not indicate the need for more than a single lifetime booster dose with IPV.

ACCELERATED IMMUNIZATION SCHEDULES FOR PEDIATRIC TRAVELERS

Routine pediatric vaccination may need to be accelerated before the standard primary vaccine series can be completed when travel of young infants is imminent. Table 13-7 lists the recommended minimum

Table 13-7. Acceleration of Routine Childhood Immunization

VACCINE	EARLIEST AGE FOR FIRST DOSE	MINIMUM INTERVAL BETWEEN DOSES
DTaP	6 wk	4 wk Minimum interval between dose 3 and dose 4 and between dose 4 and dose 5 is 6 months.
IPV	6 wk	4 wk
OPV	Birth	4 wk
Hib	6 wk	4 wk Minimum interval between Hib dose 3 and Hib dose 4 is 8 weeks. Minimum age for Hib dose 4 is 12 months.
HepB	Birth	Minimum interval between dose 1 and dose 2 is 4 weeks. Minimum interval between dose 2 and dose 3 is 8 weeks (with 16 weeks between dose 1 and dose 3).
Pneumococcus	6 wk	4 wk Minimum interval between dose 3 and dose 4 is 8 weeks.
Rotavirus (monovalent and pentavalent)	6 wk[88]	4 wk
MMR	6 mo However, all doses given before 12 months of age should not be counted as part of the complete series.	4 wk
Varicella	12 mo	3 months preferable, 4 weeks acceptable
HepA	12 mo	6 mo
HPV	9 y	Interval is 1 to 2 months between dose 1 and dose 2 and 6 months between dose 1 and dose 3.

Abbreviations: DTaP, diphtheria, tetanus, and acellular pertussis; HepA, hepatitis A; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IPV, inactivated poliovirus; MMR, measles, mumps, and rubella; OPV, oral poliovirus.

From Advisory Committee on Immunization Practices, American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists. Catch-up immunization schedule. *Red Book Online*. http://redbook.solutions.aap.org/SS/Immunization_Schedules.aspx. Accessed July 9, 2015.

amount of time between doses. The minimum interval is required to produce an immunologic response; however, longer intervals are preferred.

KEY POINTS

- Most travelers need a combination of routine childhood vaccines and vaccines specifically indicated for international travel.
- The requirement of vaccines is determined by
  - —Traveler's itinerary
  - —Traveler's immunization status
  - —Traveler's health status
  - —Entry requirement of the country visited
  - —Traveler's personal choice and insurance coverage
  - —Length of time until departure
  - —Compatibility of certain immunizations with other immunizations, antibiotics, and antimalarials
- Yellow fever vaccine can be administered only by state government–certified health facilities, and the traveler should be issued an ICVP.
- The traveler should also have a letter of exemption if there is a medical reason for not receiving the yellow fever vaccine.
- The travel advisor should be knowledgeable about the indications, contraindication, and duration of protection for all the vaccines.

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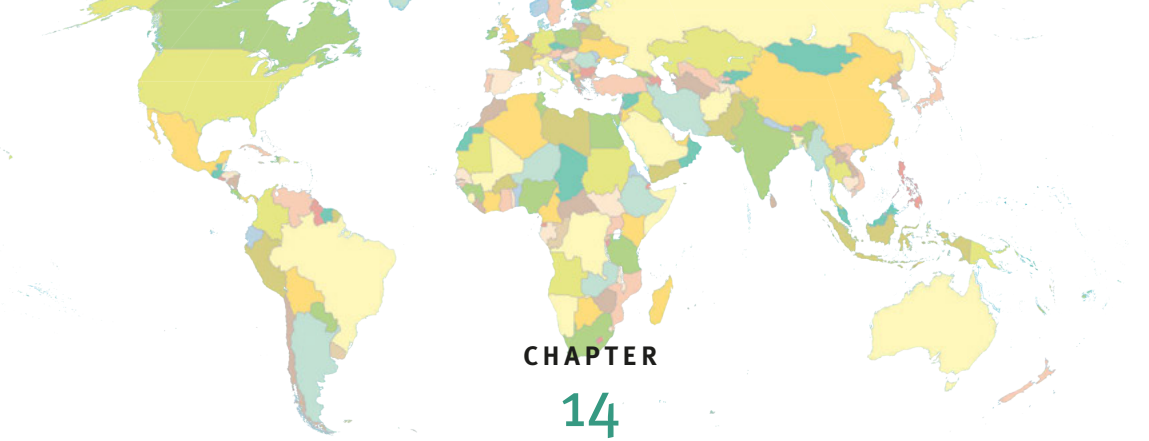

CHAPTER

14

Traveler's Diarrhea

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INTRODUCTION

Children often accompany adults as they travel overseas for pleasure, business, or employment. Unfortunately, during travel, children can encounter several enteric pathogens, some of which are associated with traveler's diarrhea (TD), the most frequent condition among travelers, especially to lower-income countries.[1] Although TD is generally self-limiting, it is a frustrating condition and negatively affects the travel experience. Data on etiology, incidence, and management of TD in children are limited. This chapter reviews recommendations addressing prevention, prophylaxis, and self-treatment of TD. These recommendations are not standardized in children and are largely based on expert opinion extrapolated from studies on TD in adults.

DEFINITION

Definitions of TD in the literature are varied. In adults, classic TD is defined as 3 or more loose stools per day along with other symptoms (eg, nausea, vomiting, abdominal pain or cramps, fever, blood in stool).[2] Normally, stool frequency and consistency vary during different periods in childhood.[3] Stool frequency can range from a mean of 3 times per day at 4 weeks of age to 1 time a day at 42 months of age.[3] In babies, stool consistency can be soft and liquidy.[3] Therefore, TD, as defined by the 1985 National Institutes of Health consensus report as a syndrome lasting for 2 to 3 days and characterized by a 2-fold or greater increase in

the frequency of unformed stools, is more applicable for pediatric TD.[4] *Persistent TD* refers to the condition when it lasts longer than 14 days, while *chronic diarrhea* is used when it occurs for a period longer than 30 days.[5,6]

EPIDEMIOLOGY

Incidence of TD varies in relationship to the numerous risk factors present and can be as high as 60%.[2] Risk factors for TD include host factors (age, dietary behavior, country of origin, genetic) and environmental (destination).[2] Travel destination is the leading risk factor, with countries in Asia (except Singapore), Africa, Latin America, and parts of the Middle East considered high risk because incidence rates can range from 20% to 90%.[2] China, South Africa, Israel, southern Europe, and some Caribbean islands are considered intermediate risk areas with incidence rates ranging from greater than 8% to less than 20%.[2] Low-risk areas include most of the industrialized countries, where incidence rates are lower than 8%.[2] The second most frequent risk of TD is travel in summer and during the monsoon or rainy seasons.[7,8]

Studies on the incidence of TD in children are lacking. A study by Pitzinger et al[9] evaluated 363 children (birth–20 years of age) who recently traveled to the tropics and subtropics from Switzerland to determine the incidence and characteristics of TD in children. Within 2 weeks of travel, the overall incidence of TD was 31%. The highest rate was seen in young children (birth–2 years of age) at 40%, followed by adolescents (15–20 years of age) at 36%. Incidence rates of 8.5% and 22% were found among children aged 3 to 6 years and 7 to 14 years, respectively. Traveler's diarrhea incidence rates varied by location and were 67% for North Africa; 61% for India; 27% to 31% for East Africa, Southeast Asia, and Latin America; and 17% for West Africa.

Another study of TD in 174 Portuguese children (aged 2 months–16 years) visiting tropical countries found a lower TD attack rate of 21.8% and lower rates by world regions: 31.5% for India, 26.9% in southern Africa, 22.2% in West Africa, and 6.7% in Latin America compared with the TD rates reported by Pitzinger et al.[9,10]

RISK FACTORS FOR TRAVELER'S DIARRHEA

In addition to environmental risk factors by destination, age, gastrointestinal conditions, and genetic susceptibility to enteric infections can also influence susceptibility to TD.

Age

Traveler's diarrhea is observed with higher frequency among toddlers, which is probably because of their immature immune system combined with their active environmental exploration (particularly oral exploration).[9] Traveler's diarrhea is also observed more frequently among young adults, possibly because of their more adventurous lifestyles and lower vigilance in avoiding contaminated food and water.[2,7,9]

Gastrointestinal Conditions

Individuals with underlying gastrointestinal disorders and those receiving antacids, H_2 blockers, and proton pump inhibitors are at increased risk for TD.[7]

Genetic Susceptibility to Enteric Infections

With the advent of genomic testing, a genetic basis for host susceptibility to infectious diseases including TD was demonstrated. Only a few studies have been published about this association. Genetic variability in inflammatory response has been associated with increased risk for TD.[11–15]

Subjects with polymorphism in the lactoferrin gene,[13] osteoprotegerin gene,[14] promoter region of interleukin 8 (IL-8),[11] interleukin 10 (IL-10),[12] and lipopolysaccharide receptor CD14[15] were found to be associated with increased risk of TD from different pathogens.

Lactoferrin is a glycoprotein found in milk, mucosal secretions (ie, tears, saliva, and intestinal mucus), and secondary granules of neutrophils.[16] Multiple activities of lactoferrin (antimicrobial,[17] anti-inflammatory,[18] and immunomodulatory[19]) have been described. Fecal lactoferrin is a marker of intestinal inflammation in patients with diarrhea. Lactoferrin concentrations have been found to be elevated in stool specimens obtained from travelers with diarrhea.[20,21] A study investigating the effect of a single nucleotide polymorphism (SNP) in the human lactoferrin gene and susceptibility to TD was conducted among North American adult travelers to Mexico.[13] The study found that an SNP in the lactoferrin gene (the T/T genotype in position codon 632) in these individuals with TD was associated with susceptibility to diarrhea.[13] Although lactoferrin levels in stools were higher in those subjects with pathogen-confirmed diarrhea, fecal lactoferrin levels did not correlate with the SNP genotype.

In a study among travelers with enteroaggregative *Escherichia coli,* subjects with an SNP in the promoter region of IL-8 were associated with the occurrence of diarrhea and increased levels of fecal IL-8 suggestive of cytokine-mediated intestinal inflammation.[11]

Osteoprotegerin is an immunoregulatory gene that is a member of the tumor necrosis factor receptor superfamily. It is reported to be upregulated in human intestinal cells after infection with enteropathogens.[22] An SNP in the gene encoding osteoprotegerin was found to be associated with increased susceptibility to TD with various *E coli* pathogens among North American travelers to Mexico.[14]

Symptomatic enterotoxigenic *E coli* (ETEC) diarrhea was more common in travelers with an SNP in IL-10 promoter gene where they produced higher levels of IL-10.[12]

Additional studies are needed to better understand the contribution of genetic host factors and susceptibility to enteric pathogens.

ETIOLOGY

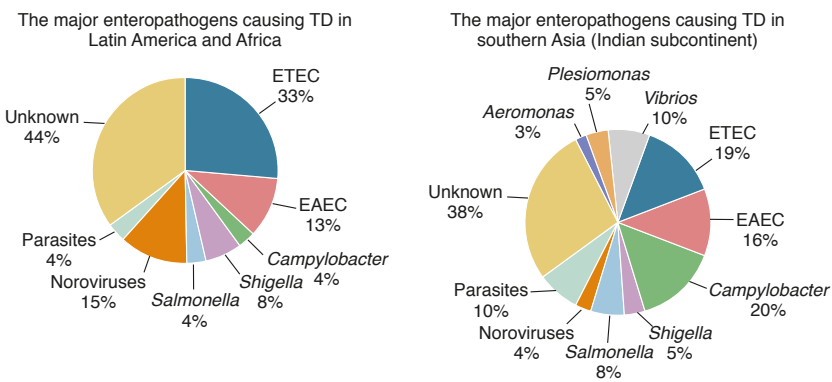
Etiology of TD in children is not adequately studied. According to an update on pediatric diarrheal illness in developing countries,[23] rotavirus and diarrheagenic *E coli* are the most common pathogens associated with acute diarrhea in children. Diarrheagenic *E coli* include enteropathogenic (EPEC), ETEC, Shiga toxin producing, enteroaggregative, and enteroinvasive. Enteroaggregative *E coli,* EPEC, and ETEC cause endemic diarrhea and are seen in children younger than 2 years. Enteroinvasive *E coli* causes invasive diarrhea associated with fever and is indistinguishable from other enteroinvasive pathogens (*Shigella*). Shiga toxin–producing *E coli* has been reported to cause bloody diarrhea and hemolytic uremic syndrome in children, and outbreaks have been reported in some developed and developing countries.[24–27] In poorer areas of the world, other organisms (*Shigella, Salmonella, Campylobacter, Vibrio, Aeromonas,* and *Plesiomonas*) are more commonly seen.[23] On the other hand, protozoa and helminths are seen in areas with extremely poor environmental sanitation.[23]

Bacteria are the most common causative agents (up to 70% of cases) of TD in adults, with viruses and parasites associated with the remaining cases.[28,29] Among bacterial causes, ETEC is isolated in the majority of cases (between 50% and 70%) of TD.[28] Enteroaggregative *E coli* is increasingly recognized as a cause of TD and may be responsible for up to 33% of cases.[30] Other *E coli* species, such as enteroinvasive *E coli* and EPEC, are also isolated from patients with TD.[28,31] Enterohemorrhagic *E coli* has caused outbreaks in the United States,[32] Europe,[33] and Japan,[34] with complication of hemolytic-uremic syndrome, but is rarely reported in children who traveled. Other invasive bacterial pathogens associated with TD include *Shigella, Campylobacter,* and non-typhoid *Salmonella*. *Aeromonas* and *Vibrio* are seen less frequently.

Shah et al[29] reviewed all TD studies published between 1973 and 2008 to determine the global etiology of TD by regions of the developing world. Indeed, there were regional differences among different pathogens identified. While *E coli* is responsible for the majority of TD cases identified in these areas, invasive pathogens (*Campylobacter, Shigella,* and *Salmonella*) were more commonly seen in southern Asia compared with Latin America and Africa (Figure 14-1). Knowledge concerning regional differences in causative etiologies of TD is important. This information will help guide recommendations on the appropriate use of antimicrobial agents for chemoprophylaxis treatment (where applicable) as well as the use of vaccines for TD.

Viruses, especially *Norovirus,* rotaviruses, and enteric adenoviruses, are associated with diarrhea among children in developing countries and are responsible for 2% to 25% of TD cases.[28] Parasitic infestations also occur in travelers who visit lower-income countries for prolonged periods and are usually associated with persistent diarrhea. *Giardia intestinalis* is the most common parasite associated with TD,[28] especially in South and Southeast Asia.[29] *Entamoeba histolytica*, *Cryptosporidium parvum,* and *Cyclospora cayetanensis* are the other parasites associated with TD but are less common compared with *G intestinalis*.[28]

Figure 14-1. Major Causes of Traveler's Diarrhea According to World Regions Visited



ETEC = enterotoxigenic *E. Coli*; EAEC = enteroaggregative *E Coli*; Parasites - *Giardia*, *Cryptosporidium*, and *Entamoeba histolytica*

From DuPont HL. Systemic review: the epidemiology and clinical features of travellers' diarrhoea. *Aliment Pharmacol Ther.* 2009;30(3):187–196, with permission. © 2009 Blackwell Publishing Ltd.

CLINICAL PRESENTATION

In most patients with TD, symptoms occur within the first 2 weeks of travel.[35] However, symptoms can begin even after completion of travel. Typical symptoms of TD include loose stools associated with abdominal pain, cramps with nausea, and vomiting; fever; fecal urgency; tenesmus; and passage of mucus or blood in the stool. The majority of patients have abdominal pain or cramps; about 25% of patients have fever and vomiting, while a small number (<10%) have mucoid or bloody stools.[7,9,36] Traveler's diarrhea is generally self-limited. In a single pediatric study,[9] TD started on the eighth day of travel; the average duration was 11.5 days and median duration was 3 days. Children younger than 3 years had a more prolonged illness, averaging 29.5 days, while older children and adolescents 3 to 20 years of age had a shorter duration of symptoms ranging from 2.6 to 4 days.

COMPLICATIONS

The primary complication observed in TD is dehydration. Young children usually suffer from a more severe and prolonged course of TD. Children have a high proportion of water per body mass and turn over 25% of total body water per day and are therefore at a higher risk of dehydration from acute water loss associated with diarrhea than adults.[7,9,36] Treatment of children with fluids containing inappropriate electrolyte concentrations can result in neurologic complications such as altered sensorium, seizures, and coma.[37–39] Other complications associated with dysentery are intestinal perforation and sepsis[39] as well as diaper dermatitis (probably caused by skin breakdown by enzymes in the stool or superinfection with *Candida* from prolonged diarrhea and inability to change diapers frequently and keep the area dry).

Sequelae associated with TD are increasingly reported in adults. In particular, postinfectious irritable bowel syndrome (IBS-PI) is observed more frequently. Incidence of IBS-PI, characterized by persistent gastrointestinal signs and symptoms (ie, acute onset of symptoms of at least 3 months, persistent abdominal discomfort or pain, and altered bowel habits) after the initial episode of acute diarrhea, is reported to be between 4% and 32%.[40]

In children, the relationship between TD and IBS-PI is not well studied. Saps et al[41] investigated the development of postinfectious functional gastrointestinal disorders (FGIDs) in children aged 3 to 19 years after a documented episode of culture-proven acute bacterial gastroenteritis (AGE). The study aimed to determine the proportion of AGE cases progressing to FGIDs compared with age- and sex-matched control

subjects without AGE. Questionnaires were administered to the parents to assess symptoms of FGIDs (eg, pain, diarrhea, disability) in their children at 6 months or older after the initial positive culture. Subjects with abdominal pain were additionally classified as having IBS, dyspepsia, or functional abdominal pain.

Among the 88 patients recruited (44 exposed and 44 control), 54% of the exposed subjects had *Salmonella,* 32% had *Campylobacter,* and 14% had *Shigella* AGE. Significantly more exposed patients complained of abdominal pain (36%) compared with the control group (11%) ($P < .01$). Among the 16 exposed patients who complained of abdominal pain, 14 (88%) had changes characteristics of IBS and 4 (22%) had dyspepsia (ie, nausea, bloating, and early satiety). Overall, there was a 36% prevalence of postinfectious FGIDs in the exposed group versus 11% in the control subjects. The study supports the existence of postinfectious FGIDs as an entity in children, with most patients having symptoms of IBS.

In adults, reported risk factors for IBS-PI include younger than 60 years, female, psychologic factors (depression and anxiety), and severity of diarrhea.[42–44] The underlying mechanism of IBS-PI is still not well understood; however, ongoing chronic inflammation appears to play an important role, including an increase in serotonin-containing enterochromaffin cells, proinflammatory cytokines, numbers of T lymphocytes, mast cells, and intestinal permeability.[42,45] Management of IBS-PI is not standardized and can be challenging.[46] Further understanding of the pathologic mechanisms of IBS-PI is needed to develop new and effective medications to treat this disease. Identification of enteric pathogens more likely to cause IBS-PI can be important, leading to early treatment and careful follow-up. Prophylaxis for TD may need to be reconsidered as a primary means of preventing IBS-PI if agents most likely to cause IBS-PI are identified.

In addition to IBS-PI, inflammatory bowel disease (Crohn disease or ulcerative colitis),[47] tropical sprue,[48] and reactive arthritis[49] following TD in susceptible persons are also reported after travel.

PREVENTION

Because of the high rate of TD among travelers to developing countries and the potential complications associated with TD such as IBS-PI, it is important to prevent TD. Prevention of TD can be divided into 2 broad categories, dietary and non-dietary prevention.

Dietary Prevention

Consuming contaminated food and drinks is known to be the main source of enteric pathogens and can lead to TD. Although unproven,

counseling families about properly selecting and preparing food and drinks appears to be the most important strategy for preventing TD.

Water Disinfection

Safe water should be used not just for drinking but also for brushing teeth and preparing food and formula for infants. Travelers should be reminded to buy bottled water from reliable sources.

Water can be made safe and potable by 3 standard methods (heat, filtration, and halogenation) outlined in Table 14-1. Heating water is the most reliable method. Water should be boiled (100°C) for at least 1 minute to kill most pathogens (eg, bacteria, viruses, protozoa, parasites). Using a filter with a micron size of less than or equal to 0.2 µm for bacteria and less than or equal to 1 µm for parasites effectively eliminates most organisms except viruses, such as hepatitis A, which are too small to be filtered. An additional process (halogenation) is therefore necessary and can be done before or after filtration. Halogenation, chemical disinfection with halogens, is performed using iodine or chlorine. Halogenation is effective in eliminating bacteria and viruses but is considered unreliable for protozoan cysts such as *Cryptosporidium* and *Giardia*.[29,50,51] The effectiveness of halogenation depends on contact time, temperature, pH, organic contaminants, and turbidity.[50] For example, if the water is cold, contact time should be longer. Similarly, if the water is turbid, concentration of halogens should be increased. Chlorine preparations are more likely to be affected by these factors compared with iodine preparations. A summary of water disinfection is provided in Table 14-2.

Iodine water disinfection should be limited to a few weeks of emergency use because iodine has physiologic activity. It is not recommended in persons with uncontrolled thyroid disorder, known iodine allergy, or pregnancy because of potential effect on fetal thyroid. Chlorine and iodine are available in liquid and tablet form (Table 14-3).

The taste of halogens in water can be improved by several methods, including increasing contact time and reducing concentration and adding a tiny pinch of vitamin C (available in most flavored drinks in powder or crystal form) after contact time, which converts chlorine to chloride or iodine to iodide, which have no color or taste.

Food Safety and Personal Hygiene Precautions

The gold standard for safely consuming milk and food continues to be, "Boil it, cook it, peel it, or forget it." Consume only boiled or pasteurized milk. Avoid fresh vegetables. Encourage breastfeeding in infants to reduce

Table 14-1. Comparison of Water Disinfection Techniques

TECHNIQUE	ADVANTAGES	DISADVANTAGES
Heat	• Does not impart additional taste or color. • Single step that inactivates all enteric pathogens. • Efficacy is not compromised by contaminants or particles in the water.	• Does not improve taste, smell, or appearance of water. • Fuel sources may be scarce, expensive, or unavailable. • Does not prevent recontamination during storage.
Filtration	• Simple to operate • Requires no holding time for treatment • Large choice of commercial product designs • Adds no unpleasant taste and often improves taste and appearance of water • Can be combined with halogens to remove or kill all pathogenic waterborne microbes	• Adds bulk and weight to baggage. • Many do not reliably remove viruses. • Channeling of water or high pressure can force microorganisms through the filter. • More expensive than chemical treatment. • Eventually clogs from suspended particulate matter and may require some maintenance or repair in the field. • Does not prevent recontamination during storage.
Halogens (chlorine, iodine)	• Inexpensive and widely available in liquid or tablet form. • Taste can be removed by simple techniques. • Flexible dosing. • Equally easy to treat large and small volumes. • Will preserve microbiologic quality of stored water.	• Impart taste and odor to water. • Flexibility requires understanding of principles. • Iodine is physiologically active, with potential adverse effects. • Not readily effective against *Cryptosporidium* oocysts. • Efficacy decreases with low water temperature and decreasing water clarity. • Corrosive and stain clothing.

Adapted from Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2014*. Atlanta, GA: US Department of Health and Human Services, Public Health Service; 2014.

the chance of contamination. Fruits that can be peeled, such as bananas and oranges, are safe to eat. Wash all other fruits with clean water and then peel with a clean knife before eating. Consume only freshly cooked food that is thoroughly prepared; avoid leftover food. Baked foods, such as bread, and hyperosmolar food, such as candy, are safe. Always wash hands with soap and water (or with a commercially available hand sanitizer if water is unavailable) prior to touching or preparing food.

Table 14-2. Summary of Water Disinfection				
TECHNIQUE	**BACTERIA**	**VIRUSES**	***GIARDIA* OR AMEBIC CYSTS**	**CRYPTOSPORIDIUM**
Heat	+	+	+	+
Filtration	+	±[a]	+	+
Halogens	+	+	+	–

+, susceptible; –, not susceptible; ±, inconsistent.

[a] Manufacturers of most filters make no claims with regard to viruses. General Ecology, Inc, claims virus removal by use of its First Need filter. Reverse osmosis filtration can remove viruses.

Adapted from Backer H. Water disinfection for international and wilderness travelers. *Clin Infect Dis.* 2002;34(3):355–364, by permission of Oxford University Press.

Table 14-3. Iodine and Chlorine Formulations and Doses		
IODINATION TECHNIQUES ADDED TO 1 L OR QT OF WATER	**YIELD 4 mg/L CONTACT (WAIT) TIME 45 MIN AT 30°C 180 MIN AT 5°C[a]**	**YIELD 8 mg/L CONTACT (WAIT) TIME 15 MIN AT 30°C 60 MIN AT 5°C[a]**
Iodine tablets (tetraglycine hydroperiodide) (eg, Potable Aqua)	½ tablet	1 tablet
2% iodine solution (tincture)	0.2 mL 5 gtts[b]	0.4 mL 10 gtts[b]
Saturated solution: iodine crystals in water (eg, Polar Pure)	13.0 mL	26.0 mL
CHLORINATION TECHNIQUES	**YIELD 5 mg/L**	**YIELD 10 mg/L**
Sodium hypochlorite Household bleach 5%	0.1 mL 2 drops	0.2 mL 4 drops
Sodium dichloroisocyanurate		1 tablet
Chlorine plus flocculating agent (eg, Chlor-Floc)		1 tablet

[a] Very cold water requires prolonged contact time with iodine or chlorine to kill *Giardia* cysts. These contact times have been extended from the usual recommendations in cold water to account for this and for the uncertainty of residual concentration.

[b] Drops per minute.

Adapted from Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2010.* Atlanta, GA: US Department of Health and Human Services, Public Health Service; 2010.

Non-dietary Prevention

Reports indicate that 60% of travelers do not comply with dietary recommendations during international travel.[9,52] However, TD occurs at about the same frequency among dietary compliant and noncompliant travelers[53,54]; thus, non-dietary factors also contribute to the development of TD. Therefore, it is essential to advise travelers about non-dietary precautions, which include immunization and chemoprophylaxis, to prevent TD.

Immunization

Vaccines for prevention of ETEC-related TD are being developed because ETEC is the main cause of TD and natural development of anti-ETEC immunity is known to occur in persons living in ETEC-endemic areas. Presently, the only licensed vaccine with an indication for prevention of diarrhea due to ETEC is an oral inactivated cholera vaccine. The oral vaccine is made of inactivated whole-cell *Vibrio cholerae* strains combined with the inactivated B-subunit of cholera toxin. Because of the antigenic similarity between the B-subunit of cholera toxin and ETEC heat labile enterotoxin (LT), immunization using the oral B-subunit of cholera toxin combined with whole-cell cholera vaccine was found to be 67% and 85% protective against episodes of diarrhea caused by ETEC and *V cholerae,* respectively.[55,56] The vaccine is marketed as Dukoral in Canada and Europe and is indicated for prevention and protection against TD caused by ETEC and *V cholerae* in adults and children 2 years and older. This vaccine is not available in the United States.[55]

Another vaccine for prevention of TD is the transcutaneous purified ETEC-LT patch vaccine.[57] This vaccine utilizes the novel method of transcutaneous immunization with antigen applied to the skin through a patch; antigens are then processed by antigen-presenting Langerhans cells and transported to the lymph node with subsequent production of anti-LT antibodies. A study on the use of the patch vaccine given twice before travel was conducted among 170 travelers (59 vaccinees, 111 placebo patients) to Mexico or Guatemala.[58] The vaccine was found to be safe and immunogenic. Patch vaccine recipients were protected against moderate to severe diarrhea compared with placebo patients. However, in a recent phase 3, randomized, double-blind, placebo-controlled trial conducted among healthy adult travelers (821 vaccinees; 823 placebo patients), the vaccine did not protect against diarrhea caused by ETEC or other organisms.[59]

Effective oral and injectable *Salmonella enterica* subspecies *enterica* serovar *Typhi* vaccines are available but recommended only for travelers

to areas where the risk of exposure to *S Typhi* is recognized.[60] Risk for acquiring *S Typhi* infection is highest for travelers to the Indian subcontinent, Latin America, the Middle East, and Africa who may have prolonged exposure to contaminated food products.

Cholera vaccine is not available in the United States; however, vaccination is not currently recommended for US travelers because of the low risk of acquiring cholera.

Chemoprophylaxis

Chemoprophylaxis can be achieved by using antimicrobial or non-antimicrobial agents. Chemoprophylaxis for TD is less preferred by many travel medicine experts because effective antimicrobial agents are available to treat TD if diarrhea develops.[61] Therefore, chemoprophylaxis for TD should only be considered in certain groups of people traveling to high-risk regions. Persons to whom chemoprophylaxis may be considered include those on a tight schedule in which short-term illness may severely affect the purpose of the trip, those who have chronic medical conditions in which diarrhea may potentially complicate the underlying illness, and those who had prior TD, which may suggest genetic susceptibility to TD. Travelers should be monitored for the development of adverse events and drug resistance while receiving chemoprophylaxis; chemoprophylaxis should not be continued for more than 2 weeks.[61]

Non-antimicrobial Agents

Bismuth Subsalicylate as Chemoprophylaxis

Bismuth subsalicylate (BSS) is the primary non-antimicrobial agent studied for TD prevention. When taken as 2 oz of liquid or 2 (263 mg) tablets 4 times a day, the protection rate for TD was 62% and 65%, respectively.[62] Bismuth subsalicylate undergoes acid hydrolysis and dissociates in the mouth or stomach, which results in release of salicylate and insoluble bismuth metabolites. It causes blackening of stools and tongues from the bismuth sulfide salt metabolites, which are generally harmless. The insoluble bismuth metabolites appear to have antibacterial property.[63] The free salicylate, which has antisecretory and anti-inflammatory properties, is absorbed.[64] Tinnitus and encephalitis rarely occur. Bismuth subsalicylate should be avoided in patients with a history of aspirin allergy as well as those taking aspirin for other reasons.

Although used in adults, BSS is not recommended as a prophylactic agent in children because the dose of BSS for TD prevention in children is currently unknown. Furthermore, frequent and prolonged BSS use

may cause salicylate intoxication[65] and increases the risk of Reye syndrome in patients with concomitant influenza or chickenpox infection.[66]

Probiotics as Chemoprophylaxis

Probiotics are other non-antimicrobial prophylactic agents used to prevent TD. They act by interfering with the colonization of the gut by pathogenic organisms. There are limited studies on the use of probiotics in the prevention of TD in children.

Two meta-analyses on the use of probiotics for the prevention of TD yielded conflicting results.[67,68] More studies are needed on the efficacy, optimal dosing, and frequency of administration of probiotics for TD prevention. In the future, probiotics may offer a safe and effective method to prevent TD. A wide range of probiotics products (eg, capsules, liquid, powder) with varying quality are available in the market. The dose of probiotics varies in children; regardless of the preparation, the minimum daily dose is suggested to be between 5 and 10 billion colony-forming units.[69]

Antimicrobial Agents

Antibiotic prophylaxis is reported to be about 80% to 90% effective in preventing TD. Although trimethoprim-sulfamethoxazole (TMP/SMX) had been used successfully in the prevention of TD, due to widespread resistance, its use is now limited. Even though fluoroquinolones are very effective in adults, they are not routinely used in children younger than 18 years. Fluoroquinolone use in children is limited because fluoroquinolones cause arthropathy in juvenile animals.[70] Fluoroquinolones have been associated with reversible musculoskeletal events in children.[71]

Azithromycin is used successfully in treating TD, especially in cases caused by ciprofloxacin-resistant *Campylobacter.*[72]

Rifaximin, a poorly absorbed rifamycin antibiotic, recently became available; it has in vitro activity against important enteric pathogens[73] with very few adverse effects. It offered 72% to 77% protection against TD when studied among travelers to Mexico where the predominant pathogen was *E coli.*[74] Despite high concentration in the gut, it did not alter colonic flora significantly. It is unclear whether rifaximin will be effective in preventing invasive forms of TD caused by *Shigella, Salmonella,* and *Campylobacter;* more studies are needed. Rifaximin is currently indicated for treatment of TD caused by noninvasive strains of *E coli*.

Use of prophylactic antibiotics for TD has the potential for development of drug-related adverse events, including allergic reaction and

resistant bacteria, and thus is not recommended routinely. When considering all types of prophylaxis, including antimicrobial chemoprophylaxis, against TD, the risk of developing adverse events from prophylaxis should be weighed against the benefit of using prompt and effective self-treatment for TD when signs and symptoms of TD develop.

Antimicrobial chemoprophylaxis is not recommended for infants 12 months or younger. Because the safety and efficacy of chemoprophylaxis in young infants is still not known, potential adverse events may outweigh the benefit of using antimicrobial chemoprophylaxis.

TREATMENT

The mainstay of TD treatment in children is preventing and treating dehydration. Traveler's diarrhea treatment can be initiated by the child's caregiver or the traveler (self-treatment). Treatment can also be prescribed by a physician after appropriate evaluation.

Prevention and Treatment of Dehydration

Dehydration and electrolyte abnormalities are more commonly observed in infants and children with TD compared with adults. It is essential that preventive measures against dehydration be instituted at the very onset of diarrhea to prevent the complications discussed previously. Children with diarrhea should be started on oral rehydration solution (ORS).[75] Treatment with ORS enables management of uncomplicated cases of diarrhea and should begin at home. Early intervention can reduce complications such as dehydration and death.

The World Health Organization (WHO) introduced a new ORS solution with reduced osmolarity for global use in 2002.[75] Oral rehydration solution from the WHO contains glucose (13.5 g/L), which facilitates the absorption of sodium and water in the small intestine; sodium chloride (2.6 g/L) and potassium chloride (1.5 g/L), which replace essential ions that are lost from diarrhea and vomiting; and trisodium citrate (2.9 g/L), which corrects the acidosis resulting from diarrhea and dehydration. Acute diarrhea was reportedly improved by the use of the reduced-osmolarity solutions, as evidenced by less stool output, less vomiting, and a decreased need for supplemental intravenous therapy on reduction of the sodium concentration from 90 to 75 mEq/L, the glucose concentration from 111 to 75 mmol/L, and total osmolarity from 311 to 245 mOsm/L.[75] Small packets of ORS containing glucose and sodium chloride in powder form are available commercially in most developing countries and can be reconstituted with appropriate quantities of clean water as instructed by the manufacturer to prevent hyponatremia

or hypernatremia. Families should be advised to carry ORS packets and encouraged to start therapy as soon as diarrhea begins. When commercial ORS packets are not available, home-prepared sugar and salt solution can be made by adding 1 teaspoon of table salt and 8 teaspoons of sugar to 1 L of clean water (bottled or boiling water for 1–3 minutes) and given early during the diarrhea episode to prevent dehydration.[76] However, errors can occur while preparing these products. Infants who are breastfed should continue to be breastfed even if they develop TD.

Supplemental Zinc Therapy

Zinc is a vital micronutrient essential for protein synthesis, cell growth, immune function, and intestinal transport of water and electrolytes.[77] Zinc deficiency is associated with an increased risk of gastrointestinal infections.[77] Dietary deficiency of zinc is common in low-income countries because of a low dietary intake of zinc-rich foods. Randomized, controlled trials of zinc supplementation performed in children living in developing countries have reported improvements in the duration and severity of diarrhea when compared with placebo.[78]

Despite the lack of data on the use of zinc supplementation in management of diarrhea in children from developed countries, WHO has endorsed zinc supplementation for all children with acute diarrhea.[79]

The role of zinc supplements in the treatment of children with gastroenteritis in developed countries needs further evaluation. A clinical trial of oral zinc for the treatment of acute diarrhea is currently in progress in the United States.

Antimicrobials for Treatment of Traveler's Diarrhea

Because enteric pathogens are the causative agents in most instances of TD, antibiotic treatment remains the best form of TD management. Use of antibiotics and antidiarrheal agents is shown to be safe and decrease severity and duration of diarrhea to about 1 day in adults.[80,81] Pediatric antibiotic treatment recommendations for TD are limited and elucidated from expert opinions and case reports. There is belief that the benefits of antibiotics outweigh the risks of potential side effects; thus, many experts believe that antibiotic treatment should be provided in pediatric patients with TD,[82] especially in patients with severe diarrhea (ie, diarrhea associated with fever or blood in stool).

Choice of Antimicrobials

The choice of antimicrobials for TD treatment depends on a number of factors—patient's age, pregnancy status, travel destination, antimicrobial susceptibility pattern of the enteropathogen, duration of diarrhea,

drug allergies, and other medications used by the traveler. Antimicrobial choices for TD treatment in children are presented in Table 14-4.

Fluoroquinolones are the antibiotics of choice for treating TD in adults but are not yet approved by the US Food and Drug Administration (FDA) in children and adolescents younger than 18 years for treatment of gastrointestinal infections. Azithromycin recently gained popularity in treating TD and is the preferred agent for treating TD acquired from South Asia, where invasive pathogens, including ciprofloxacin-resistant *Campylobacter,* are more prevalent. Azithromycin is considered the drug of choice in treating TD in children because of its safety, tolerability, and ease of administration. Rifaximin has been approved to treat noninvasive TD caused by *E coli* in persons 12 years and older.[83] Nitazoxanide is another agent used in the treatment of persistent TD caused by *G intestinalis* and *Cryptosporidium*.[84]

Other drugs that have been used to treat TD are TMP/SMX, nalidixic acid, and furazolidone. Trimethoprim-sulfamethoxazole is currently not used because of resistance developed by multiple organisms. However, it should be considered for treatment of TD in areas such as Nepal where *Cyclospora* is prevalent.[85] Although nalidixic acid treats enteric pathogen, it is not widely used because newer-generation quinolones are now available and more effective. Furazolidone is mainly used for treating *Giardia* and may be effective against a broad range of enteric pathogens.[51,86]

Antidiarrheal Medications for Symptomatic Treatment

Bismuth subsalicylate and loperamide are the 2 most commonly used drugs in adults to provide symptomatic relief from TD. Bismuth subsalicylate has antisecretory[64] and antibacterial[63] effects, while loperamide has antisecretory and anti-motility effects.[87] A combination of the antiperistaltic agent diphenoxylate and atropine (Lomotil) is also being used to treat TD.

Studies show the benefit of BSS in adults with mild to moderate episodes of TD. Two tablets or 2-oz liquid preparation given every 30 minutes for a maximum of 2 days reduces the number of unformed stools by 16%.[88] This drug is not widely available in Europe, New Zealand, or Australia.

Three randomized, controlled trials[89–91] compared BSS with placebo in infants and young children with acute watery diarrhea and found that although BSS reduced the duration and severity of diarrhea, the reduction was modest.[92] The use of BSS for treatment of diarrhea requires frequent dosing and has potential toxicity from salicylate absorption.[65] Bismuth subsalicylate is not routinely used in management of children with gastroenteritis.[93,94]

Table 14-4. Antimicrobial Choices for Treatment of Traveler's Diarrhea in Children				
DRUG	**DOSE**	**PEDIATRIC PREPARATION**	**ANTIMICROBIAL COVERAGE**	**COMMENTS**
Azithromycin	10 mg/kg/d for 3 d (maximum 500 mg/d)	100 mg/5 mL 200 mg/5 mL	Gram-negative enteric pathogens, *Escherichia coli, Salmonella;* including multidrug-resistant *Shigella* and quinolone-resistant *Campylobacter*	Ease of administration, once-daily dosing; no need to refrigerate; not FDA approved for this indication
Ciprofloxacin	20–30 mg/kg/d in 2 divided doses (maximum 1.5 g/d) for 1–3 d	250 mg/5 mL	Most gram-negative enteric pathogens, except quinolone-resistant *Campylobacter* from Southeast Asia (Thailand)	Not FDA approved in children younger than 18 years except for treatment of inhalational anthrax and complicated urinary tract infection
Furazolidone	6 mg/kg/d in 4 divided doses for 7–10 d (maximum 400 mg/d)	50 mg/15 mL	Antiprotozoal agent, active against *Giardia intestinalis;* also an antibacterial agent, active against enteric gram-negative pathogens (*E coli, Salmonella, Shigella, Vibrio cholera*)	Used mainly in the treatment of giardiasis or cholera; used with caution in patients with G6PD deficiency; not recommended for infants younger than 1 year
Nalidixic acid	55 mg/kg/d in 4 divided doses (maximum adult dose 4 g/d)	250 mg/5 mL	First-generation quinolone; coverage same as quinolones (ciprofloxacin)	Not given to infants younger than 3 months; duration for TD treatment not determined, likely same as quinolones; in general, not being used because of availability of newer quinolones
Nitazoxanide	1–3 y: 100 mg every 12 h 4–11 y: 200 mg every 12 h ≥12 y: 500 mg every 12 h Taken for 3 d	100 mg/5 mL	Activity against anaerobic bacteria (*Clostridium difficile*), protozoa (*Cryptosporidium, G intestinalis*), tapeworms (*Hymenolepis nana*), and viruses (rotavirus)	FDA approved for treatment of cryptosporidiosis and giardiasis

Table 14-4. Antimicrobial Choices for Treatment of Traveler's Diarrhea in Children, continued

DRUG	DOSE	PEDIATRIC PREPARATION	ANTIMICROBIAL COVERAGE	COMMENTS
TMP/SMX	Dose based on TMP component; 5 mg/kg/d divided in 2 doses for 7–10 d for treatment of cyclosporiasis (maximum dose 320 TMP/d)	40 mg TMP/ 200 mg SMX per 5 mL	Antibacterial agent: most enteric pathogens are resistant to TMP/SMX. Antiprotozoal agent: *Cyclospora cayetanensis, Isospora belli.*	Not recommended for use in infants younger than 2 months; not FDA-labeled for treatment of protozoal diseases
Rifaximin	≥12 y: 200 mg 3 times/d for 3 d	No pediatric suspension available	Effective against *E coli* (noninvasive strains ETEC and EAEC); not effective against *Campylobacter jejuni;* effectiveness against *Salmonella* and *Shigella* not known	Poorly absorbed antibiotics; few adverse effects; FDA approved for treatment of TD from noninvasive strains of *E coli* in persons 12 years and older

Abbreviations: EAEC, enteroaggregative *Escherichia coli;* ETEC, enterotoxigenic *Escherichia coli;* FDA, Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; TD, traveler's diarrhea; TMP/SMX, trimethoprim-sulfamethoxazole.

Adapted from Ang JY, Mathur A. Traveler's diarrhea: updates for pediatricians. *Pediatr Ann.* 2008;37(12):814–820. Reproduced with permission of SLACK Incorporated.

Loperamide use for children with acute diarrhea was reviewed in a meta-analysis.[95] The study included 13 trials with 1,788 children younger than 12 years (975 children in the loperamide group; 813 children in the placebo group). Dosing of loperamide varied: 6 studies used loperamide doses at less than or equal to 0.25 mg/kg/d, while 4 studies used doses at greater than 0.25 mg/kg/d; the maximum doses were not clear for the 3 remaining studies. The study reported benefit of loperamide use in children with acute diarrhea. Patients in the loperamide group were less likely to continue to have diarrhea at 24 hours, had a shorter duration of diarrhea by 0.8 days, and had a lower count of stools at 24 hours compared with patients in the placebo group. Serious adverse events (ie, ileus, lethargy, or death) were reported in 8 out of 927 children younger than 3 years in the loperamide group and none in the placebo group. The authors concluded that loperamide may be a useful adjunct to oral rehydration and early refeeding in children older than 3 years with mild to no dehydration.

Nevertheless, according to a recent evidence-based review of self-therapy for TD by renowned travel experts, loperamide is not recommended in children due to lack of data addressing its efficacy and concern for associated adverse events.[93]

Other antisecretory agents are being developed to treat various forms of diarrhea; these drugs are still not available in the United States except for crofelemer. Crofelemer is a chloride channel blocker; it reduces high volume water loss in patients with diarrhea. Crofelemer is the first drug to be approved by the US FDA to treat diarrhea in patients with HIV infection. Crofelemer is also being evaluated in patients with other conditions associated with diarrhea, such as TD and IBS.[96]

Zaldaride maleate is a calmodulin inhibitor that alters the intracellular calcium transport process. Racecadotril is an antisecretory agent that works by inhibiting intestinal enkephalinase and thus prevents breakdown of endogenous opioids (enkephalin), thereby reducing secretion of water and electrolytes into the gut without interfering with motility. Zaldaride[97] and crofelemer[98] are reported to reduce the frequency of stool output in patients with TD. Racecadotril was found to reduce the stool output and duration of diarrhea in children[99] and is widely in use in Europe, including France, in the management of pediatric acute gastroenteris.[100]

KEY POINTS

- Traveler's diarrhea affects children who travel just as it does adults; however, presently, it is an ill-defined entity in children.

- Traveling families should be counseled before they travel on prevention and self-treatment of TD.
- Mild forms of TD can be effectively managed by the appropriate use of ORS; thus, families should be advised to carry ORS packets and start treatment in children as soon as diarrhea begins.
- In cases of severe diarrhea, self-treatment with antibiotics, such as azithromycin, should be considered. Caregivers should contact local health authorities if there is no improvement, especially after self-treatment with antibiotics.
- Because most TD studies were conducted in adults, further studies are needed to determine the clinical and microbiological characteristics of TD exclusively in children. Additional studies are also needed to further determine the role of genetic factors and susceptibility to TD and its potential complications, such as IBS-PI, so treatment and preventive strategies can be designed to help reduce and prevent TD.

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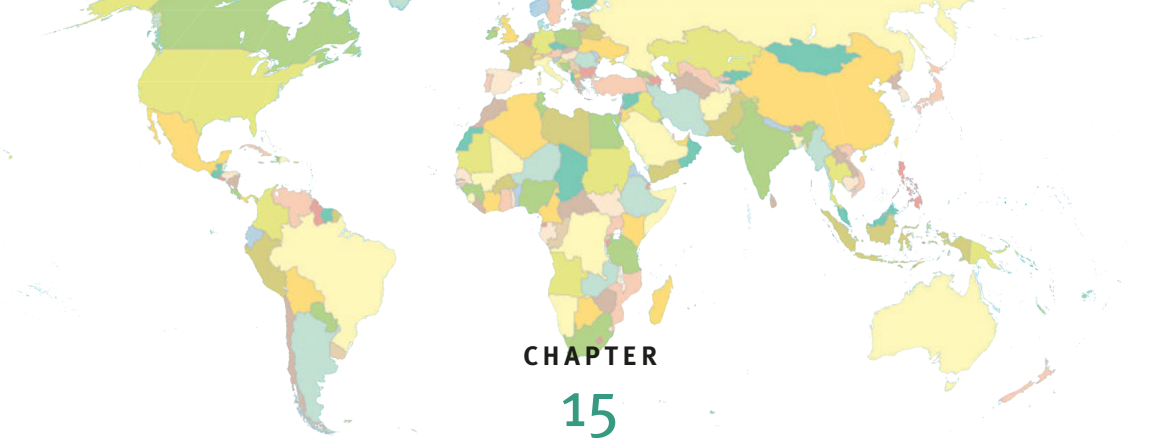

CHAPTER

15

Pediatric Travel Injuries: Risk, Prevention, and Management

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INTRODUCTION

World travel has reached unprecedented proportions in the past 2 decades, with international tourist arrivals increasing from 541 million in 1995 to more than 1 billion in 2013.[1] This figure includes more than 61 million Americans who traveled outside the United States.[2] In today's increasingly globalized world, travel itineraries are constantly expanding to include new locations previously inaccessible to most travelers, making many travel destinations accessible to new populations, including children and adolescents. The number of children who travel or live outside their home country has also increased dramatically; an estimated 2.2 million children traveled overseas in 2010.[3]

Children are now exposed to greater injury risks while traveling as a result of the increase in the number of travelers. Most travelers do not encounter any serious health problems; however, injuries are one of the leading causes of death among international travelers and the leading cause of death to healthy Americans traveling overseas. Injuries cause 23% of tourist deaths, compared with infectious diseases, which account for approximately 2% of deaths.[4] Exposure to unfamiliar and risky travel environments, differences in language and communications, exposure to unsafe products, inadequate safety standards for vehicles, unfamiliar rules and regulations, inadequate safety standards for travel

and tour operators, and a carefree spirit on vacation leading to greater risk-taking behaviors all contribute to the number of injuries that occur while traveling.[5]

Injuries are not inevitable and can be prevented or controlled. Travel clinics and health care practitioners can play a critical role in helping reduce injury risk among children and adolescents who travel by discussing travel and country risk factors and strategies to help avoid injury. Travelers should be advised about traffic and water safety, environmental risks, and personal safety. Families should be prepared to develop a plan for dealing with medical emergencies and advised on the importance of purchasing adequate medical and emergency evacuation insurance coverage. Adult caregivers should be prepared to provide closer supervision of children, be aware of basic first-aid procedures, and know how to access appropriate care, if needed, in their preferred language at their travel location.[6]

EPIDEMIOLOGY OF TRAVEL INJURIES

Global data on the incidence of various pediatric injuries associated with international travel are limited. It is likely that many of the injury risks that children face while traveling are similar to the risks they face at home, but the levels of protection available overseas and access to quality medical care may be substandard or absent. Hence, closer supervision of children while traveling overseas may be warranted to prevent injuries.

Mortality

According to the World Health Organization (WHO), injuries are among the leading causes of death and disability in the world, and they are the leading cause of preventable death in travelers. Among travelers, data show that injuries are one of the leading causes for consulting a physician, hospitalization, repatriation, and death. Worldwide, among people aged 5 to 29 years, injuries account for 7 of the 15 leading causes of death. US citizens abroad are 10 times more likely to die as the result of an injury than from an infectious disease; injuries cause 23% of deaths of US citizens while abroad, compared with only 2% caused by infectious diseases.[4] In a study that estimated the American tourist population using data from the World Tourism Organization, the injury mortality rate among US international travelers was higher than that among Americans residing abroad.[7]

From 2011 through 2013, an estimated 2,466 US citizens died from nonnatural causes, such as injuries and violence, while in foreign countries (excluding deaths occurring in the wars in Iraq and Afghanistan).

Motor vehicle crashes—not crime or terrorism—are the number 1 killer of healthy US citizens living, working, or traveling in foreign countries. From 2011 through 2013, road traffic crashes accounted for 25.2% of deaths to US citizens abroad. Other common causes of death included homicides (22.5%), suicides (15.9%), and drowning (12.5%).[4] Other less common but serious injuries are related to natural disasters, aviation accidents, drugs, terrorism, falls, burns, and poisoning and electrical shocks (1%).[8]

Morbidity

Although injuries may be the most likely health hazard for international travelers, very little epidemiologic data are available on the incidence of nonfatal injuries occurring during travel.[9] Injuries are reported as the primary reason US travelers are transported back to the United States by air medical evacuation; the main nonfatal causes are motor vehicle traffic–related injuries (45%); falls (8%); sports injuries, including diving into shallow water (4.5%); boating incidents (2%); aircraft crashes (1.5%); and burns. Contributing to the injury toll while traveling are exposure to unfamiliar and perhaps risky environments, differences in language and communications, less stringent product safety and vehicle standards, unfamiliar rules and regulations, a carefree holiday or vacation spirit leading to more risk-taking behavior, and overreliance on travel and tour operators to protect one's safety and security.

EPIDEMIOLOGY OF PEDIATRIC TRAVEL INJURIES

Epidemiology of Pediatric Injuries Across the Globe

Injuries account for about 36% of all child deaths throughout the world.[10] In 2010, injuries caused approximately 939,000 deaths in children and adolescents younger than 19 years.[10] Worldwide, injuries account for 6 of the 15 leading causes of death among people 5 to 44 years of age. Unintentional injuries account for almost 90% of these cases and are the leading cause of death for children 10 to 19 years of age.[11] Most of these injuries are the result of traffic crashes, drowning, burns (fire or scalds), falls, or poisoning.

Injuries vary by age. Suffocation, fires, drowning, and falls are among the leading causes of injury deaths among infants in many countries. Among 1- to 4-year-olds, drowning is often a leading cause of injury-related death, as is injury from road traffic crashes (including pedestrian injuries) and fires (as children become more independent). Drowning, road traffic injuries, and animal bites are the main causes of death in children 5 to 9 years of age in Asia, for example.[11]

Cuts and bruises are the most frequently seen nonfatal injuries in children. Arm and leg fractures are the most common nonfatal injuries requiring hospitalization in children younger than 15 years.

Traumatic brain injury (TBI) is the single most common—and potentially most severe—type of injury sustained by children[11] and can be mild (often referred to as concussion), moderate, or severe. Falls are the leading cause of TBI, especially in young children, with a significant risk of long-term consequences.[11]

COMMON PEDIATRIC TRAVEL INJURIES

Road Traffic Crash Injuries

Although young children do not drive motor vehicles, they do use roads as pedestrians, bicyclists, motorcyclists, and vehicle passengers.[4] Children's small stature makes them less visible and increases their injury risk on the road. Children are also more likely than adults to sustain a head or neck injury. A child's head, chest, abdomen, and limbs are still growing and relatively soft, making them physically more vulnerable to the impact of injury.[11]

Mortality

Road traffic injuries are the most common cause of injury death for tourists. Nearly 3,500 people die every day, including 1,000 children, worldwide as a result of traffic crashes involving cars, buses, motorcycles, bicycles, trucks, and pedestrians—a number likely to double by 2020.[12] More than 85% of these casualties (and 96% of child deaths) occur in low- and middle-income countries.[11] More than one-third of road traffic deaths in low- and middle-income countries are among pedestrians and cyclists. However, fewer than 35% of low- and middle-income countries have policies in place to protect these road users.[12]

In 2004, road traffic injuries accounted for approximately 262,000 deaths among children younger than 1 year to 19 years, which accounts for almost 30% of all injury deaths among children.[11] Globally, road traffic injuries are the leading cause of death among 15- to 19-year-olds and the second leading cause among 5- to 14-year-olds. Children up to 9 years of age are more likely to be accompanied by parents when traveling, in vehicles or as pedestrians, while older children tend to travel more independently, initially as pedestrians and later as bicyclists, motorcyclists, and finally drivers and passengers. The higher rates of mortality among older children are likely a result of this increased mobility as well as their increased tendency to engage in risk-taking behaviors.[11]

Morbidity

The number of children injured or disabled each year as a result of road traffic crashes is not precisely known but is estimated at around 10 million. This estimate is based on data from health care institutions, suggesting that children make up 20% to 25% of people admitted to a hospital because of injuries from a motor vehicle crash.[11] However, community-based surveys from Asia suggest that figure could be much higher.[13]

Motor vehicle traffic injures are the 10th highest cause of burden of disease in children younger than 15 years.[11] A child's head and limbs are the most common parts of the body injured in a motor vehicle crash. Injury severity varies depending on the child's age, road user, and whether protective devices (eg, seat belts) were used.

Risk Factors

In many low-income countries and rural areas, unsafe roads and vehicles and inadequate transportation infrastructure contribute to traffic crashes and injuries. Streets and roads in many countries often do not have crosswalks, signals, signs, and pedestrian refuge islands. Safely driving or crossing the road in a country where cars drive on the opposite side can be challenging and dangerous. An additional risk for crashes and injuries in developing countries includes cars, buses, and large trucks sharing the road with pedestrians, motorbikes, bicycles, rickshaws, and animals. Other factors that can increases the risk for motor vehicle crashes and injuries include

- Exposure to unfamiliar and risky roads and environments
- Use of alcohol, sleep aids, or drugs (including use among hired drivers)
- Lack of seat belt use
- Lack of motorcycle helmet use
- Increased risk-taking behavior as a result of a carefree vacation spirit
- Driving on the opposite side of the road
- Difficulty reading road signs and signals
- Unfamiliar road rules and regulations
- Overreliance on travel and tour operators to provide safety and security in vehicles
- Inadequate vehicle standards and poorly maintained cars, buses, and trucks
- Travel fatigue and jet lag
- Poor visibility from lack of adequate lighting on the road[4]
- Overcrowded buses and public transport conveyances
- Poorly constructed or designed roads, especially in mountainous terrain

For other tips for preventing motor vehicle traffic injuries for travelers, see Advice for Parents and Caregivers on page page 327.

Drowning

Mortality

Global data show that approximately 28% of all unintentional injury deaths among children are from drowning.[11] The overall global rate for drowning among children is 7.2 deaths per 100,000 population. Approximately 175,000 children and adolescents younger than 20 years around the world died as a result of drowning in 2004.[11] Drowning is the leading cause of injury-related deaths in children in many southeast Asian and western Pacific countries. Drowning accounts for 13% of deaths among Americans abroad and is the second leading cause of death in young travelers.[10] Drowning is also the leading cause of injury death among Americans visiting countries where water recreation is a major tourist attraction. There were 3,582 fatal unintentional incidences of drowning within the United States in 2005, an average of 10 deaths per day, and children 14 years and younger account for more than 25% of the drowning deaths. Children also die in boating-related incidents, which include drowning and other causes.[4]

Morbidity

There are no accurate estimates of serious nonfatal cases of drowning among children and adolescents. The WHO global estimates for nonfatal drowning among children younger than 1 year to 14 years are between 2 and 3 million each year.[11] For every child who dies from drowning in the United States, another 4 receive emergency department care.[14] Nonfatal drowning can cause brain damage that may result in long-term disabilities such as memory problems, learning disabilities, and permanent loss of basic functioning (ie, permanent vegetative state). One study also found that two-thirds of quadriplegic spinal injury admissions were linked with a history of steeply diving into shallow water while on vacation.[15]

Risk Factors

Risk factors for drowning among international travelers are not clearly defined but are suspected to be related to unfamiliarity with local water currents, riptides, and changing water conditions. General risk factors for drowning in children and adolescents, whether traveling or at home, include

- *Age and developmental stage.* Children younger than 5 years are at highest risk for drowning, followed by adolescents 15 to 19 years of age. A small child can drown in a few centimeters of water in a bucket, bath, or agricultural setting; children younger than 1 year most often drown in bathtubs, buckets, or toilets. In the United States, most drowning occurs in residential swimming pools among children 1 to 4 years of age.[16]
- *Gender.* Boys drown nearly twice as often as girls.
- *Lack of lifeguards.* Many swimming facilities may not have lifeguards. Studies show that lifeguards, especially those trained in attention and surveillance, can be a protective factor.[17,18]
- *Caregiver supervision.* Inadequate parent or caregiver supervision is an important risk factor for pediatric drowning. Most young children who drown in pools were last seen in the home, out of sight less than 5 minutes, and in the care of one or both parents.[19]
- *Lack of barriers.* In many countries, swimming pools, open bodies of water, wells, and rainwater collection container systems are not protected by fencing or barriers to keep children from gaining access.[20]
- *Natural water settings.* Most drowning in children older than 15 years occurs in natural water settings, such as lakes, rivers, and oceans and seas.[21] Children may not recognize hazards in an unfamiliar ocean or river. Hypothermia, rather than drowning, is the main cause of death at sea.
- *Absence of life jackets.* In 2013, the US Coast Guard counted 4,062 boating incidents involving injuries. Where cause of death was known, 77% of fatal boating accident victims drowned. Of those drowning deaths, 84% were not wearing a life jacket. Sixty-three percent (63%) of children who drowned were not wearing a life jacket.[22]
- *Unsafe vessels.* People are regularly transported in unsafe or overcrowded boats in many countries. Capsizing boats, ferries, and launches are a particular risk during the rainy season and certain times of the year, such as national holidays, when many people are likely to crowd onto boats.[4] Vessel safety standards and their enforcement vary widely around the world.
- *Alcohol.* Alcohol use is involved in up to half of adolescent and adult deaths associated with water recreation and about 1 in 5 reported boating fatalities.[23] Alcohol can trigger hypoglycemia and cause a rapid fall in body temperature, and it influences balance, coordination, and judgment. In addition, sun exposure and heat heighten the effects of alcohol.

- *Seizure disorders.* Drowning is the most common cause of unintentional death among children and adolescents with seizure disorders.[11]
- *Pools and spas.* Serious injuries can occur near outlets where suction is strong enough to catch small body parts or hair, trapping the head underwater. Other risks include slipping and tripping, which can lead to loss of consciousness on impact.

Burns

Mortality

A little more than 310,000 people worldwide died as a result of fire-related burns in 2004; 30% were younger than 20 years.[10] Fire-related burns are the 11th leading cause of death for children between 1 and 9 years of age. Children are at a high risk for death from burns; the global rate is 3.9 deaths per 100,000 population. Globally, infants have the highest death rate. Small children have a lower resistance to burn trauma and are less able to escape in a fire emergency. Smoke inhalation is strongly associated with mortality for children older than 3 years.

Morbidity

Little global data are available for nonfatal outcomes from burns. However, the Global Burden of Disease project makes it clear that burns are an important contributor to the overall disease burden in children.[10]

While burns from fire contribute to most burn-related deaths in children, scalds and contact burns are an important factor in overall morbidity and a significant cause of disability. The skin of infants and young children burns more deeply and quickly and at lower temperatures than thicker skin of adults. In addition, children's larger ratio of body surface area to volume means the size of a burn for a given volume of hot liquid will be greater than for an adult and there will be more fluid lost from the burnt area, thus complicating injury management. Chemical and electrical burns are relatively rare among children.[10]

Scald burns are the most frequent type of burn among children younger than 6 years. Typical scald burns occur when a child pulls down a container of hot fluid, such as a cup of tea or coffee, which spills on the child's face, upper extremities, and trunk. These are typically superficial second-degree burns. Despite the pain this causes the child and the parents' distress, these burns will typically heal within weeks, leaving little or no permanent damage.[10]

Burns to the palms of the hands are common among infants younger than 1 year as a result of touching cooking equipment, heaters, hot-water pipes, and cups containing hot liquid. Such contact burns may

be deep and require prolonged and careful therapy during the healing phase to prevent flexure contractures because the skin on a child's palm is thinner and withdrawal reflexes are slower.[10]

Risk Factors

Fires can be a significant risk in developing countries where building codes are not present or enforced and where there may not be smoke alarms or access to emergency services.[4] Other risk factors for burn injuries in children include

- *Unsafe equipment.* Hotels and residences in many countries are not designed to accommodate the safety of small children and often have unsafe electrical appliances, plugs, wires, and other connections that increase the risk of electrical burns.[10] Bathroom faucets may use different letters or colors for hot and cold water, and hot water from the tap may be scalding (in some developed countries, plumbing standards require temperature-limiting devices to protect from accidental scald burns). In addition, equipment used for heat, light, and cooking during trekking and camping may be inherently unsafe. Heating or cooking on open fires that are not enclosed or that stand at ground level pose significant dangers to children.[20]
- *Preexisting conditions.* Children with disabilities have a significantly higher incidence of burn injuries than children with no disabilities. Children with uncontrolled epilepsy also appear to be at greater risk for burn injuries.[10]
- *Fireworks.* Many countries celebrate religious or national festivals with fireworks, which pose a significant risk of burn injuries for children, particularly adolescent boys.[10] Fireworks manufactured in many foreign countries can be inherently dangerous and pose risks to anyone handling them. Firework displays should always be left to the professionals.
- *Environmental hazards.* Flammable substances such as gasoline, kerosene, and paraffin can combust easily and are poisonous. Most children's burns occur in the kitchen or in areas where food is prepared. This poses a special risk to children who congregate near the fire or stove during meal preparation.
- *Sun exposure.* In addition to skin cancers, overexposure to the sun, especially in countries close to the equator, can cause severe, debilitating sunburn and sunstroke, particularly in light-skinned individuals. Unprotected skin that is exposed to sunlight can experience a variety of dermatologic problems—some acute and some cumulative. Adverse skin reactions can also occur with sun exposure and the use of some

antimalarial drugs and antibiotics. Ultraviolet radiation may penetrate clear water to a depth of 1 meter or more.[24]

Falls

Mortality

An estimated 424,000 people of all ages died from falls worldwide in 2004, nearly 47,000 of whom were children and youth younger than 20 years. Falls are the 12th leading cause of death among 5- to 9-year-olds and 15- to 19-year-olds.[10]

Morbidity

Global nonfatal injury statistics are not readily available on falls in children. In most countries, falls are the most common type of childhood injury seen in emergency departments, accounting for 25% to 52% of assessments.[25] In addition, the Global School-based Student Health Survey identified falls as the leading cause of injury among 13- to 15-year-olds in 26 countries.[26]

Limb fractures, particularly of the forearm, are the most common type of fall-related injury in children beyond the age of infancy because children tend to protect their heads with their arms when falling.[27] Falls are also a leading cause of TBI, especially in young children, with a significant risk of long-term consequences. Approximately one-third of the 1.4 million people who sustain TBI in the United States are children aged 0 to 14 years.[11]

Risk Factors

Risk factors for falls in children include

- *Gender.* Boys are at greatest risk for fatal and nonfatal falls.
- *Family and social factors.* Falls in children are associated with single parenthood, unemployment, younger maternal age, low maternal education, caregiver stress, and mental health problems.[11]
- *Height of fall.* In general, the greater the height from which a child falls, the more severe the injury. Fall injuries from heights of more than 2 stories typically involve windows, balconies, and roofs. Falls from stairs, trees, and playground equipment are also common, as are falls into ditches, wells, shafts, and other holes in the ground.[11] Trees can be particularly hazardous, as can bunk beds, particularly in unfamiliar settings.[20]
- *Physical environment.* Safety regulations may not be enforced or even exist in many lower-income countries. As a result, there may be a variety of risks to children, such as high-rise buildings without window

guards, low balcony railings with enough space for young children to crawl through or over, or amusement park rides that are rarely inspected.[20] In addition, falls are more likely to occur with greater exposure to overcrowding and environmental hazards.[11]

- *Animals*. In recent years, studies from several developing countries have shown an increase in the number of children and young people presenting to the hospital as a result of falling from horses[11] and pets.[28]

Animal Bites and Stings

Mortality

Children account for 36% of all dog-bite fatalities in Australia and between 70% and 80% in the United States, with those 0 to 4 years of age and 5 to 9 years of age the most vulnerable.[11] There are limited data on fatal animal bites and stings in low- and middle-income countries.

Morbidity

Children tend to be fascinated with animals and insects, often use poor judgment around them, and may not report minor bites and stings. Children are particularly vulnerable to dog bites as a result of their small stature and because their face is usually close to the dog's mouth. Dog bites are a potentially serious injury and a frequent cause of hospitalization. Nonfatal dog bite–related injuries are highest among children 5 to 9 years of age. Children are more likely than adults to be bitten on the head or neck, which can lead to more severe injuries.[11]

A 2001 survey in Vietnam showed that around 360,000 Vietnamese children suffer animal bites each year, with dog bites accounting for almost 80% of these.[11] Animal bites in many developing countries can carry the added risk of rabies. In many areas where rabies exists, including India, China, and many parts of Africa, 40% of rabies cases occur in children. Rabies is the 10th most common cause of death from infection worldwide. There is evidence that between 30% and 60% of dog bite victims in endemic areas of canine rabies are children younger than 15 years.[11] Children who die from rabies were not treated or received inadequate postexposure treatment. Many bite victims do not receive rabies immunoglobulin due to a perennial global shortage.

Risk Factors

In many areas where rabies exists, 40% of cases occur in children. Stray dogs are common in many developing countries. Bat caves are popular tourist attractions in many countries. Monkeys, some of which have rabies, congregate around temples and other shrines in Southeast Asia.[4,20]

Swimming in unfamiliar waters, camping without repellents or protection, outdoor exposure at night, and walking in hostile and unfamiliar environments can increase risk of bites and stings.

Poisoning

Mortality

An estimated 345,814 people of all ages died worldwide as a result of poisoning in 2004. Of this number, an estimated 45,000 were children and adolescents younger than 20 years.[10] Poisoning is the 13th leading cause of death among 15- to 19-year-olds. The global death rate from poisoning is 1.8 per 100,000 population for children younger than 20 years.[11] Children younger than 1 year have the highest rate of fatal poisoning. The higher mortality rate in very young infants may be explained by greater susceptibility of the infant body to damage by toxins.[11]

Morbidity

Accurate global data on nonfatal outcomes of poisoning are not available. Data for 2006 from the American Association of Poison Control Centers showed that the most common poisonings among children were caused by pharmaceutical products. Inquiries relating to children younger than 6 years made up 50.9% of cases and 2.4% of total reported fatalities.[29]

Risk Factors

Common risk factors for children accidentally ingesting toxic substances include

- *Appearance.* Studies show that children prefer liquids over solids, clear liquids over dark, and small solids over large, and are more likely to ingest these.[11] Brightly colored solid medications may also be more attractive to children.
- *Storage and access.* A toxic substance within reach of a child is the most obvious risk factor for ingestion. Children may still ingest dangerous products that are stored in distinctive containers with visual warning labels (eg, skull and crossbones) because they often do not understand the meaning of these signs.[11] Some studies indicate that stickers, such as skull and crossbones and Mr. Yuk, are ineffective deterrents and can even attract children to the toxic product.[30,31]
- *Safety precautions.* No child-resistant container is the perfect deterrent. Tests show that up to 20% of children between the ages of 42 and 51 months may be able to open a child-resistant container.[32] The poison-prevention value of a tamperproof container is lost when the

top is not replaced properly. Thus, child-resistant containers should never replace parent or caregiver supervision.

Data from poison control centers and hospitals in the United States[11] indicate that the most common agents involved in child poisonings include

- Over-the-counter medications, such as aspirin, ibuprofen, cough and cold remedies, iron tablets, antihistamines, and anti-inflammatory drugs
- Prescription medications, such as antidepressants, narcotics, and analgesics
- Recreational drugs, such as cannabis and cocaine
- Household products, such as bleach, disinfectants, detergents, cleaning agents, cosmetics, and vinegar
- Pesticides, including insecticides, rodenticides, and herbicides
- Poisonous plants
- Animal or insect repellent

Factors determining the severity of poisoning and its outcome in children include

- Poison type
- Dose
- Formulation
- Exposure route
- Child's age
- Presence of other poisons
- Child's nutrition status
- Presence of other diseases or injuries

ADVICE FOR PARENTS AND CAREGIVERS

Clinicians should advise parents that the best way to keep their children safe is to practice prevention.[4,9,20,33] Families should be encouraged to use their judgment about what types of travel are appropriate for their children. Families should be advised to

- Check the health, safety, and security information for their destinations on the Centers for Disease Control and Prevention (CDC) Travelers' Health (www.cdc.gov/travel) and the US Department of State (www.travel.state.gov) Web sites.
- Consider learning basic first aid and cardiopulmonary resuscitation, as well as bringing a travel medical (first aid) kit customized to their anticipated itinerary and activities. The kit should include basic health information (eg, name, birth date, vaccination history, current medication use [with dosages noted], known medical allergies, blood type,

chronic health conditions). Antiseptic solutions and lotions, bandaging supplies, and perhaps splinting material could also be included.[20]

- Educate their children. Parents should inform and educate their children in age-appropriate ways about risk factors for injuries, as well as how injuries can be prevented. Parents should always encourage their children to wear safety devices, and they should act as role models by adopting safe behaviors and using safety devices.[3,20]
- Wear MedicAlert identification if they have chronic health conditions. Such identification may help a health care professional access medical information about the traveler in event of an emergency.[20]
- Avoid unnecessary risk taking while traveling. Understandably, many tourists travel to participate in activities that are not part of their usual routine. Doing so provides novel experiences but can also lead to situations in which the traveler is completely inexperienced (eg, driving a motorcycle for the first time). Adolescents, in particular, may be inclined to take risks that can lead to injury or death.[6]
- Identify doctors and hospitals in the cities they are visiting prior to departure. Names and addresses of local health care professionals at the travel destination can be obtained from a number of sources, including the International Society of Travel Medicine (www.istm.org) and International Association for Medical Assistance to Travelers (www.iamat.org). Embassies and consulates also have lists of local English-speaking physicians.[4,20,33]
- In the event of an emergency, try to take their children to the largest medical facility in the area. Such facilities are more likely to have pediatric units and trauma services. Parents should ask for the diagnosis, test results, and treatments administered before leaving the facility; this information will be very helpful for ongoing treatment.[20] Travelers should seek medical care in a neighboring country if medical care facilities in the country they are visiting cannot provide rapid, effective, or safe medical treatment.
- Carry an international-capable cell phone for emergency contacts within the country of travel, as well as for any help needed while abroad.

Some specific recommendations that clinicians should provide to travelers for avoiding common pediatric travel injuries are described as follows:

Motor Vehicle Traffic Crash Injuries

- Bring a child safety seat(s) from home.
- Use safety belts and child safety seats whenever possible. Safety belts reduce the risk of death in a crash by 45% to 60%, child safety seats by 54%, and infant seats by 70%.[4]
- When possible
  - —Rent newer, better-maintained vehicles with safety belts and air bags.
  - —Avoid riding a motorcycle or motorbike for the first time. Vacationing in a foreign land is not a safe way to learn how to ride.
  - —Rent larger vehicles, if possible, because they provide more protection in a crash.
  - —Try to ride only in taxis with functional safety belts, and ride in the rear seat.
  - —Avoid driving at night or on mountainous roads (or both).
- Wear a helmet when riding a motorcycle, motorbike, bicycle, or horse. Helmets should be brought from home if they are likely to be unavailable at the travel destination.
- Consider hiring a driver who is familiar with the travel destination and language and is an expert in maneuvering through local traffic.
- Avoid riding on overcrowded, overweight, top-heavy busses or minivans or with any driver who has consumed or is consuming alcohol.
- Visit the Web sites of the Association for Safe International Road Travel (www.asirt.org) and Make Roads Safe (www.makeroadssafe.org). These organizations have useful safety tips for international travelers, including road safety checklists and country-specific driving risks.

Drowning

- Closely supervise children around water at all times. No one is advised to dive in water whose depth is unknown.
- Children should always wear flotation devices, such as life jackets. Appropriate water safety devices, such as life vests, may not be available abroad; families should consider bringing them from home.
- Wear protective footwear in water to avoid injury in marine environments.
- Avoid boarding unsafe or overcrowded vessels.
- Seek advice from local sources or tour guides about potential dangers, such as currents and tides, before swimming in open water.
- Travelers who wish to participate in potentially dangerous water activities, such as diving and jet skiing, should only use reliable, scheduled, and official water sports services. Travelers should ensure

they are thoroughly briefed by operators on safety procedures of the particular water sport in which they will be participating. Operators should ensure the safety of tourists as much as possible.[3,4,20]

Burns

- Select accommodations on the sixth floor or below (fire ladders generally cannot reach above the sixth floor) whenever possible to minimize the risk of fire-related injuries. If possible, stay in hotels with smoke alarms and, preferably, sprinkler systems. Carry your own battery-operated smoke alarm if you are not sure that the hotel has them. Travelers should identify 2 escape routes from buildings and remember to escape a fire by crawling under the smoke and covering their mouth with a wet cloth.[4]
- To avoid scalds, always check the temperature of water coming from the tap and supervise young children bathing to reduce the chances of expelling scalding water.
- Always carry and use sunscreen to avoid severe burns from sun, especially in tropical climates.
- Teach children to stop, drop, and roll in the event that their clothes catch on fire.
- If a child does suffer a serious burn, he or she should be stabilized before being transported to a hospital. Explain to parents that
  - The overall aim of first aid is to cool the burn and prevent additional burning and contamination.
  - First aid treatment for burn injuries is best accomplished with cool, clean water.
  - Traditional treatments, such as applying butter, oil, or other substances on burns, can be harmful, as they can cause the skin to slough away, leaving lower layers exposed and susceptible to infection.[11]
- The American College of Surgeons and American Burn Association recommend that children with the following conditions be treated in a burn center[34]:
  - Partial-thickness (second-degree) burns greater than 10% of the total body surface area
  - Burns involving the face, hands, feet, genitalia, perineum, or major joints
  - Full-thickness (third-degree) burns

Falls

- Wear an approved helmet, correctly fitted and specific to the sport, when engaging in adventure activities (eg, zip lines, rock climbing, horseback riding). Bring a helmet from home if they are unlikely to be available at the travel destination.[4,5,20]
- Be aware that hotels and homes visited may not be childproofed. There may not be gates on stairs.

Animal Bites and Stings

- Do not allow children to play with a dog unless an adult supervises. Never leave infants or young children alone with a dog.
- Careful supervision is required of children traveling to tropical, subtropical, and desert areas for risks from venomous snake, scorpion, and spider bites and stings. All venomous bites should be considered a medical emergency requiring immediate medical attention.
- Aquatic animals, such as eels, stingrays, scorpion fish, jellyfish, and sea lice, can inflict serious harm. Swimming in waters populated with these organisms carries a high risk for children.
- Mosquito, tick, flea, fly, and other insect bites can transmit diseases such as river blindness, dengue, Lyme disease, and sleeping sickness in some parts of the world; children should be protected with bed nets, mosquito nets, and insect repellents.
- Repellents should be used in strict accordance with manufacturer instructions; the dosage must not be exceeded, especially for young children and during pregnancy.[24]
- Children should be taught to immediately tell adults about any contact, bites, or stings from any animal or insect.
- Seek medical care immediately in the event of a bite. Thoroughly wash mammal-associated injuries with water and soap (and povidone-iodine if available) and promptly assess the child to see if rabies post-exposure prophylaxis is needed.
- Avoid eating food around animals, such as dogs or monkeys, in case they jump for the food and bite the child in the process.[3,4,11,20]
- Obtain local advice on the presence of dangerous aquatic animals before swimming.
- Wear shoes when walking on the shore or water's edge.
- Seek medical advice if a bite or sting from a poisonous animal is suspected.

Poisoning

- Keep all drugs in secure containers and locations that young children cannot reach.
- Avoid taking medicine in front of children because they often copy adults.
- Be alert for improperly vented heating devices, which may cause poisoning from carbon monoxide.
- Do not call medicine "candy."
- Be aware of any legal or illegal drugs that guests may bring into your home. Do not let guests leave drugs where children can find them, such as in a pillbox, purse, backpack, or coat pocket.
- Do not put the next dose of medicine on the counter or table where children can reach it.
- Never leave children alone with household products or drugs. If an adult is using chemical products or taking medicine and has to do something else, such as answer the phone, children should accompany the adult.
- In the event of accidental poisoning
  - Remain calm.
  - Call a doctor or go to a hospital or clinic immediately. Carry the Poison Help number, 1-800-222-1222 (in the United States), for immediate advice on a possible poisoning incident.
  - Try to have the following information ready:
    - Victim's age and weight
    - Container or bottle of the poison, if available
    - Time of the poison exposure[3,4,11,20]

HEALTH INSURANCE AND MEDICAL EVACUATION ISSUES

Travel insurance is one of the most important safety nets available to travelers in the event of accidents and injuries; travel health advisers should reinforce this advice.[6] Clinicians and health advisors should inform travelers about the possibility of purchasing special travel insurance that includes medical evacuation or air ambulance transport if their destinations include countries where there may be difficulties accessing adequate medical care.[3,4] Such insurance generally provides worldwide, 24-hour telephone hotlines that direct callers to English-speaking physicians and hospitals, pay for treatment and hospitalization at the time of the incidence, and, when medically indicated, arrange and pay for evacuation to a medical facility that can provide necessary treatment. Examples of companies that provide such insurance include MEDEX (www.medexassist.com) and International SOS (www.internationalsos.com).[20]

If purchased, travelers should verify insurance coverage for illnesses and accidents while abroad before departure. They should be advised to read their policies carefully to see what is covered and to check for any exclusions. In particular, travelers with known preexisting conditions who are working long-term overseas or undertaking any form of hazardous recreational or occupational activities may need to obtain a special travel insurance policy. In addition, travelers who wish to participate in potentially dangerous activities, such as skydiving, mountain climbing, scuba diving, or jet skiing, should ensure that their travel insurance will cover them in the event of accidents, as many of these activities may not be covered.[6,20]

SOME PSYCHOSOCIAL EFFECTS OF CHILD INJURIES

Children's immature abilities to understand and process immediate and long-term effects of traumatic events and injuries—whether their own or exposure to events that traumatize or injure parents or loved ones—can make them vulnerable to psychosocial effects afterward. The physical and emotional consequences of experiencing or witnessing injuries can continue long after the initial event. On every level—physical, medical, psychological, emotional, and social—children have unique needs and vulnerabilities that must be taken into account after a traumatic injury.[35,36]

Children can be at risk for a variety of psychosocial responses after a traumatic injury or disaster, including post-traumatic stress disorder, anxiety, depression, somatic disturbances, learning problems, and behavioral disorders. Children's stress reactions may vary depending on age but typically include

- Reexperiencing the trauma during play, dreams, or flashbacks
  - Repeatedly acting out what happened in the disaster when playing with toys or with other children
  - Nightmares or repeated dreams about the disaster
  - Becoming distressed when exposed to reminders of the disaster
  - Acting or feeling as if the disaster is happening again
- Avoiding disaster reminders
  - Avoiding activities that remind of the disaster
  - Being unable to remember all or parts of the disaster
  - Withdrawing from other people
  - Having difficulty feeling positive emotions
- Increased arousal symptoms
  - Difficulty falling or staying asleep
  - Irritability
  - Difficulty concentrating
  - Startling more easily

- Depressive symptoms
  - General emotional numbness
  - Crying
  - Changes in appetite
  - Fatigue
  - Insomnia or not wanting to sleep alone
  - Sadness
  - Loss of interest in previously preferred activities
- Fears
  - Being left behind or separated from family
  - Thinking something will happen to a family member
  - The dark
  - Being alone
  - Believing the child caused some part of the traumatic event
- Behavioral symptoms
  - Regressive behaviors, such as acting like a younger child (eg, bed-wetting, baby talk)
  - Irritability
  - Whining
  - Clinging
  - Aggressive behaviors or angry outbursts at home or with other children
  - Hyperactive or silly behaviors
  - Dangerous risk-taking behaviors, such as high-risk sexual behavior or use of alcohol or other drugs (in adolescents)
- Somatic symptoms
  - Headache
  - Stomachache
  - Nausea
  - Dizziness

Risk Factors

A variety of studies identified risk factors that influence response to trauma and affect recovery. Children and adolescents who experienced any of the following events are more likely to experience long-term difficulties and may be at higher risk for developing psychopathology[37]:

- Injury.
- Trauma (eg, disasters, sexual abuse, motor vehicle crash).
- Witnessed a traumatic event (eg, fire, shooting, drowning, beating).
- Preexisting mental health issues (eg, depression, anxiety disorders).
- Exposure to disturbing or grotesque scenes or to extreme life threats.
- Social isolation.

- Being very upset during and after an injury or traumatic event.
- Becoming separated from parents or caregivers.
- Parents or caregivers died, were significantly injured, or are missing.
- Family members or friends died.
- Physical disabilities or illness.

Evaluations of children who experienced or witnessed injuries or traumatic events should assess

- Behavioral and psychiatric symptoms, including
  - Experiences during or soon after travel that were painful or hard to reconcile or still cause distress, anxiety, or avoidance
  - Persistent sleep disturbance or unusual fatigue
  - Excessive use of alcohol or drugs (in adolescents)
  - Behavioral or interpersonal difficulties at home or school or with friendships or relationships
- Somatic symptoms that can also be indications of distress, including
  - Unexplained somatic symptoms, such as headache, backache, or abdominal pain, and somatic disorders, such as chronic fatigue syndrome, temporomandibular disorder, and irritable bowel syndrome
  - Rashes, itching, and skin diseases, such as psoriasis, atopic dermatitis, and urticaria, which can be exacerbated by stress

Clinicians should be aware that some children and adolescents may be reluctant to acknowledge psychiatric symptoms or distress. For example, many cultures have stigmas associated with experiencing or disclosing behaviors associated with mental illness, as well as different culturally appropriate ways of expressing grief, pain, and loss. In addition, some children and adolescents may fear being stigmatized if they are labeled with a psychiatric diagnosis.[35,37]

The returning child or adolescent traveler who is having difficulty functioning or who appears unduly depressed or distressed should be referred to appropriate treatment or counseling regardless of the type or duration of travel and whether the child appears to meet criteria for a psychiatric diagnosis.

KEY POINTS

- In today's increasingly globalized world, travel itineraries are constantly expanding to include new locations previously inaccessible to most travelers, making many travel destinations accessible to many new populations, including children and adolescents.
- Children are now exposed to greater injury risks while traveling as a result of the increase in the number of child and adolescent travelers (an estimated 2.2 million children travel overseas each year).

- Injuries are one of the leading causes of death among international travelers and the leading cause of death to healthy Americans traveling overseas. Injuries are still the most frequent cause of death abroad in developing countries.
- Effective prevention strategies are available, particularly for travelers with children or adolescents who find themselves in new environments and who may be more likely to be unaware of risks or complacent in exotic surroundings.
- Health care professionals can be important allies to alert the public to the known risks and especially about simple and effective preventive measures to implement during international travel.
- Clinicians can play a critical role in helping reduce the injury risk among children and adolescents who travel by discussing travel and country risk factors and strategies to help avoid injury.
- Travelers should be advised about traffic and water safety, environmental risks, and personal safety. They should be prepared to develop a plan for dealing with medical emergencies and be advised on the importance of purchasing adequate medical and emergency evacuation insurance coverage.
- Adult caregivers should be prepared to provide closer supervision of children, be aware of basic first aid procedures, and know how to access appropriate care, if needed, at their travel location.

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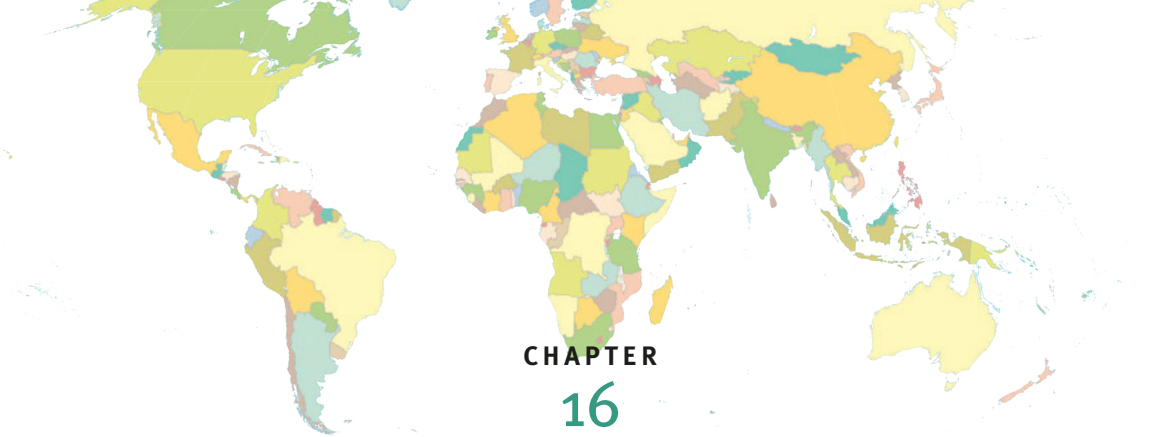


CHAPTER

16

Insect Bite Prevention

David R. Boulware, MD, MPH, CTropMed

INTRODUCTION

When one imagines the most dangerous animals in the world, images of lions stalking prey on the African Savannah, Bengal tigers silently slipping through the bush, or rampaging elephants leap to mind. In reality, the world's deadliest creature is much, much smaller—it is the mosquito. The mosquito has stopped armies, caused the rise and fall of empires, and still causes an estimated 1 to 3 million deaths annually.[1]

While mosquitoes are the most obvious insect vector of infectious diseases, there are many others. Biting arthropods that are potential disease vectors include ticks, mites, lice, tsetse flies, *Triatoma* (kissing) bugs, phlebotomine sand flies, fleas, *Simulium* blackflies, and *Chrysops* deerflies. The mechanism of infection varies by disease but primarily is from direct inoculation via bites. Yet in other cases, rubbing the arthropod's feces into bite wounds can cause disease, notably for *Triatoma* bugs (Chagas disease), human body louse (typhus, *Bartonella quintana*), and fleas (murine typhus). Regardless, avoiding infectious vectors and bites is the best prevention for vector-borne disease.

Malaria and mosquitoes are typically the primary focus for insect bite prevention, as malaria is the leading killer of children younger than 5 years in sub-Saharan Africa. Before the World Health Organization (WHO) Roll Back Malaria Partnership, an estimated 1 in 17 persons worldwide died of a mosquito-borne illness.[2] Caution and perspective are warranted because, although mosquitoes are insects, not all insects are mosquitoes. Results from mosquito studies cannot be generalized to

all biting insects. Table 16-1 lists the primary flying insects that serve as vectors for human disease.

Interventions for insect avoidance can be summarized into interventions on public and individual levels. Although many interventions are one and the same, what will work for an individual often may fail to protect a population. Thus, the intended goal affects the choice of intervention. In general, interventions that require an individual's active compliance with use, such as frequently applying insect repellent, will fail to protect a population. Individual personal protective measures to prevent vector-to-human contact, while effective, are often the least reliable means of disease control because they require considerable motivation, perseverance, and financial resources to maintain ongoing effectiveness.

PRINCIPALS OF PUBLIC HEALTH INTERVENTIONS

Three critical components (Figure 16-1) are necessary for vector-borne disease transmission.

1. *Reservoir* of disease
2. *Susceptible host*
3. Competent *vector* with contact between the reservoir and susceptible host

The appropriate public health intervention may vary depending on specifics of each of these factors for a given disease.

Disease Reservoir

Every infectious disease has a reservoir. Zoonotic diseases, by definition, cross the species barrier. Eliminating the reservoir of disease is often impossible when zoonotic diseases cross species. However, when the reservoir is only humans, such as smallpox or polio, eradication is possible. The current list of diseases with only human reservoirs that could potentially be eradicated includes poliomyelitis, dracunculiasis, mumps, rubella, lymphatic filariasis, and trichuriasis (whipworm). Although reservoir eradication can be the most effective method to confront disease, most vector-borne diseases are not amenable to eliminating the disease reservoir.

Elimination of Susceptible Hosts

Elimination of susceptible hosts can prevent vector-borne disease. Vaccination is the primary method to decrease susceptible hosts. Three basic necessities are generally needed for vaccine development. The first is the experiment of nature, as natural infection should convey a long-lasting natural immunity following recovery from primary infection.

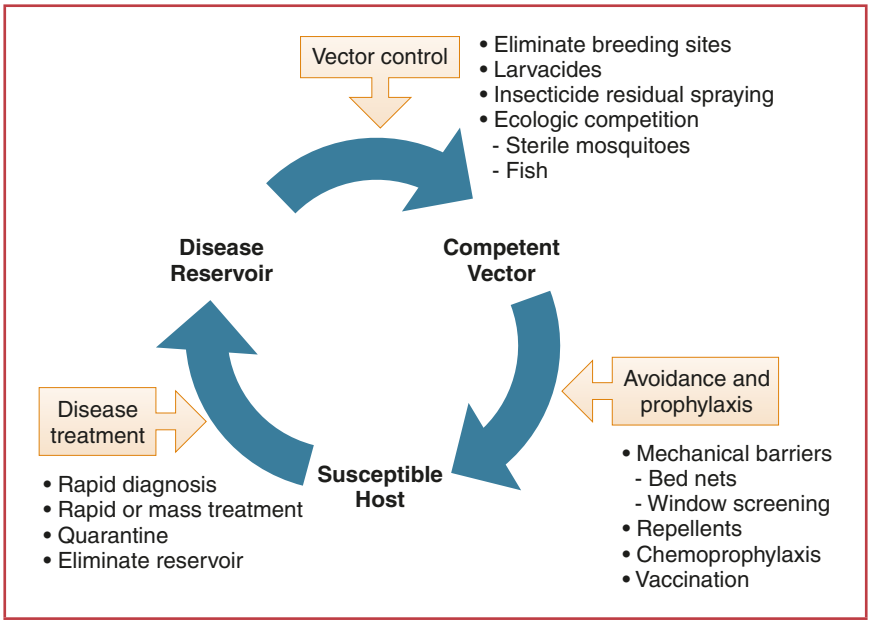
Table 16-1. Summary of the Principal Flying Insect Vectors for Human Disease Transmission				
DISEASE	**PRINCIPAL VECTOR[a]**	**GEOGRAPHY**	**LOCALE**	**BITING TIME**
Malaria	*Anopheles* (approximately 45 competent vectors)	Tropics worldwide	Temperature: 16°C–33°C Altitude: <2,000 m	Dusk to dawn primarily
Dengue	*Aedes aegypti* *Aedes albopictus*	Tropics, subtropic areas Tropics, subtropics	Urban	Daytime
Yellow fever	*Aedes aegypti* *Aedes africanus* *Haemagogus*	Tropic/subtropics Africa South America	Urban Forest/jungle Forest/jungle	Daytime
Chikungunya	*Aedes aegypti* *Aedes albopictus*	Tropic/subtropics	Urban	Daytime
Viral encephalitis				
• Japanese encephalitis	*Culex tritaeniorhyncus*	Asia	Pig is preferred feeding source.	Night
• West Nile encephalitis	*Culex pipiens, Culex univittatus;* also *Aedes, Anopheles*	Worldwide	Varies and is indoors	Night
• Eastern equine encephalitis	*Coquillettidia perturbans, Aedes sollicitans, Aedes taeniorhynchus, Culiseta,* other *Culex, Aedes*	Western hemisphere	Freshwater hardwood swamps	Various
• Western equine encephalitis	*Culex tarsalis, Aedes dorsalis, Aedes melanimon*	Western hemisphere	Warm, moist environments	Various
• La Crosse encephalitis	*Aedes triseriatus*	North America	Deciduous forest	Daytime
• St. Louis encephalitis	*Culex* (*Culex nigripalpus, Culex pipiens, Culex quinquefasciatus, Culex tarsalis*)	Western hemisphere	Various	Night
• Murray Valley encephalitis	*Culex annulirostris*	Australia	River valleys	Dusk and dawn
• Venezuelan equine encephalitis	*Culex* (*Melanoconion*), approximately 40 species implicated	Latin America	Wetlands	Varies

Table 16-1. Summary of the Principal Flying Insect Vectors for Human Disease Transmission, continued

DISEASE	PRINCIPAL VECTOR[a]	GEOGRAPHY	LOCALE	BITING TIME
Filariasis				
• Lymphatic filariasis (*Wuchereria bancrofti, Brugia malayi, B timori*)	Multiple mosquito species, including *Anopheles, Aedes, Culex, Coquillettidia, Mansonia*	Africa Asia Indonesia	Various	Dependent on local vector; most at midnight
• *Mansonella*	*Culicoides* (midges or no-see-ums) (*Simulium* blackflies for *M ozzardi*)	Africa, South America Latin America	Various, often near banana plantations	Midnight
• *Loa loa*	*Chrysops silacea* and *C dimidiata* (deerflies)	Africa	Rain forest	Bright sunlight
• Onchocerciasis	*Simulium* (blackflies)	Africa, foci in Latin America	Savannah or forest; do not enter homes	Day
Leishmaniasis	*Phlebotomus* and *Lutzomyia* (sandflies)	Africa, South Asia, Latin America, Mediterranean foci		Dusk and night
Tularemia	*Chrysops discalis* (deerfly) and also ticks	Western North America	Shady areas	Daytime
Trypanosoma				
• Acute sleeping sickness *T brucei rhodesiense*	*Glossina* (tsetse flies)	East Africa	Savannah	Daytime, bright sunlight
• Chronic sleeping sickness *T brucei gambiense*		West Africa	Waterside	Daytime, bright sunlight

[a] Mosquito vectors unless otherwise stated.

Figure 16-1. Vector-borne Disease Prevention Strategies



Second, the type of immune response needed for protection must be known. Third, an organization must be willing to fund and support vaccine development. Unfortunately, many vector-borne diseases are limited in their geographic scope or are neglected diseases with minimal commercial incentive. Where there is global interest, such as with malaria, the challenge remains great. Diseases, such as malaria, without natural long-lasting immunity and in which reinfection frequently occurs are not easy vaccine candidates. The goal of current malaria vaccine development is to reduce disease severity and prevent mortality, not prevent infection. Such pragmatic goals can improve global health, but the complete elimination of susceptible hosts is often near impossible.

Vector Control

When neither the reservoir nor susceptible hosts can be eliminated, the focus of public health interventions turns to disrupting the vector-mediated transmission of disease. Successful public health interventions often require targeting more than one aspect of transmission. Appreciating the vector ecology and life cycle allows targeting multiple stages of the vector's life cycle to interrupt transmission. Classic strategies are to remove breeding sites, kill the ova or larvae, kill the vector, repel the vector, or use community-wide measures to develop physical

separation between the vector and susceptible host. For mosquitoes, successful prevention techniques are often multifaceted to target multiple stages of the mosquito life cycle and behavior.

BREEDING SITE REMOVAL

Mosquito breeding is confined to water collection that is amenable to drainage, such as swamps, rain pools, stagnant sewage, or water cisterns. Removing larvae breeding sites is the most effective method of mosquito control. This may be possible through engineering to create better drainage and prevent standing water. In cases of sizable wetlands, drainage is not possible without significant adverse ecologic impact.

Historically, eliminating breeding sites was the primary method of mosquito control. After Walter Reed proved that the *Aedes aegypti* mosquito transmitted yellow fever, William C. Gorgas famously eliminated yellow fever from Havana in 30 days even though yellow fever had been present in Cuba for 300 years. Gorgas' approach was 2-fold. First, *Aedes aegypti* breading sites were aggressively eliminated by enacting fines for property owners harboring breeding sites (a punitive public-private partnership). The transmission cycle was then interrupted by isolating hospitalized yellow fever patients with screening and netting to create physical separation between the reservoir and vector.

Breeding site elimination requires significant, sustained, and well-coordinated public health efforts. The urban nature of *Aedes aegypti,* coupled with the ubiquitous use of plastic containers, creates an infinite amount of suitable breeding sites for this and *Aedes albopictus* species. However, each species of mosquito has unique behaviors, breeding patterns, and ecologic niches. Knowledge of the vector and its habits is essential to eliminate breeding sites.

LARVAL CONTROL

Larval control methods historically used oils and hydrocarbons to coat the surface of stagnant water to kill mosquito larvae. More bio-ecologically friendly approaches now focus on products with minimal adverse environmental effect. The WHO recommends the addition of 1 bacterial larvicide and 4 insecticide chemical compounds to drinking water as larvicides: *Bacillus thuringiensis israelensis,* methoprene, pyriproxyfen, temephos, and novaluron. These have been assessed by the WHO International Programme on Chemical Safety and are believed to be safe for use in potable water. A summary of the larval control compounds is provided in Table 16-2.

Bacillus thuringiensis israelensis is a natural soil gram-positive bacterium used to disrupt larval progression. It produces d-endotoxins that

Table 16-2. Larval Control Measures

LARVAL CONTROL METHOD	MECHANISM	TARGET
Bacillus thuringiensis israelensis	Crystal δ-endotoxin, gut disruption, enteric bacterial infection, death	Mosquitoes and blackfly larvae
Methoprene	Juvenile hormone analog, stops development	Mosquito pupa
Pyriproxyfen	Juvenile hormone analog, stops development	Mosquito pupa
Temephos	Nonsystemic organophosphate	Flea, mosquito, blackfly, or sand fly larvae
Novaluron	Inhibits chitin synthesis, prevents molting	Mosquito larvae

are toxic to mosquito larvae gut epithelium by forming pores that lead to cell lysis. This disrupts mosquito larvae gut epithelium, leading to sepsis from enteric *Enterococcus* and *Enterobacter* species present in the larval midguts.[3] *Bacillus thuringiensis israelensis* is a highly effective intervention with no apparent adverse ecologic effect. It has been incorporated into bioengineered crops to resist pests and decrease chemical pesticide usage.[4]

Another method is methoprene, which disrupts the mosquito's biological life cycle by keeping larval mosquitoes from maturing into adults. Methoprene mimics the juvenile hormone found in immature mosquitoes.[5] The juvenile hormone must be absent for a mosquito pupa to molt into an adult. Pyriproxyfen acts by similar mechanisms, as a juvenile hormone analog; it is also used in many countries on citrus fruit to decrease agricultural pests.[6]

Temephos is a nonsystemic organophosphate larvicide used to treat water infested with flea, mosquito, blackfly, or sand fly larvae. Temephos is the primary larvicide used in the guinea worm (dracunculiasis) eradication program and the WHO Onchocerciasis Control Programme.[7] While temephos has a very short persistence in the water (approximately 2 hours), it does have toxicity for freshwater aquatic invertebrates, saltwater shrimp, oysters, and some fish species. Use in all geographic areas is not possible and depends on local aquatic species.

Lastly, novaluron is a benzoylphenyl urea insecticide that inhibits chitin synthesis. This affects the molting stages of larvae development because chitin is a necessary cytoskeleton component. Prior field studies

demonstrated effectiveness at suppressing immature mosquito larvae and pupa for 3 to 7 weeks after a single application in polluted water and without any adverse effect on freshwater fish or aquatic plants.[8] Novaluron is the most recent of the larvicides, registered in the United States in 2004 and the European Union in 2007.

KILLING ADULT VECTORS

Insecticides have been used since the 1940s for mosquito control. The most infamous insecticide is DDT. The insecticide properties of DDT were not discovered until 1939 by Paul Hermann Müller, who was subsequently awarded the 1948 Nobel Prize in Physiology or Medicine. DDT is active against a wide variety of arthropods, including mosquitoes, fleas, and lice. In World War II, environmental spraying reduced malaria in the South Pacific and eliminated typhus spread by lice. DDT was the cornerstone of the WHO malaria eradication program from 1955 to 1969 with widespread environmental spraying; however, with extensive indiscriminate use, resistance in mosquitoes developed and toxicity in wildlife occurred. DDT is concentrated up the food chain with avian species; notably, the American bald eagle is dramatically affected, with increased fragility of its eggs. DDT was banned in the United States in 1972, but worldwide use continued. Three of the major mosquito vectors for human disease are displayed in Figure 16-2.

Indoor Residual Spraying

Indoor residual spraying (IRS) is the application of long-acting insecticides inside domestic housing. The primary effects of IRS toward curtailing malaria transmission include reducing mosquito life span so that mosquitoes can no longer transmit malaria parasites from one person to another and reducing the density of the vector mosquitoes. In some situations, IRS can lead to the elimination of locally important malaria vectors.

Figure 16-2. Principal Mosquitoes Responsible for Human Disease

Malaria vector in West and Central Africa

Vector for dengue, yellow fever

Vector for chikungunya; secondary vector for dengue

With IRS, insecticide is sprayed on the internal walls and roofs of houses to kill adult vector mosquitoes that land on treated surfaces. Typically, after feeding, mosquitoes land on nearby surfaces to rest and digest their blood meal. While resting, the mosquitoes pick up the insecticide and are poisoned by the neurotoxic effects. *Anopheles* species have a predilection toward landing on vertical surfaces; thus, indoor walls are a target for IRS treatment. Most insecticides act through acetylcholine esterase inhibition; however, development of resistance is possible with transient instead of fatal neurotoxicity. As well, some mosquitoes can exhibit behavioristic avoidance in which they alter their behavior and avoid landing on treated surfaces.

The majority of IRS systems use insecticides; DDT is one of these. The current estimate is that 4 to 5 million kg of DDT are used annually for targeted IRS programs worldwide, primarily in Africa and India. DDT is less expensive than some other organophosphate and carbamate insecticides, such as malathion; however, DDT is approximately the same cost or more than synthetic pyrethroids, such as deltamethrin and permethrin, which require less frequent applications than DDT and thus a lesser amount for IRS treatment.[9]

Example of Public Health Interventions

The WHO Global Malaria Eradication Program (1955–1969) focused on vector control with DDT and reducing the reservoir by treating infected persons with chloroquine. Although ultimately unsuccessful, temporary gains were achieved where the program was implemented. Notably, this program was never implemented in sub-Saharan Africa. After the malaria eradication program was discontinued, malaria and dengue rapidly increased in many regions.

Several lessons were learned from this program. Interventions must be sustained or the premature discontinuation will result in disease resurgence. Multiple interventions are often necessary; relying on a single agent (eg, DDT and chloroquine) will eventually generate resistance and fail. While vectors may align with climate, ecosystem, and altitude, vectors rarely align with geopolitical map lines. Thus, implementation strategies for reducing disease burden need to encompass the geographic boundaries of the disease and vector, not political boundaries. Filariasis control programs are a good example of projects defined by disease boundaries and not by geopolitical borders. Lack of political leadership can greatly hamper control programs, a good example being a polio eradication program.

A representative public health program that uses a multitiered strategy is the current Roll Back Malaria Partnership, launched in November

1998. Roll Back Malaria has 4 pillars (Table 16-3) and a goal to decrease malaria-related mortality. The mechanisms to achieve this goal are multi-focused to decrease vector transmission, as well as to implement rapid effective treatment, which decreases the disease reservoir.

COMMUNITY-WIDE PREVENTION MEASURES

Improving local living conditions is often an effective intervention for preventing some vector-borne diseases. Simple interventions, such as screened windows and doors, decrease mosquito-to-human contact. The marked reduction in malaria in the United States during the 1920s and 1930s was principally the result of improvement in housing and living conditions. For diseases such as American trypanosomiasis (Chagas disease), replacing thatched roofs and dirt floors is a highly effective intervention to decrease *Triatoma* infestation and reduce vector-to-human contact.[10,11]

Community-wide surveillance of disease is necessary. Promptly identifying and treating newly infected persons eliminates disease reservoirs. For diseases with obvious stigmata, such as yellow fever, smallpox, or measles, surveillance is straightforward. For malaria, access to diagnostic medical care and public health surveillance are essential. Historically, standard approaches used passive surveillance and reporting at the national level. Not surprisingly, such approaches are slow and largely locally dependent. In resource-limited areas, the ability to generate a timely response is difficult.

With increased technology such as the use of mobile phones, novel approaches for disease surveillance may be more successful. The penetration of mobile phones worldwide creates a potential ubiquitous information platform even for moving populations such as travelers. Harnessing this technology may be an innovative approach to rapidly report field epidemiology. Rapidly identifying malaria outbreaks is a pillar of the WHO Roll Back Malaria Partnership.

Table 16-3. World Health Organization Roll Back Malaria Partnership

ROLL BACK MALARIA PARTNERSHIP PILLARS	PUBLIC HEALTH STRATEGY
1. Prevention, with an emphasis on insecticide-treated nets	Vector avoidance
2. Rapid diagnosis and treatment	Reservoir reduction
3. Rapid response to malaria epidemics	Reservoir reduction/susceptible host
4. Treatment of pregnant women	Susceptible host

Personal Protective Measures

Methods of personal protection are quite effective, when used. There are a variety of behavioral interventions known to reduce insect bites for an individual (Box 16-1). Since the 1950s in North America, mosquitoes were viewed as pests that cause annoyance or discomfort but rarely disease. With the emergence of West Nile virus, the North American general population has more recognition of the dangers of mosquito-borne illness. While mosquito avoidance is traditionally recommended in regions with malaria, one must recognize that other mosquito- and tick-borne illnesses are worldwide. For example, *Aedes aegypti,* the dengue vector, is an urban daytime-biting mosquito expanding in geographic range since the 1960s.[13] Tick-borne disease also occurs worldwide, with increasing incidence of Lyme disease and anaplasmosis in North America. Exposure in recreational populations is frequent. In one prospective cohort study of US Appalachian Trail backpackers, nearly 5% acquired Lyme disease.

Box 16-1. Behavioral Recommendations for Mosquito Avoidance

- Avoid unprotected exposure during peak biting periods.
  - *Anopheles* species feed before and after sunset and again before dawn (malaria vector).
  - *Aedes aegypti* feed throughout the day (dengue, yellow fever vector).
  - *Aedes triseriatus,* eastern tree-hole mosquito. Females feed any time (La Crosse encephalitis vector).
  - *Culex pipiens* species feed throughout the evening and night (West Nile virus, St. Louis virus, *Sindbis* virus, Rift Valley fever, bancroftian filariasis vector).
  - *Culex tritaeniorhyncus* feeds primarily on pigs, with a short average flight span of less than 2 km (Japanese encephalitis vector).
- Stay in well-screened housing.
  - Window screens should be in good state of repair.
  - Doors and window should be tight fitting.
- Minimize exposed skin with long-sleeved shirts and long trousers.
- Light-colored clothing is less attractive for mosquitoes.[12] In tick regions, tuck trouser legs into boots or socks.
- Avoid blue-colored clothing in tsetse fly areas.
- Use insecticide-treated mosquito netting when sleeping outdoors or in poorly screened or unscreened buildings.
- Use insecticide-treated mosquito netting on children younger than 2 years.
- Indoor residual spraying is a primary vector control intervention to create spatial protection against mosquitoes for a living unit.
- Outdoor spraying with insecticidal fog or mist (often permethrin) is effective only for 7 days or fewer. Permethrin is degraded by ultraviolet light.
- Insect light electrocuting devices (“bug zappers”) do not reduce biting mosquitoes.

Repellents

Preventive measures, including the use of repellents (Box 16-2), are simple and effective. Not all repellents act against all insects; the effectiveness of repellents may vary by mosquito species. Even when standard, safe, effective repellents are available, lack of individual compliance jeopardizes repellents' effectiveness. In a plethora of studies, including American travelers to Africa, soldiers,[14] aid workers,[15] and Boy Scouts,[16] antimosquito measures were employed by fewer than 50%, even when recommended. Although repellents are protective for an individual, repellent use often does not correlate with reduced incidence of vector-borne disease in a population.[14,15] First, most repellents require frequent application (eg, every 4 to 6 hours), and erratic application does not protect individuals. Second, personal repellents simply shift vector-feeding behaviors to other unprotected persons. Thus, while an individual may be protected, those individuals not using a repellent in the immediate vicinity are at higher risk of acquiring mosquito bites.

DEET

Insect repellents are very effective for a compliant individual willing to reapply every 4 to 6 hours. Diethyltoluamide (DEET) is the first choice among repellents because it has been extensively tested for more than 50 years and performs reliably under a variety of real-world conditions.[17]

Box 16-2. General Suggestions for Repellents

- Apply diethyltoluamide (DEET) sparingly on exposed skin.
- Do not use repellent under clothing.
- Do not use DEET on the hands of young children (ie, those putting their hands in their mouth).
- Have parents or older children apply DEET to young children.
- Avoid applying to areas around the eyes and mouth.
- Do not use DEET over cuts, wounds, or broken skin.
- Wash treated skin with soap and water after returning indoors.
- Do not use on clothing. DEET is a plasticizer and will dissolve many synthetics.
- Do not use combination DEET-and-sunscreen protection as application frequency and amount differ.
- Avoid spraying in enclosed areas.
- Do not use DEET near food.
- Use caution with newer synthetic insect repellents (toxicity in children is unknown; efficacy against variety of insects is unknown).
- Icaridin at 20% concentration is likely equivalent to 20% DEET, though with less of a safety record in children.
- Icaridin at 9% to 10% is a reasonable substitute for DEET where the risk of serious disease is low (eg, North America) or exposure is short (<2 hours).

DEET concentrations up to 30% have increasing repellency, but further protection above 30% is minimal.[18] In a field trial, the percent protective efficacy of extended-duration 32% DEET against *Anopheles stephensi* at 3, 6, and 9 hours was 99.3%, 92.8%, and 79.7% for females and 100%, 97.6%, and 91.9% for males.[19] In a field trial, extended-duration 35% DEET provided more than 10 hours of protection against the daytime biting *Aedes* mosquito.[20] In an arm box study, 23.8% DEET offered complete protection for 6 hours compared with a soybean oil–based repellent (1.5 hours).[18] In a field trial, a mosquito-repellent soap (20% DEET with 0.5% permethrin) reduced malaria to 3.7% (23 of 618) compared with 8.9% (47 of 530) of the placebo soap group.[21]

SAFETY DATA ON CHILDREN

DEET

The skin absorption of DEET in relation to age has not been studied specifically. However, data from similar substances suggest that skin absorption should not differ above 2 months of age. DEET is not water soluble, but unlike many sunscreens, it does not wash off. Sunscreens require more frequent application and in greater concentration than DEET. Thus, combined sunscreen-and-DEET products should not be used. Repeated excessive DEET application increases the risk of toxicity. The American Academy of Pediatrics Council on Environmental Health states that DEET concentrations of 10% appear to be equally safe in children as concentrations of 30% when used according to the product directions.[22] Reapplication is recommended for most repellent products every 4 to 6 hours, and repellents should not be used on non-intact skin. DEET is not recommended for use on newborns and infants younger than 2 months.

Icaridin/Picaridin

Icaridin (also known as picaridin and KBR 3023; trade names Bayrepel and Saltidin) is a relatively new mosquito repellent with similar efficacy at 19.2% concentration compared with 20% DEET over 9 hours.[23] Attractive features of icaridin are lack of odor and that it does not dissolve plastics or synthetic polymers, such as nylon or Gore-Tex, unlike DEET. Icaridin may be an option for those unwilling to use DEET. There is accumulating evidence of icaridin efficacy from in vitro laboratory studies and field trials. In arm box studies, *Aedes aegypti* and *Anopheles stephensi* mosquitoes, as well as the sand fly *Phlebotomus papatasi,* were repelled by DEET and icaridin.[24–27] The originally marketed US commercial formulations did not use the proven 19.2% concentration but

rather lesser concentrations of 5% to 10%. Efficacy of 9.3% icaridin is less, with complete protection for only 2 hours.[23,28–34] While this may be adequate protection in areas with few mosquitoes, such as suburban North America, extended duration of protection is suboptimal. Long-term safety data are unknown, as icaridin has been distributed only since 1988. Safety data in children remain limited.

Key findings from a series of field trials in different locations, with different vectors, different mosquito biting pressures, and a variety of temperatures and humidity levels, have revealed the following findings[23–34]: First, icaridin repellence of 19.2% concentration in field trials generally appears equivalent to recommended DEET concentrations. A second key finding is that icaridin has dose-dependent repellence activity and the 19.2% formulation is superior to the 9.3% formulation. Icaridin is widely used in Germany as a mosquito repellent, but data on other arthropods are scant. The efficacy of icaridin against the vector of African tick fever (*Amblyomma hebraeum*) at 2 hours was 56% compared with DEET efficacy of 84%.[27] In a study of lone star ticks *Amblyomma americanum,* 10% and 20% formulations of icaridin had protection for 12 hours.[35] In vitro studies and laboratory arm box studies cannot fully substitute for field trials.

Permethrin Passive Protection

Passive methods to reduce mosquito exposures are more likely to be consistently effective. Three primary examples exist: the first is IRS; the second is sleeping under a bed net, which is ideally pretreated with an insecticide; and the third is to soak or spray clothes pretravel with 0.5% permethrin. Permethrin binds to clothing and is still effective after up to 10 washings.[36] Treating clothes or objects, such as tents, not only protects the individual but also offers nearly 50% protection to others in the immediate vicinity.[16] Permethrin-treated clothing alone has a 70% mosquito reduction rate and, in combination with DEET, a 99% effectiveness against ticks and mosquitoes, even under extremely high biting pressures.[37,38] Repellents are still highly recommended, but such a recommendation is tempered by the real-world practicality that fewer than 50% of individuals consistently comply with the reapplication needed for repellency efficacy.[14–16]

It is important to note that permethrin is not a repellent but an insecticide that causes toxicity to the mosquito by acting as an acetylcholinesterase inhibitor. However, permethrin is not approved by the US Food and Drug Administration for chronic application to the skin and should not be used topically. Permethrin, a semisynthetic insecticide derived from the chrysanthemum flower, is shown to reduce the incidence

of bloodsucking arthropod attachment and mosquito bites for longer than 6 weeks after a single application to clothing. Treating bed nets and clothing with permethrin can be used as an adjunctive measure in addition to repellents. Pyrethroids are stable in heat and humidity and through a number of wash cycles. Washing permethrin-treated uniforms reduces permethrin concentration by 60%, but the concentration is not reduced further after subsequent washings (up to 20 times).[39]

One interesting aspect of permethrin use is the ability to provide passive prophylaxis in the immediate vicinity by treating other objects. A randomized, double-blind, controlled trial of 0.4% permethrin used to treat canvas tents at a Boy Scouts summer camp showed that permethrin-treated campsites had 44% fewer bites over an 8-week period after a single permethrin application.[16] Two previous pilot studies examined permethrin-treated tents. Eight volunteers sleeping inside a permethrin-treated tent had an 84% to 94% reduction of mosquito bites.[40] Even those sleeping outside of a treated tent had a 43% to 82% reduction of mosquito bites.[40] The duration of effectiveness of tent treatment is at least 6 to 12 months.[41,42]

There are variety of pyrethroid analogs. Deltamethrin is a common pyrethroid used in the treatment of mosquito bed nets. Beyond bed nets, other options exist where compliance with a bed net may be imperfect, most often due to heat and humidity. In a field trial in a malaria endemic area, treating bedsheets with permethrin, α-cypermethrin, or deltamethrin reduced the incidence of bites, but deltamethrin caused more skin irritation.[43] In one field trial, deltamethrin-treated bed nets significantly reduced the incidence of malaria transmitted by *Anopheles culicifacies*.[44]

DEET AND PERMETHRIN

Permethrin-treated clothes are more effective for preventing mosquito bites when used with a repellent applied to exposed skin. The combination of permethrin on clothing and DEET on skin results in a formidable barrier that provides 99.9% protection against mosquito bites, even under conditions in which unprotected subjects received an average of 1,188 bites per hour.[14] The US military uses a DEET-based repellent and permethrin-treated clothing to prevent arthropod-borne disease. Permethrin and DEET have shown efficacy, alone and in combination, also against *Aedes taeniorhynchus*. In a field trial, combined use was most effective (average of 1.5 bites per 9-hour day), compared with 53.5 bites with permethrin-treated clothing only and 98.5 bites with only DEET on exposed skin.[45] Against tsetse flies, the combination of

permethrin-impregnated clothing and controlled-release DEET provided 91% mean protection but was not significantly better ($P>0.05$) than DEET alone.[46]

NEW REPELLENTS

Use caution when considering the use of newer synthetic insect repellents, particularly for children. The rationale for this recommendation is that DEET has a 70-year track record of known efficacy and safety, and not all insects are the same. Testing methods are important because some repellents perform well in low biting-pressure situations, but as mosquito bites and landings increase, efficacy and duration of protection may decrease dramatically. Oddly, some of the marketed, commercially available concentrations of new repellents do not match their field-tested concentrations. This is particularly true for the less than 10% icaridin formulations marketed in North America. Until more field testing of new synthetic agents is completed for a wide variety of arthropods, do not substitute any of the following agents for DEET:

- α-Permethrin
- Deltamethrin (useful for pyrethroid resistance)
- N,N-diethyl acetanilide (DEPA)
- 1-(3-cyclohexen-1-yl-carbonyl)-2-methylpiperidine (AI3-37220)
- Metofluthrin
- Icaridin at 5% to 10% concentrations (Some caution should exist for advocating icaridin use in locales where there is a prolonged exposure of >2 hours and serious risk of vector-borne disease.)

The rationale for not widely substituting where vector-borne diseases exist is 4-fold. First, isolated tests against a single insect species may not predict protection against a variety of insects or different species of the same insect. Second, while various botanical and essential oils show promise as repellents, field testing under high-biting conditions is needed. Third, the active moiety of a new repellent is not always well characterized, and minor manufacturing differences may make significant real-world differences. For example, AI3-37220 has multiple optical stereoisomers that have 2-fold differences in mosquito repellency.[47] Thus, minor manufacturing differences could significantly alter the repellence. Fourth, human toxicity data are limited on many of the newer compounds, particularly in children. Overall, there remains significant consumer appeal for natural alternatives to chemical repellents, so testing of promising agents will likely continue in the future.

Existing Evidence on Newer Repellents

DEPA showed repellence against *Aedes aegypti* for 6 to 8 hours in the laboratory. Under field conditions, there was no significant difference between DEPA and DEET at 0.25 and 0.5 mg/cm^2 against blackflies and mosquitoes.[48] In a study comparing 25% piperidine repellent AI3-37220 with 35% DEET, both provided more than 95% protection against *Anopheles kiliensis* for 2 hours.[49] Metofluthrin-impregnated multilayer paper strips reduced bites from *Culex quinquefasciatus*, *Anopheles balabacensis,* and *Anopheles sundaicus*.[50] In a follow-up on field study, hanging metofluthrin-impregnated plastic strips in homes in Tanzania decreased indoor mosquitoes by 99%, including *Anopheles gambiae*.[51] Another field trial in Vietnam also demonstrated efficacy of metofluthrin-impregnated strips against *Aedes albopictus* and *Culex quinquefasciatus*.[52] Fifteen controlled trials of slow-burning mosquito coils showed a reduction in the number of bites; however, none of the trials used malaria prevention as an outcome.[53] These slow-burning mosquito coils effectively vaporize airborne insecticides.[54]

Repellency data on essential oils are limited but not very promising compared with synthetic repellents. Essential oils should not be recommended for use where vector-borne disease exists. In a study of the mosquito repellent activity of 38 essential oils, undiluted oils of *Cymbopogon nardus* (citronella), *Pogostemon cablin* (patchouli), *Syzygium aromaticum* (clove), and *Zanthoxylum limonella* (makaen) provided at least 2 hours of repellent effect. Diluted oils showed little effect. Clove oil was the most effective overall but is a potential contact allergen.[55] Oils of lemon eucalyptus (*Eucalyptus maculata citrodion*), rue (*Ruta chalepensis*), oleoresin of pyrethrum (*Chrysanthemum cinerariaefolium*), and neem (*Azadirachta indica*) all show some repellent action. Oil of lemon eucalyptus, DEET, and pyrethrum were more effective than rue and neem.[56] A eucalyptus-based repellent containing 30% p-menthane-diol provided 97% protection against an *Anopheles* mosquito for 4 hours, similar to DEET.[57] Andiroba oil 100% (*Carapa guianensis*) was superior to soybean oil but inferior to 50% DEET as a repellent for *Aedes*. The first and third bites occurred at 60 and 101 seconds with soy oil and at 56 and 142 seconds with Andiroba oil. There were no bites within 1 hour in the DEET group.[58] Cocoa oil has shown some protection against *Simulium damnosum*.[59] Among other botanical repellents, 2% a-terpinene, a citrus essential oil, was superior to DEET against *Culex pipiens* in one study.[60] Similarly, g-terinene was highly toxic to *Aedes albopictus* larvae.[61] In another botanical study, neem oil and DEPA showed similar repellent activity against *Phlebotomus papatasi* (sand fly), a vector of

leishmaniasis.[62] Regarding ticks, in a field trial, lemon eucalyptus extract reduced *Ixodes ricinus* tick bites. While the repellent was used, the median number of attached ticks decreased from 1.5 to 0.5 ($P<0.05$).[63] One of the critical considerations in assessing insect repellents' effectiveness is the biting pressure in which a study is conducted.

KEY POINTS

- Fundamental methods of decreasing vector-borne disease include decreasing the disease reservoir, susceptible hosts, and the vector or contact with the vector.
- Vector control requires sustained efforts, financial resources, and public health infrastructure.
- Insect repellents are effective for an individual if used as recommended; however, they are not effective on a population level.
- In infants and children older than 2 months, DEET less than 30% is likely the preferred insect repellent.
  - —DEET has a long safety record.
  - —Combination sunscreen-and-DEET products should not be used.
- Icaridin 19.2% has similar efficacy as 20% DEET.
  - —Dose-dependent activity up to at least 19.2%
  - —Limited safety data in children

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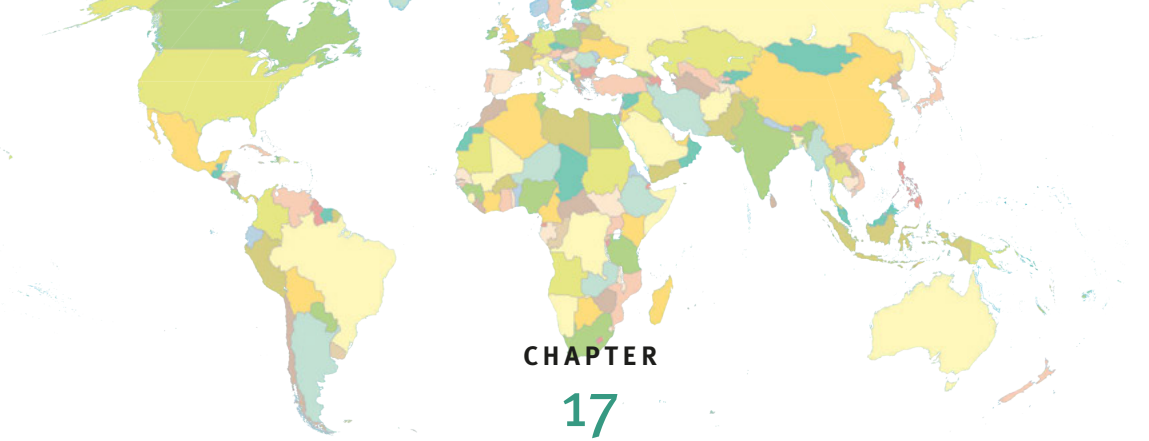

CHAPTER

17

The Ill-Returned Traveler

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INTRODUCTION

Children commonly accompany their parents to international destinations; an estimated 2.2 million children travel overseas annually.[1] The purpose of parents' travel may be leisure, business, mission work, or visiting friends and relatives. When children return ill after international travel, they typically present to their primary physician's office or the emergency department. Evaluating and managing illness in the returned pediatric traveler is often a challenging process because of the extensive list of possible infectious etiologies that must be considered. Routine as well as destination-specific pathogens are common, the epidemiology of which is influenced by age-specific variation in immunity and behavior. When fever is one of the presenting complaints, urgent evaluation is mandatory to identify and promptly treat potentially life-threatening infections such as malaria.

Research on illnesses in returning pediatric travelers is limited. Diarrheal illness is usually the most common diagnosis, followed by dermatologic conditions and systemic febrile and respiratory illnesses.[2,3] A prospective controlled study of travelers to the tropics revealed that diarrhea and abdominal pain are the most frequent complaints of children and adults.[4] When evaluating an ill-returning traveler, it is important to obtain a comprehensive history and perform a detailed physical examination to promptly identify more serious infections and narrow differential diagnoses. Approaching the evaluation in a systematic fashion helps ensure a timely and cost-effective workup.

HISTORY

When taking the history of a returned traveler, document details about the trip, including the destination(s) and activities. Box 17-1 lists topics about which questions can be asked to help obtain specific details about the trip. It is important to ask if pretravel medical advice was sought, if the child is up-to-date on routine vaccines, and whether the child received the recommended destination-specific vaccines. Many travelers visiting friends and relatives do not receive pretravel consultation and destination-specific vaccines and thus lack protection during their travel. This is keenly important to people previously from malaria-endemic areas who appear to lose their acquired immunity after living outside of the endemic area for a year or two. They often underestimate their need of malaria chemoprophylaxis, placing themselves at risk for symptomatic severe malaria. In addition to inquiring about chemoprophylaxis, it is also important to determine if bed nets and other personal protective measures, such as insect repellents, were regularly used.

Gathering these details about the trip allows the practitioner to determine exposures that may have led to the present illness. Exposures to consider typically include those related to food and water, the environment, insects, contact with animals, and various activities. Table 17-1 lists possible exposures with their corresponding risks for particular infections. The risk of certain infections varies by age group secondary to age-dependent immunity and behavior. Children younger than 2 years have a relatively immature immune system, which increases their risk for routine and travel-related infections. As children become older and more mobile, they often spend more time outdoors, where they may come into contact with various pathogens, vectors, or animals. Furthermore, adolescents who engage in a variety of high-risk activities may be susceptible to infections related to intravenous drug use, sexual contact, body piercing, and tattooing.

Comparing the time of exposure with the incubation periods of specific pathogens and the patient's symptom sequence enables the practitioner to narrow the list of potential diagnoses. Many resources

Box 17-1. Trip Specifics

- Destination(s)
- Travel dates/duration of trip
- Rural versus urban location
- Type of lodging (eg, upscale hotel, budget hotel, tent, private homes)
- Type of activities

Table 17-1. Example Exposures and Corresponding Risk for Certain Infections	
EXPOSURE	**INFECTION RISK**
INGESTION	
Untreated water	Hepatitis A and E, enteric bacteria, amebiasis, *Giardia*
Unpasteurized dairy	Brucellosis, salmonellosis, listeriosis
Undercooked meat	Cysticercosis, trichinosis, enteric bacteria
BITES	
Mosquito	Malaria, yellow fever, dengue, filariasis, other arboviruses
Sand fly	Bartonellosis, leishmaniasis
Tsetse fly	African trypanosomiasis
Tick	Rickettsioses, Q fever, borreliosis, ehrlichiosis/anaplasmosis, tularemia
Flea	Plague, tungiasis
Reduviids	American trypanosomiasis (Chagas disease)
Blackfly	Onchocerciasis
Mites	Scrub typhus
Lice	Epidemic typhus, trench fever
Mammal	Rabies, tularemia, bacterial cellulitis, rat-bite fever
ACTIVITY EXPOSURE	
Freshwater contact	Schistosomiasis, leptospirosis
African game parks	African trypanosomiasis, malaria, rickettsial diseases (eg, Africa tick bite fever), botfly
Caves	Histoplasmosis, Marburg virus
Rivers	Leptospirosis, onchocerciasis
Barefoot (sand, dirt, mud)	Strongyloides, hookworm, cutaneous larva migrans
Body fluid exposure	Hepatitis B or C, HIV, syphilis, chlamydia, gonorrhea

From Summer A, Stauffer WM. Evaluation of the sick child following travel to the tropics. *Pediatr Ann.* 2008;37(12):821–826. Reproduced with permission of SLACK Incorporated.

are available that summarize incubation periods for a variety of travel-related infections. Table 17-2 provides an abbreviated list of common infections with typical incubation periods. GIDEON (www.gideononline.com) is a very useful diagnostic travel program that formulates an extensive differential diagnosis based on a patient's symptoms, destination, and reported exposures.

PHYSICAL EXAMINATION

A thorough physical examination may provide additional clues for the diagnostic process. Carefully review vital signs for evidence of severe systemic illness such as fever, tachycardia, tachypnea, or hypotension, which can be associated with a life-threatening infection such as malaria. A child with a fever and relative bradycardia may have an infection with an intracellular pathogen such as *Salmonella enterica* subspecies *enterica* serovar *Typhi* or *Babesia*. Respiratory findings such as wheezing and rales are commonly associated with viral or bacterial infections but may also occur with more exotic pulmonary infections. The presence

Table 17-2. Typical Incubation Periods for Certain Travel-Related Infections

SHORT (<14 d)	MEDIUM (≤2–6 wk)	LONG (>4–6 wk)
Arboviruses	Amebiasis	American trypanosomiasis
Babesiosis	Babesiosis	Enteric protozoa/helminths
Dengue	Brucellosis	Fascioliasis
Enteric bacteria	Hepatitis A, E	Filariasis
Leptospirosis	Leptospirosis	Hepatitis B, C
Malaria	Malaria	HIV
Meningococcal disease	Melioidosis	Leishmaniasis
Plague	Schistosomiasis	Malaria
Polio	Strongyloides	Strongyloides
Rickettsial disease	Trichinosis	Trichinosis
SARS	Tuberculosis	Tuberculosis
Strongyloides	Tungiasis	Typhoid Fever

Abbreviation: SARS, severe acute respiratory syndrome.

From Summer A, Stauffer WM. Evaluation of the sick child following travel to the tropics. *Pediatr Ann.* 2008;37(12):821–826. Reproduced with permission of SLACK Incorporated.

of a petechial rash is worrisome because it may indicate a serious infection, such as meningococcemia, rickettsial, yellow fever, or other hemorrhagic fever. Altered mentation, meningism, or a focal neurologic deficit should prompt an immediate evaluation for central nervous system (CNS) infections.

Developing a Differential Diagnosis by Signs and Symptoms

All presenting symptoms should be recorded even if they initially appear unrelated. Fever, reported in up to 25% to 30% of cases, is of special concern.[5] Documenting the timing and sequence of symptoms relative to potential exposures is imperative. When a fever is present, initial efforts should focus on identifying and treating potentially life-threatening infections. Once life-threatening infections are eliminated, a systematic approach may be used to determine appropriate laboratory and imaging studies.

Life-Threatening Infections

Malaria

Travelers presenting with fever who visited a malaria-endemic area must be assumed to have malaria until proven otherwise. In humans, malaria is caused by 1 of 5 protozoan *Plasmodium* species, which is transmitted by the bite of an infected female *Anopheles* mosquito: *P falciparum, P vivax, P ovale, P malariae,* or *P knowlesi*. Malaria transmission occurs in much of Africa (highest rates of transmission), Asia, Central and South America, Hispaniola, and the South Pacific. Africa is also where *P falciparum,* the most lethal and drug-resistant species, predominates.[1] *P vivax,* the most prevalent species in Asia, is associated with a relapsing course but is typically not fatal. In children, malaria usually presents with nonspecific symptoms such as fever, chills, myalgia, fatigue, and headache. Classically described periodic fever patterns are not helpful for diagnosis because they are seldom noted until the infection has been present for many days. In young children, respiratory and gastrointestinal symptoms may also occur, which can easily confuse the evaluation and lead to mistaken diagnoses of gastroenteritis or respiratory infections. A febrile child who traveled to a malaria-endemic region should always have malaria excluded, even in the presence of other symptoms, such as gastroenteritis.

Laboratory findings in children with malaria are also nonspecific but often include thrombocytopenia, neutropenia, and an elevated C-reactive protein. Anemia commonly occurs but may be due to a variety of other causes, including nutritional deficiencies.

Hyperbilirubinemia and mildly elevated liver enzymes may also be observed, especially in children with severe or chronic infection. Hypoglycemia, hyponatremia, and acidosis are indicative of a severe disease. Other indicators of severe malaria include impaired consciousness and respiratory distress, which are shown to be associated with a high risk of death.[6,7] Cerebral malaria can occur in children infected with *P falciparum* and leads to a spectrum of neurologic symptoms ranging from mildly depressed sensorium to deep coma. Focal motor deficits and opisthotonic posturing may be observed. Mortality rates vary depending on available resources and timeliness of treatment but range from 7% to 50%.

Diagnosing malaria is traditionally accomplished with thick and thin blood smears, the sensitivity and specificity of which depend on the parasitemia level and laboratory personnel experience. Alternative, non-microscopic methods, such as rapid antigen tests and polymerase chain reaction (PCR)-based methods, are being used more commonly. Rapid antigen tests are generally fast, easy to use, and have high sensitivity and specificity, especially for *P falciparum*.[8,9] When rapid diagnostic methods are not available, presumptive treatment should always be initiated until the diagnosis can be confirmed.

Bacterial Etiologies

Potentially life-threatening bacterial infections can also occur in pediatric travelers, most notably typhoid fever and meningococcemia. Vaccines are available for these infectious diseases; however, they are not fully protective. Typhoid fever is caused by the bacterium *S Typhi* and is transmitted by the fecal-oral route. The highest incidence of typhoid fever occurs in south-central and southeast Asia.[10] Regions of medium incidence include the rest of Asia, as well as less-developed areas in Africa, Latin America, and the Caribbean. Approximately 400 cases of typhoid fever and 100 cases of paratyphoid occur annually in the United States, the majority of which are reported in travelers.[1] Clinically, typhoid presents with fever, headache, abdominal pain, constipation, diarrhea, and rash. Diagnosis is made by isolating the causative organism in blood or stool, although neither method is very sensitive. Treatment options include a third-generation cephalosporin, fluoroquinolones, and azithromycin; however, emerging antibiotic resistance, especially to fluoroquinolones, is increasingly reported.[11]

Travelers to sub-Saharan Africa, as well as those who participate in the hajj pilgrimage in Saudi Arabia, may be at risk for meningococcal disease. Attack rates of the serogroup A meningococcal strain peak annually during the dry season within the “meningitis belt” of Africa,

which extends from Mali to Ethiopia.[12,13] Serogroup W-135 has caused epidemic disease in West Africa and in hajj visitors.[14] Clinical signs and symptoms of meningitis most often include fever, headache, nausea, vomiting, and stiff neck. These symptoms can rapidly progress and result in death if they are not recognized and treated promptly with antibiotics. Immediately administering antibiotics is justified, even before performing a lumbar puncture, unless it can be performed without delay. Meningococcal meningitis is characterized by typical cerebrospinal fluid (CSF) findings (eg, high white blood cell count, low glucose) and confirmed by isolating the causative agent in blood or CSF. The slightly increased risk of negative cultures from early antibiotic administration is more than offset by decreased risk of mortality. Meningococcal infections are typically treated with ceftriaxone or penicillin G (in cases in which the isolate is proven susceptible).

Dengue

Dengue, a mosquito-borne *Flavivirus* infection, is prevalent in warm-weather climates in rural and urban areas of Asia, Africa, and the Americas. The infection is carried by the *Aedes aegypti* mosquito and has a short incubation period (3–14 days). Symptoms often include fever, headache, myalgia, arthralgia, and rash. Muscle aches can be so severe that the infection is sometimes referred to as breakbone fever. Diagnosis is clinical and may be confirmed through dengue-specific antibody tests. Treatment is supportive care. Patients should be monitored for bleeding complications that may occur in dengue hemorrhagic fever or dengue shock syndrome. These complications rarely occur in travelers but are important to recognize because they may progress to disseminated intravascular coagulation and hemodynamic instability. Cases of dengue have increased considerably over the past several years, which is possibly caused by climate change.[15,16]

Other Febrile Illnesses

Routine Infections

Once potentially life-threatening infections are eliminated, other causes of febrile illness should be considered. Several studies show that routine viral and bacterial infections are commonly reported in travelers of all ages, especially children. A child presenting with fever and focal findings (eg, rhinorrhea, cough, sore throat) would most likely have a common upper respiratory viral infection. In a prospective study that followed nearly 800 Americans who traveled to lower-income countries, 26% experienced cough, sore throat, congestion, or earache, and 46%

reported diarrhea for an average of 3.7 days.[17] For these travelers, risk of illness was most strongly correlated with travel duration; each additional day of travel increased the chance of illness by 3% to 4%.

Exotic Infections

Travelers may be at risk for rickettsial diseases if they engage in recreational activities that expose them to arthropods associated with these intracellular pathogens. Rickettsioses are traditionally divided into 3 main groups: spotted fevers, typhus, and scrub typhus. Clinical symptoms vary but often include fever, headache, myalgia, arthralgia, and rash. Rickettsial infections have been reported more commonly over the past couple of decades and are most often diagnosed by serology, although culture and PCR tests are sometimes used.[18] Treatment is usually with a tetracycline antibiotic, even in children.

Schistosomiasis, a parasitic infection caused by trematodes (flukes) of the genus *Schistosoma*, results from wading or swimming in infected freshwater. *Schistosoma* infection occurs widely throughout the tropics, especially in Africa, and appears to be becoming more common in travelers.[19,20] Acute infections are generally asymptomatic but occasionally can present with a constellation of findings known as Katayama fever (ie, fever, abdominal pain, fatigue, headache, myalgia, diarrhea, and cough). In a study by GeoSentinel, the most commonly reported symptoms were fever, fatigue, and complaints related to the gastrointestinal or genitourinary tracts.[21] Furthermore, travelers with schistosomiasis who presented within 6 months after travel had more respiratory symptoms than those who presented later. Diagnosis can be made by identifying *Schistosoma* eggs in stool or urine or by antibody detection. Praziquantel is the preferred drug for all *Schistosoma* infections.

Leptospirosis, caused by spirochetes of the genus *Leptospira,* is distributed worldwide, with a higher incidence in tropical areas, and is becoming increasingly more common in travelers.[22] Human infection occurs through direct contact with urine or tissues of carrier animals, typically during recreational water exposure in contaminated rivers or lakes. Symptoms are variable and nonspecific early in the illness but may progress to jaundice, renal failure, and hemorrhagic manifestations. Diagnosis is usually by serology. Treatment options include penicillin antibiotics and doxycycline.

Chikungunya fever, a tropical arbovirus that is mosquito-borne and similar to dengue, is also reported in travelers. Symptoms are usually flu-like, with severe joint pain that can persist for months following infection.[23] Diagnosis is by serology and treatment is supportive. Chikungunya virus was identified for the first time on islands in the

Americas in late 2013. Since that time, it has become widespread in the Caribbean, and local transmission is now being reported in both North and South America.

African trypanosomiasis, or African sleeping sickness, is another rare but important cause of fever in travelers. There are 2 forms, East and West African, of this protozoal infection, both of which are transmitted by the bite of the tsetse fly. Most cases in travelers are acquired in East African game parks.[24,25] Symptoms usually include fever, rash, fatigue, and lymphadenopathy; altered mental status or coma may also occur as the disease progresses. Diagnosis can be confirmed by identifying motile trypanosomes in the blood or CSF. Treatment includes a course of antitrypanosomal therapy, with the specific regimen depending on the infecting species and stage of infection.

Respiratory Infections

Respiratory infections commonly develop in travelers of all ages, with estimates ranging from 10% to 20%. Air travel alone is associated with an increased risk of respiratory infections and is shown to be related to the proximity of the traveler to an infected passenger.[26] The spectrum of clinical presentation varies from mild upper respiratory tract infections to life-threatening pneumonias. In a review conducted by GeoSentinel, which comprised 25 globally dispersed clinics, nonspecific upper respiratory infection was the most common diagnosis, with pharyngitis, otitis media, and sinusitis occurring significantly more often in younger persons.[27] In a study that examined the etiology of respiratory infections in travelers, influenza virus was detected in 38% of those with respiratory symptoms, followed by rhinovirus, adenovirus, and respiratory syncytial virus.[28]

Viral pneumonitis due to common or novel respiratory viruses can sometimes lead to epidemics. Examples include severe acute respiratory syndrome and Middle East respiratory syndrome, both of which are caused by novel coronaviruses. Diagnosis should be considered in children who have traveled to affected areas who are severely ill with respiratory symptoms.[29]

Tuberculosis and more exotic pulmonary infections must also be considered, especially if history is concerning for exposures to rodents (eg, tularemia, plague), bird or bat droppings (eg, histoplasmosis), or undercooked crustaceans (eg, paragonimiasis). Furthermore, travelers to the Far East, especially Thailand, are at risk of acquiring melioidosis, an infection caused by the bacterium *Burkholderia pseudomallei*. The incubation period is variable, ranging from a few days to many years. Clinical presentation also varies but typically includes the abrupt onset

of headache, myalgia, fever, and rigor after several days of cough, shortness of breath, and occasional hemoptysis. Chest radiographs may reveal consolidation of the upper lobes and cavitation, which closely mimics tuberculosis. Treatment is usually accomplished with third-generation cephalosporin, broad-spectrum penicillin, or imipenem.

Gastrointestinal Illness

Gastrointestinal symptoms, especially diarrhea, occur frequently during and after travel.[30] When children present with complaints of diarrhea after travel, it is helpful to determine whether the diarrhea is acute or chronic (>2 weeks' duration). An invasive organism should be considered if the child also has fever, bloody stools, abdominal pain, and tenesmus. Diarrhea of longer duration accompanied by weight loss and malabsorptive symptoms may be secondary to a protozoan infection such as *Giardia lamblia* or *Cryptosporidium*. The etiology of traveler's diarrhea in children is not well studied, but data from a few small studies suggest that bacterial pathogens are common.[31] Viral etiologies (eg, rotavirus) are thought to be an important source of traveler's diarrhea in the youngest children. The most commonly identified bacterial agents include enterotoxigenic and enteroaggregative *Escherichia coli, Salmonella* and *Shigella* species, and *Campylobacter.* Diarrhea caused by *E coli* O157:H7 has not been reported in pediatric travelers.

Laboratory studies for children with traveler's diarrhea should initially include routine stool cultures even though they fail to detect diarrhea caused by pathogenic *E coli*. In cases of chronic diarrhea, *Giardia* and *Cryptosporidium* antigen tests should also be obtained, as well as a stool ova and parasite examination and special stains for *Cyclospora* and *Isospora*.[32] The most commonly used treatment in children for bacterial pathogens is azithromycin. Targeted therapy is used for most protozoal and helminth infections.

Many workups of post-travel diarrhea fail to demonstrate any specific organism and are currently thought to be caused by post–traveler's diarrhea irritable bowel. Temporary lactose intolerance may contribute to patient discomfort. Most of these cases eventually resolve with probiotics and dietary modification.

Another fairly common gastrointestinal ailment in travelers is viral hepatitis, which typically presents with flu-like symptoms and nausea followed by jaundice, abdominal pain, malaise, and vomiting. Hepatitis A and E, both widely endemic viruses readily transmitted by the fecal-oral route, are the types of hepatitis most often reported in travelers.[33,34] Hepatitis A is often minimally symptomatic in younger children but can be transmitted to older children and adults, who usually develop a

more severe disease. A highly efficacious and safe hepatitis A vaccine is routinely given to toddlers (>1 year) as part of the routine immunization series and is also recommended for anyone traveling to the developing world.[35] Treatment for hepatitis A and E is supportive care.

Dermatologic Manifestations

Skin problems in a returning traveler are often related to environmental factors, allergic reactions, infestations, and infections.[36] Key questions should focus on the characteristic primary lesion (eg, macule, papule, vesicle, petechiae), exposure history (including medications), tenderness of the primary lesion (suggesting infection) versus pruritus (suggesting allergy), presence or absence of accompanying systemic symptoms, and rash duration and evolution. Many rashes are related to allergic reactions to recent therapy.

As might be expected, many skin problems in tropical climates stem from sun or other environmental exposures. Polymorphous light eruption (sun allergy), appearing as a variable maculopapular eruption, is a sensitivity reaction to intense UV-A light in an unacclimated individual. Rash and pruritus occur soon after exposure. Sunburn, and its unpleasant aftermath, also complicates many tropical vacations but is easily preventable with some forethought. Miliaria or prickly heat usually resolves in returned travelers but its more chronic form, miliaria profunda, may follow prolonged exposure to hot, humid conditions.

Allergic and photosensitivity reactions to medications or plants are routinely encountered. Photosensitivity reactions often occur on exposed ankles and the tops of sandal-clad feet. Doxycycline, popular for malaria prophylaxis, is a common offender, but hydrochlorothiazide and ciprofloxacin also cause many reactions. Lemon or lime juice may cause an impressive photodermatitis if it drips onto skin while at the beach. Exposure to a variety of tropical plants provokes an allergic contact dermatitis resembling poison ivy. Exposure to unpeeled mangos, the rind of which cross-reacts with poison ivy, frequently causes a persistent itchy rash around the lips. Other offenders are Caribbean poisonwood, cashew nut fruits, and Asian lacquerware (Japanese lacquer tree).[37] Any prolonged self-treatment with potentially sensitizing creams (eg, Neosporin, topical diphenhydramine) or topical anesthetics (eg, benzocaine) can seriously extend rash duration.

Infectious rashes related to overseas exposures are often found in returning travelers. Impetigo and various bacterial pyoderma are most common in children. Herpes labialis or cold sores follow intense UV-A exposure. Fungal infections, especially athlete's foot and tinea cruris, are frequent in older travelers. The most common parasitic infection by

far (25% of all rashes in returning travelers in one series) is cutaneous larva migrans or creeping eruption from exposure to dog hookworm on beaches.[36] However, cutaneous myiasis from human botflies will also occasionally present as a post-vacation boil. Children often acquire scabies, head lice, or even chigoes (*Tunga penetrans*) while abroad if they have contact with local children or wear improper footwear.

Marine exposures produce their own set of rashes. Sea lice from jellyfish larvae usually produce an itchy rash beneath the bathing suit, whereas swimmer's itch, from avian cercaria, affects exposed skin. A history of freshwater swimmer's itch in the tropics may well be the first sign of infection with human schistosomiasis. Fire coral produces long-lasting areas of hyperpigmentation long after the sting subsides.

Neurologic Illness

The returned traveler presenting with neurologic symptoms, especially when accompanied by fever, is always a cause for concern. A patient complaining of headache, neck pain or stiffness, fever, and photophobia must be rapidly evaluated for meningitis or encephalitis. To rule out life-threatening infections, initial management should include obtaining CSF for laboratory studies and initiating empiric antibiotic, antiparasitic, or antiviral therapy as appropriate. Possible bacterial etiologies include *Neisseria meningitidis, Streptococcus pneumoniae, Listeria monocytogenes* (immunocompromised patients), and *Haemophilus influenzae* type b in incompletely immunized children younger than 5 years. Empiric antibiotic therapy should consist of a third-generation cephalosporin and vancomycin for the possibility of penicillin-resistant *S pneumoniae*. Ampicillin should be added if *Listeria monocytogenes* is of concern. A variety of encephalitic viruses can be transmitted by the bite of arthropod vectors such as mosquitoes, ticks, and fleas. Dengue fever, discussed previously, is the arboviral infection most often acquired by travelers. Japanese encephalitis (JE) is a mosquito-borne *Flavivirus* infection that is common in parts of Asia and occasionally reported among travelers.[38] Infection severity varies, with many JE cases being asymptomatic. Central nervous system manifestations of more serious infections may include seizures, delirium, ataxia, and cranial nerve palsies. Diagnosis can be achieved through detection of virus-specific antibodies in the CSF. Characteristic findings on magnetic resonance imaging (MRI) include abnormal intensity signals in the thalami, basal ganglia, and brain stem.[39] Severe infections have a high mortality rate, especially in children, and high rates of post-infectious neurologic sequelae.[40] It is important to remember that returning travelers are also at risk for non-exotic viral infections, so one should always assess for CNS infections

with *Enterovirus* and human herpesvirus. Acyclovir should be started to cover the possibility of human herpesvirus.

A wide variety of parasitic infections can impact the CNS, including *Taenia solium, Schistosoma, Strongyloides stercoralis,* and *Toxocara canis*. Any new onset seizure should prompt an investigation (including a head MRI scan) to exclude neurocysticercosis from the ingestion of pork tapeworm eggs. Transmission methods of CNS parasites vary from ingestion to direct contact with skin or mucous membranes. Symptoms are usually related to a host inflammatory response induced by the parasite larvae or eggs within the brain or spinal cord.[41] Eosinophilic meningoencephalitis is characterized by a pleocytosis with 10% or more eosinophils in the CSF and can result from several parasitic infections; *Angiostrongylus cantonensis* or *Gnathostoma spinigerum* are 2 of the more common causes.[42] Treatment is targeted anti-helminthic therapy with the possible addition of corticosteroids.

Lymphadenopathy

Lymphadenopathy suggests the presence of a systemic infection that could range from a transient acute illness (eg, human herpesvirus, pyoderma, tonsillitis, cat-scratch disease, mononucleosis) to a much more serious or chronic condition (eg, scrofula, acute retroviral syndrome). Localizing symptoms often point to the primary cause of lymphadenitis, but fever and malaise are far less helpful. A careful medication history is also important because certain drugs (eg, phenytoin) produce enlarged lymph nodes, often in the absence of rash.

Generalized lymphadenopathy should prompt a workup to exclude HIV infection, hepatitis B, syphilis, cancer, and lymphoma. A typical investigation should include complete blood cell count (CBC), tuberculosis skin test (purified protein derivative), tests for HIV infection, rapid plasma reagin, hepatitis B surface antigen, chest radiography, and sedimentation rate. A more challenging situation is when a traveler complains of new enlarged lymph nodes without any obvious source of infection. In such cases, it is reasonable to biopsy persistent nodes that would otherwise remain unexplained.[43]

LABORATORY EVALUATION

The initial laboratory investigation of an ill-returning traveler often includes a CBC with differential, blood films and/or rapid antigen test for malaria (if patient traveled to a malaria-endemic destination), blood cultures, liver transaminases, electrolytes, urinalysis, and a C-reactive protein or sedimentation rate. Lumbar puncture for CSF evaluation is indicated for patients with meningeal signs or altered sensorium,

especially if fever is present. Serologic testing for specific pathogens such as schistosome, dengue fever, hepatitis, and rickettsia may be useful but may often only be available at reference laboratories, delaying results. Also, cross-reactivity can occur between helminths. Evaluation of stool is recommended when diarrhea is the predominant symptom, especially in cases of bloody or persistent diarrhea. Stool should be sent for standard bacterial culture looking for common pathogens (*Salmonella, Shigella,* and *Campylobacter*), but other testing for less common bacterial pathogens should be considered (eg, *Vibrio* spp, *Aeromonas* spp). Testing for exotic pathogens often requires consultation with a diagnostic microbiology laboratory because these pathogens require specific culture media. For protozoal pathogens, consultation with a diagnostic microbiology laboratory will be necessary because these pathogens are not often looked for routinely. It should be noted that helminths rarely cause diarrhea.

Diagnostic imaging should be based on specific findings in the history or physical examination. More invasive diagnostic tests, such as colonoscopy or bronchoscopy, are rarely needed; however, biopsy of skin lesions may be useful in cases in which a laboratory evaluation is inconclusive. If the patient is severely ill, presumptive treatment should be initiated immediately and continued until results of diagnostic testing are available.

Eosinophilia in a returned traveler is usually caused by an allergic response to infections, drug reactions, connective tissue diseases, or, more rarely, malignancies. Eosinophilia may be mild (500–1,000 cells/mm^3), moderate (1,000–3,000 cells/mm^3), or severe (>3,000 cells/mm^3). A newly acquired tissue-invading helminth infection (eg, Löffler syndrome in early ascarid infection) should always be suspected; however, this finding is usually a transient phenomenon with intestinal parasites and resolves once the worms reach the gut. Fortunately, empiric dosing with albendazole is usually curative (stool ova and parasite examination results may be negative at this early stage). On the other hand, most tissue helminths, such as *Strongyloides* and trichinosis, produce significant, persistent eosinophilia in immunocompetent patients. Protozoal infections, unlike those caused by helminths, seldom cause eosinophilia. Eosinophilia is frequently found in drug hypersensitivity reactions. An allergic rash and the history of recent drug use (often an antibiotic) suggest this diagnosis.

A basic evaluation for unexplained eosinophilia should include a CBC with differential, stool ova and parasite examination with acid-fast staining, urinalysis, and chest radiograph. If these results are normal,

further evaluation for connective tissue diseases and malignancies may be necessary. Depending on prior exposure, skin snips for onchocerciasis and *Strongyloides, Schistosoma,* and filarial serologies may even be justified. It is common to have negative workup results, in which case stable patients may be given a trial of antiparasitic therapy or merely followed for 3 to 6 months to see if the condition resolves.[44]

MANAGEMENT

Treatment options are dictated by the specific pathogen. Aggressive therapy must be initiated for potentially life-threatening infections, including empiric treatment with antibiotics and antimalarials in toxic-appearing children who visited a malaria-endemic destination. Routine infections should be approached in the same manner as with the non-traveler. Empiric therapy with azithromycin is reasonable for cases of pediatric traveler's diarrhea assumed to be caused by the most common bacterial pathogens. In situations in which a more exotic infection is suspected, consultation with a specialist in infectious diseases or travel medicine is recommended.

KEY POINTS

- Travel to exotic locations has become much more common among children.
- The evaluation of the ill-returned traveler usually includes a comprehensive history, careful examination, and focused laboratory panel.
- Fever in a returned traveler should prompt immediate evaluation for potentially life-threatening infections.
- Referral to a specialist in infectious or tropical diseases is recommended in cases in which the child is severely ill or when the diagnosis is not apparent after an initial thorough evaluation.

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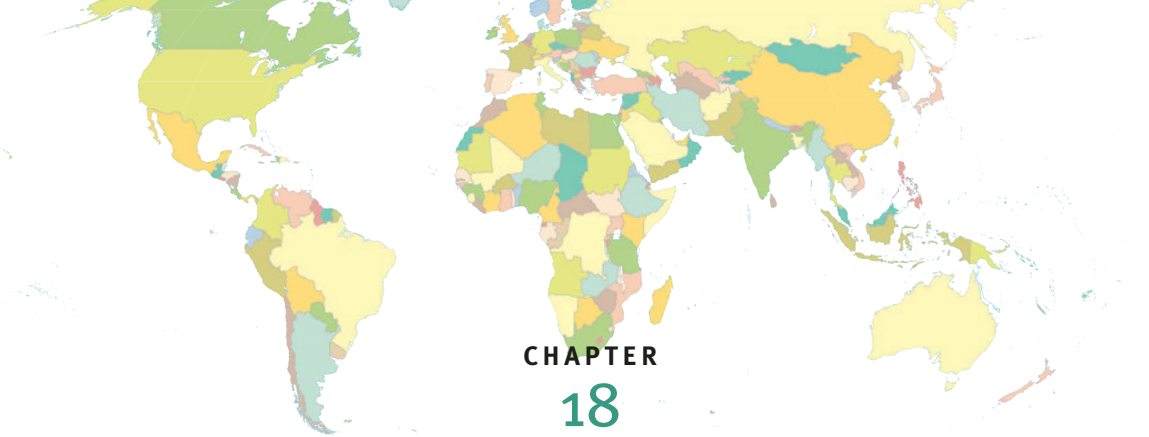

CHAPTER
18

International Adoption

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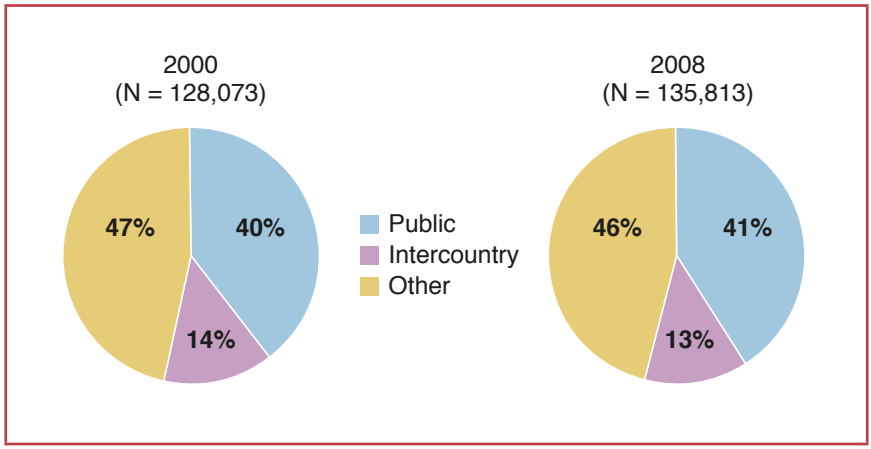
INTRODUCTION

As of 2013, approximately 7,092 children each year are adopted into the United States from countries around the world; these children experience varied caregiver arrangements, losses, separations, and emotional, nutritional, and social deprivation. Together, the child and adoptive family must forge a new relationship that supports the child's transition and adaptation to the new home and promotes healthy development. The child's and family's success in adapting to these changes in care are influenced by a complex interaction between innate, individual capabilities and external resources. The pediatrician can play a critical role in providing continuity of care, family guidance, and support for the physical, neurodevelopmental, and emotional needs of the child.

EPIDEMIOLOGY OF INTERNATIONAL ADOPTION

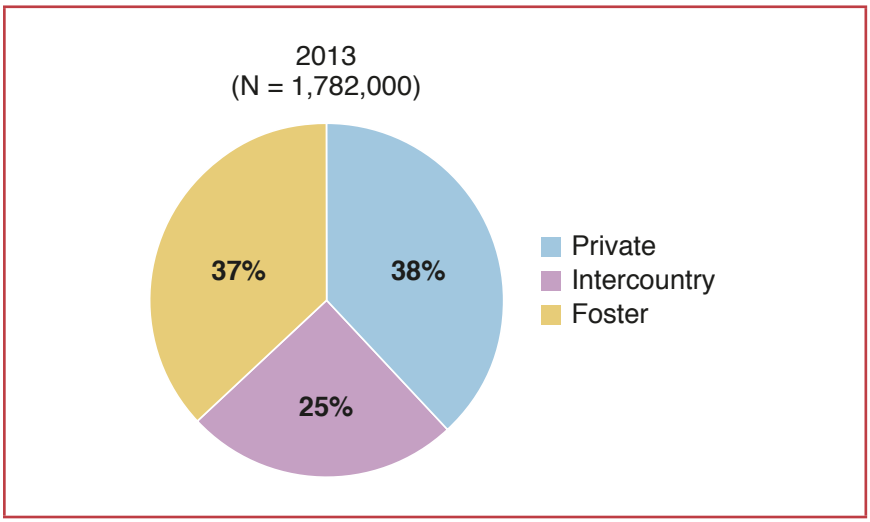
It is estimated that as of 2013, there are 1.78 million adopted children younger than 18 years in the United States[1] and that 2.5% of US families have an adopted child. Approximately 135,000 children are adopted in the United States each year (Figure 18-1a)[2]; international adoptions contribute more than 25% of this total (Figure 18-1b).[1,3] The total number of children adopted each year from other countries fluctuates and peaked in 2004 at approximately 23,000. In 2013, this number decreased to approximately 7,092 children and seems to be following this declining trend (Figure 18-2).[4] The reasons for this shift include greater efforts

Figure 18-1a. Percent of All Adoptions in the United States by Type



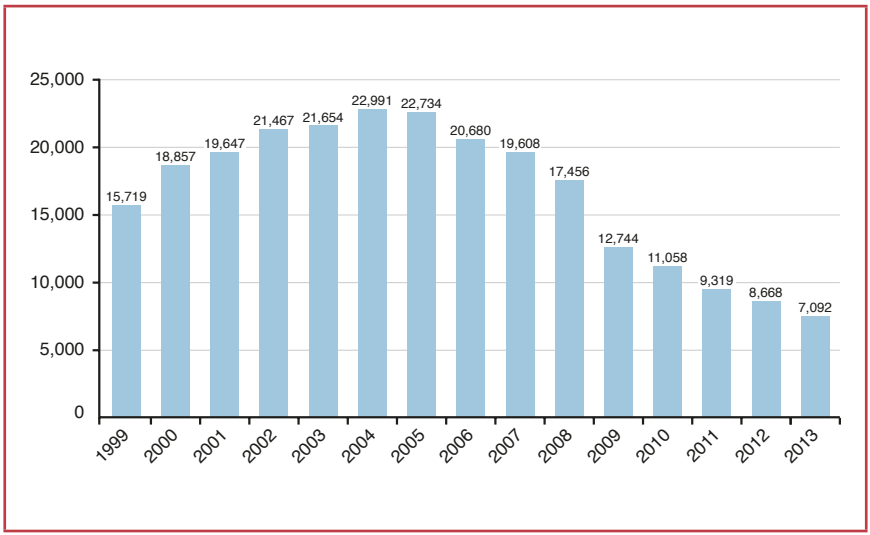
From Child Welfare Information Gateway. How many children were adopted in 2007 and 2008? http://www.childwelfare.gov/pubs/adopted0708.pdf. Accessed June 4, 2015.

Figure 18-1b. Percent of All Adoptions in the United States by Type



Data derived from Adoption USA: National Survey of Adoptive Parents, US Department of Health and Human Services. 2013. http://www.statisticbrain.com/adoption-statistics. Accessed June 4, 2015.

Figure 18-2. Adoptions to the United States



From Bureau of Consular Affairs, US State Department. Statistics. http://travel.state.gov/content/adoptionsabroad/en/about-us/statistics.html. Accessed June 4, 2015.

within countries to adopt children internally, allegations of adoption procedure fraud in foreign countries, increasing costs, changing political climates, and difficulty with implementing the Hague Convention—an international agreement with standards of practices for intercounty adoptions for which the US entered in 2008 (see Hague Convention on page 384).

The demographics of adoption also shifted over the last few decades and vary considerably by birth country. In 1986, children were primarily adopted from Korea and South and Central America. These children tended to be very young, from foster care, and without significant medical and developmental challenges.[5] In 2008, the greatest number of children was adopted from Guatemala and China, followed by Russia, Ethiopia, and Korea; children from more than 18 countries were entering the United States[4] and greater numbers of these children had lived in orphanages prior to adoption. However, as of 2012, adoptions from China and Russia decreased and Ethiopia has become the second leading country from which children are adopted by US families.[4] Since 2003, international adoptees are older on average. There have also been fewer young children (<1 year) adopted, while older children (1–2 years and 5–12 years) have been increasingly adopted.[6] The demographic of adoption will probably continue to change with time, and that makes caring for internationally adopted children challenging.

Family demographics also shifted, with increasing numbers of children being adopted into transracial, transcultural, single-parent, and same-sex families.[7] Overall, parents of international adoptees tend to be white, married, well educated, and economically stable.[5,8] Some of these characteristics are most likely due to requirements of the foreign country and the high cost of international adoption, but issues such as cultural norms and stigma around adoption may also play a part. Current estimates suggest that there are 5 to 6 adoption seekers for every completed adoption.

ADOPTION PROCESS FOR FAMILIES

The process of adopting a child from another country is characterized by long waits, uncertainty and confusion, high costs, paperwork, and bureaucracy. Families choose to adopt for many reasons; adoption is frequently the culmination of failed pregnancies, infertility, and loss of the imagined child, as well as for humanitarian reasons and to enlarge a family. Understanding these possible events can help give pediatricians greater insight into parents' experiences, expectations, and motivations leading up to the adoption. This section of the chapter provides a brief overview of the complex steps that families must follow to complete an adoption.

Agency Selection

There is considerable variability in the quality between agencies and the services they offer. Fees, experience, and reliability may vary among agencies. Agencies must currently be accredited or approved by the US Department of State designated accrediting entity to provide adoption services for Hague adoption cases.[9]

Eligibility

There are a number of US and foreign country requirements that parents must fulfill to be deemed eligible to adopt a child.

- *US requirements:* Each family must complete a home study, which typically involves at least one home visit by a social worker. Home study requirements vary per state. During this visit, the physical, mental, and emotional capabilities of the prospective parents are assessed, as well as family demographics, financial resources, criminal history, and any history of abuse or violence.
- *Country requirements:* Requirements for prospective parents vary enormously among countries; they are easily accessible on the US Department of State Bureau of Consular Affairs Intercountry

Adoption Web site (http://travel.state.gov/content/adoptionsabroad/en.html). There are often specific age, income, marital, and health requirements. Some countries have highly specific requirements, such as a maximum-allowed body mass index, and many countries do not permit adoption by same-sex couples.

Paperwork

There are various forms required by state and federal agencies and the intended adoptive country that need to be filed before a family can be approved for adoption. Documents that families must complete can be lengthy, confusing, and time-consuming. The US Citizenship and Immigration Services agency determines whether a child is eligible to immigrate to the United States.

Financial Resources

Costs for adoption vary between countries, but the Child Welfare Information Gateway estimates the cost of international adoption to range between $15,000 and $30,000.[10] This figure includes home study expenses, dossier and immigration processing and court costs, and foreign and domestic agency fees or donations. This figure does not include travel fees, which can be costly, particularly if a family needs to make more than one trip to the child's country.

Waiting

The waiting time to adopt varies between countries and can be as long as 5 or more years (current estimate to adopt a child with no special needs from China).[11] This waiting period is often frustrating, demoralizing, and fraught with anxiety and uncertainty.

Adoption by Lesbian and Gay Parents

More recently, lesbian and gay couples in some jurisdictions have been explicitly permitted by law to adopt children,[12] and they are doing so in increasing numbers.[13] Recent studies show no differences among families of lesbian, gay, or heterosexual couples on children's internalizing, externalizing, total behavior problems, or gender role behavior.[14] Supportive co-parenting was associated with better child adjustment[15] and highlights the importance of moving beyond family type comparisons to focusing on family and parenting processes as predictors of child outcomes.[16]

HAGUE CONVENTION

Safeguarding the rights of children is an important aspect of international adoption and a source of controversy around the world as to whether international adoption is beneficial to children. The UN Convention on the Rights of the Child (UNCRC) emphasizes "the right of the child to preserve his or her identity including nationality, name and family relations."[5] The UNCRC stresses that international adoption should be viewed as the last option, except for institutional care, after all efforts to place a child with existing family members or within the child's community are exhausted.

The Hague Convention on Protection of Children and Co-operation in Respect of Intercountry Adoption was drafted in 1993 to recognize the legitimacy of international adoption and to establish a set of minimum requirements and procedures to ensure that children are not exploited, trafficked, abducted, or sold. The Hague Convention was ratified by the United States in 2007 and implemented in 2008. The US Department of State is the US central authority for adoption. More than 75 countries ratified the Hague Convention. Many countries where children are commonly adopted, such as Russia and South Korea, are still non-Hague countries, and regulations differ depending on whether a country is Hague compliant. One important distinction is that parents prospectively adopting from Hague-compliant countries must now complete at least 10 hours of pre-adoption training and education. If done well, this training can help prospective parents be prepared to meet the needs of their post-institutionalized child.

PRE-ADOPTION CARE OF CHILDREN

The caregiving environment for children around the world prior to adoption varies greatly, from a loving and stable foster home to an impoverished orphanage or conditions of extreme poverty that are bereft of the very basic necessities children require to grow and thrive. Currently, more than half of all adoptees spent some of their early life in institutional care. Quality of care in these settings is highly variable, but there is generally an inadequate caregiver-to-child ratio. Nutrition and health care may be inadequate and children are exposed to a high turnover of caregivers, who often have limited training in child development.

Some international adoptees experienced abuse and neglect in the homes of their biological family or within an orphanage, although this is rarely reported on the records that prospective parents receive. Children may also have sustained some neurobiological insult as a result of poor

prenatal care and nutrition and prenatal substance use, with a high prevalence of alcohol abuse in Russia and Eastern Europe. Acute and chronic medical problems are common and include infections (eg, HIV, hepatitis, tuberculosis [TB]), malnutrition, parasitic infestations, and inadequate immunizations to developmental delays, speech and language disorders, disrupted emotional development or behavior, abnormal stress responses, and attachment disorders. These risk factors place these children at a higher risk for medical, behavioral, developmental, and mental health issues.[17]

Pediatricians are often called on to assist families prior to adopting a child for assistance with evaluating a referral for a child they are contemplating adopting. Prospective parents may have already accepted a referral but are looking for information to assist them with planning. Some prospective parents will not receive a referral until they arrive in the foreign country, such as in Ukraine. Once there, they will need assistance in understanding what to look for and how to have a referred child's record reviewed. Irrespective of the specific reasons that prospective families call on pediatricians, contact with parents prior to adoption presents an important opportunity to provide support and valuable information about potential risks, possible adverse outcomes, and appropriate expectations of the child.

PRE-ADOPTION MEDICAL RECORDS

Medical records for children in other countries are highly variable and often contain inaccuracies, omissions, and unfamiliar diagnoses.[18] There are a number of international adoption clinics across the country with specialists who regularly review these types of records and are familiar with the information that is typically available and the potential pitfalls. The American Academy of Pediatrics (AAP) Council on Foster Care, Adoption, and Kinship Care Web site (www.aap.org/sections/adoption/index.html) provides valuable information; pediatricians who specialize in services for adopted children can be searched by state. Table 18-1 lists information that may be included on a pre-adoption record. In addition, some countries provide video-recorded footage of the child, although the quality varies widely. In some countries, such as China, children are always found after abandonment, so some of the information listed in Table 18-1 is never available, such as information about birth parents and siblings. The presence or absence of information contained in the record does not ensure its accuracy. There are a number of caveats to bear in mind when evaluating a prospective child's record; this review should be completed by specialists and clinicians who are familiar with current issues in each country.

Table 18-1. Information to Look for in Pre-adoption Medical Records[a]

Basic demographics	• Date of birth • Date of placement • Information about birth family and siblings • Use of alcohol or drugs by birth mother • Age of birth mother and birth father • Prior pregnancies
Birth information	• Birth weight • Place of birth (hospital vs nonhospital settings) • Prenatal care • Gestational age • Apgar scores • Complications
Child's social history	• Age at placement • Reason for placement • Number of placements
Child's medical history	• Hospitalizations • Medications • Laboratory and other evaluations • Chronic and acute illnesses • Vaccinations
Growth	• Birth growth parameters • Current growth parameters, including height, weight, and head circumference
Laboratory studies	• HIV • Syphilis • Hepatitis B • Hepatitis C
Developmental status	• Language • Cognition • Motor • Personal-social • Behavior

[a] All of this information may not be available, and the absence of information such as prenatal alcohol exposure does not confirm that it did not happen.

Birth Information

The prevalence of low birth weight is approximately 10% to 40% in developing countries,[19] and prematurity rates are reported on records as high as 25%.[20] Maternal alcohol use tends to be severely underreported on records despite high rates of alcohol abuse in parts of Eastern Europe. Additional risk factors that may be seen on a record include parental mental health or cognitive issues, history of sexually transmitted

infections, poverty, single or teenaged birth mother, and involuntary termination due to abuse or neglect.[21]

Child's Social History

The longer a child spends in institutional care, the greater the risk for adverse developmental, behavioral, and mental health issues. In addition, the greater the number of placements and disruptions, the higher the likelihood that the child will have greater difficulty establishing intimate and secure relationships. It is often tempting to minimize the psychosocial risks seen on medical records to a child's outcome, but this should be avoided. Such children may be more vulnerable because they are often placed in understaffed and impoverished orphanages after being removed from a neglectful or abusive home. If there is a maternal history of alcohol consumption or if the child is from Russia or Eastern Europe, it is critical to carefully evaluate the child's record for growth failure and developmental delay and examine pictures and videos for facial features to consider the possibility of a fetal alcohol spectrum disorder (FASD).

Fetal alcohol spectrum disorder is an umbrella term that includes a range of anomalies and disabilities caused by maternal consumption of greater than minimum quantities of alcohol during pregnancy. Fetal alcohol syndrome (FAS) and partial FAS are the most extreme and are characterized by growth deficiency, central nervous system dysfunction, and a unique cluster of facial anomalies.[22,23] Conversely, children with neurobehavioral disorder associated with prenatal alcohol exposure lack facial dysmorphology and growth deficits but have a confirmed history of prenatal alcohol exposure. Fetal alcohol spectrum disorder is the leading preventable cause of birth defects and developmental disorders in the United States, with a reported incidence of 1 per 100 live births.[24] The prevalence estimates of FASDs in other countries are unclear, in part, because of disagreements on diagnostic criteria for the disorder.[25] It is estimated that at least 30% of women of childbearing age in Russia drink alcohol on a regular basis.[26] The prevalence of drinking women in South Korea is also on the rise, and it is estimated that the number of female drinkers has increased by 3% a year since 1995, mostly because of the increased presence of women in the workforce.[25]

Child's Medical History

It is not unusual to see diagnoses that are unfamiliar to US physicians, particularly in Eastern European records. Sorting out which have meaning and which do not requires some familiarity with foreign medical

records. Diagnoses, such as perinatal encephalopathy, are common in Russian records and usually carry little risk for adverse outcomes of the child.[19]

Growth

It is not unusual to see growth delays in children reared in impoverished settings and orphanages. Some studies show that being raised in a family-like setting such as foster care is better for nutrition, growth, and development.[27,28] For example, in the Bucharest Early Intervention Project (BEIP), a randomized trial using quality foster care as an intervention for deprivation conferred by early institutionalization, institutionalized children showed significantly lower scores on all physical growth parameters compared with the group who were never institutionalized.[29] However, children placed in high-quality foster care exhibited near-normal levels of height and weight after 12 months.[28] The rule is that for every 3 months a child spends in a neglectful situation, that child loses 1 month of linear growth[5]; however, this rule may no longer apply, as an increase in the quality of nutritional care has been seen. Microcephaly is also more commonly seen in children who were institutionalized.[19]

Laboratory Studies

It is extremely rare for a child with HIV to escape detection because testing across the world is fairly reliable. Timing of testing is important, and it is always possible that a child recently infected with HIV may not have positive laboratory study results. Parents need to be informed that quality of testing varies around the world and there is an inherent risk of under-detection.

Developmental Status

Developmental delay is the rule rather than the exception for children in institutional care, and most children are reported to have some delays.[20] Video recordings and photographs can be helpful in corroborating narrative reports and examining the quality of development across domains. It is helpful to parents who will be making more than one trip to the child's country if the pediatrician gives them specific guidance about what to look for. It is important to bear in mind that video recordings may be misleading because children may be evaluated in unfamiliar settings by people whom they have never met.

ADOPTION OF OLDER CHILDREN AND CHILDREN WITH SPECIAL NEEDS

As waiting times for adoption continue to grow, there are an increasing number of older children and children with special health care needs being adopted. Countries like China have a well-established program of placing children with "medically and surgically correctable" diagnoses, which can encompass a wide range of disorders. Pediatricians can help families understand the effect these disorders have on children and plan for their ongoing needs. Children placed on a waiting list include those with the following conditions, some mild but some more medically severe: albinism, cleft lip and palate, clubfoot, extra or missing fingers or toes, hearing loss, cardiac conditions such as atrial or ventricular septal defect and complex congenital heart disease, deafness, hemangioma, hepatitis B, hypospadias, missing limbs, orthopedic needs, severe scars or birthmarks, and vision loss.[30] It is very important to realize too that these recognized diagnoses may be just one part of a larger syndrome, so prospective parents always need to consider that there may be even greater complexity to the child's medical problems beyond what has been presented to them.

In addition, these older children are at a much higher risk for adverse developmental, behavioral, emotional, and cognitive outcomes that may ultimately hold greater significance than the identified medical diagnosis.

PEDIATRICIANS' ROLE PRIOR TO ADOPTION

Working with families prior to an adoption is an important opportunity for pediatricians to provide support and guidance during this highly vulnerable and often frightening period. Pediatricians can work with families to help clarify their goals and more fully understand what challenges they can accept and what their limitations may be. Families should be encouraged to openly discuss these questions with their pediatrician and adoption agency and among themselves so that the best possible fit can be made between a waiting child and prospective parents.

Box 18-1 provides a list of items that parents can consider bringing with them when they travel to meet the child. Parents may also wish to contact their new child's pediatrician or adoption specialist while they are traveling. Some families traveling to very remote regions may benefit from bringing antibiotics and, in consultation with a clinician, use them if they are unable to see a doctor locally.

Box 18-1. Items for Parents to Consider Bringing When Traveling to Meet a Child

MEDICATIONS
- Acetaminophen
- Diphenhydramine (eg, Benadryl)
- Ibuprofen
- Cortisone cream or ointment
- Bacitracin ointment
- Antifungal cream or powder (eg, Lotrimin)
- Oral rehydration solutions or powders (eg, Pedialyte)

SUPPLIES
- Adhesive bandages (eg, Band-Aids)
- Gauze pads
- Alcohol pads
- Hand sanitizer
- Thermometer
- Tweezers
- Disinfectant (eg, Betadine pads)
- Insect repellent
- Sunscreen, if appropriate
- Water purification system, if necessary

ITEMS FOR THE CHILD
- Sweets and treats to soothe or engage the child
- Age-appropriate toys

ITEMS IF ADOPTING AN INFANT
- Foods and formula for babies
- Diapers
- Baby-feeding essentials (eg, bottles, baby spoons, sippy cups)
- Pacifiers
- Diaper rash ointment
- Baby soap and baby shampoo
- Baby wipes
- Bibs
- Baby fingernail and toenail clippers

ITEMS FOR THE ORPHANAGE
- Gifts for orphanage director, orphanage staff, adoption facilitators, translators, etc
- Donation of medical supplies, clothing, or toys to the orphanage

Adapted from Adoption ARK. Travel packing tips.

AFTER THE ADOPTION

Placement of a child in an adoptive home is often the culmination of an unpredictable long wait and exhausting journey that brings excitement and uncertainty about the future. In many ways, it is similar to the pregnancy and birth of a biological child. However, with adoption, there

exists an adoptive triad consisting of the child, birth parent(s), and adoptive parent(s), who are each forever present, if perhaps only in the psychological sense.[31] Throughout the adopted child's life, he or she must blend life experiences and feelings toward the adoptive family with the reality of a birth family that may exist in another country. Confusion over identity, fantasies about birth parents and their reasons for relinquishing the child, and feelings of rejection may arise and influence the child's sense of belonging and self-esteem. An open and accepting family attitude toward adoption is shown to be predictive of a child's positive adjustment to these psychological issues. The pediatrician has the opportunity to help and support families as they navigate this journey. The AAP Healthy Foster Care America program (www2.aap.org/fostercare/resourceLibrary.html) provides many resources related to the health and well-being of children and teens in foster care, and many of the materials are applicable to a child adopted internationally as well.

Common Behaviors

For internationally adopted children, the transition to their new home signifies a radical shift from everything familiar and predictable, which includes different sensory input, such as scents, textures, climate, and tastes, as well as new routines, culture, relationships, and language. Even the child's name may change. Further, children experience a significant loss during this transition even if the prior living arrangement was suboptimal. This seismic shift often exacerbates underlying problems for children who often already have poorly developed regulatory capacities and limited ability to manage transitions well.

There may be greater ambivalence about adoption for older children even if they endorsed it.[32] If they lived in difficult family situations or experienced many unstable and changing living environments prior to adoption, older adoptees may be anxious about another transition, instability, and loss. They will have conscious memories that they may or may not be willing to share and distorted expectations about what adoption may represent. For many older adoptees, there may be a reluctance or an inability to allow themselves to be vulnerable within relationships, and they may initially resort to more primitive defenses to protect themselves.

Box 18-2[33] shows some of the common behaviors seen in international adoptees shortly after adoption. Many of these behaviors tend to quickly abate after adoption[32,34]; however, they may persist in some children.[35]

Box 18-2. Common Behaviors Seen After Adoption

- Sleep disturbances
  - Difficulty falling asleep
  - Frequent awaking
  - Nightmares
  - Reluctance to sleep alone
- Eating disturbances
  - Overeating
  - Poor appetite regulation
  - Hoarding of food
  - Poor appetite
  - Food refusal
  - Food texture aversions and refusal to eat solid food
- Developmental regression
  - Loss of toileting skills
  - Regression in language, attention, and adaptive skills
- Mood lability or instability
  - Temper tantrums
  - Irritability
  - Impulsivity
- Apathy and withdrawal
- Hypervigilance and exaggerated fear response
- Indiscriminate sociability
- Self-stimulating behaviors
  - Excessive masturbation
  - Rocking
  - Repetitive movements
- Aggression
- Relationship disturbances
  - Avoidance of eye contact
  - Dislike of physical touch

Adapted from Berman B, Weitzman C. Foster care and adoption. In: Rudolph C, Rudolph A, First L, Gershon A, eds. *Rudolph's Pediatrics.* 22nd ed. New York, NY: McGraw-Hill Education; 2011.

First Visit With the Pediatrician

The first visit with the pediatrician should optimally occur within the first week after adoption. Although the family may still be jet-lagged, this visit offers an opportunity to assess the early adjustment of the child, parents, and any siblings and to identify any potential areas of significant concern. Box 18-3[17] outlines a strategy that allows the pediatrician to be an effective advocate, a source of support and information for parents, and a careful monitor of the child's and family's well-being.[33,36–39]

Box 18-3. Supportive Role of the Pediatrician in the Care of the Adoptive Child

- Prior to adoption
  - Preview information on the child, eg, medical records, prenatal information, family history, video recordings.
  - Consider referring family to an adoption medicine specialist.
  - Advise on supplies to take to pick up the child, eg, medicines, formula.
  - Advise on vaccines, medicines for parents traveling to a foreign country.
  - Plan for evaluation of the child on return.
  - Refer family to support group for international adoption.
  - Deliver anticipatory guidance to new parents.
  - Refer family for a medical examination of the adoptive child by a panel physician who is a US Department of State–designated medical doctor.
- Immediate visit (within 3 weeks of arrival to United States)
  - Obtain available records, including prenatal and birth history, growth curves, immunization records, hospitalizations, results of health screenings (eg, lead, anemia), and medications.
  - Evaluate and treat acute illnesses.
  - Perform routine screening for infectious diseases, environmental risks, and vision and hearing difficulties
  - Measure baseline growth, including accurate height, weight (unclothed), and head circumference.
  - Check nutritional status of the child. Obtain levels for iron, zinc, and vitamin D.
  - Address any immediate concerns the family may have.
  - Assess immediate family coping and adjustment.
  - Provide support.
- Comprehensive examination (4–6 weeks)
  - Complete physical evaluation: check for congenital anomalies, chronic conditions, and nutritional disorders.
  - Perform screenings: vision, hearing, and dental. Formal audiologic screening is justified for all international adoptees.
  - Update immunizations. Establish a timeline for catch-up immunizations. Catch-up schedule should be based on *Red Book* (http://redbook.solutions.aap.org/SS/Immunization_Schedules.aspx).
  - Recheck newborn screening if infant is younger than 3 months.
  - Screenings, when appropriate, should include CBC, thyroid function tests, lead, iron (look for hemoglobinopathies), urinalysis, TB (PPD), stool O+P for parasitic infections, hepatitis B, hepatitis C, HIV, syphilis, and malaria (if appropriate). May need to reorder laboratory tests if the laboratory is unable to obtain necessary volume of blood to perform all the required tests.
  - Perform a developmental evaluation: gross and fine motor, communication, adaptive and cognitive skills, and initial behavior and coping responses.
  - Perform a developmental screen for language, autism spectrum disorders, and learning or attention difficulties if appropriate.
  - Perform anticipatory guidance: refer to support groups, appropriate literature.
  - Obtain more specific information about the child's experience in the new home.

Box 18-3. Supportive Role of the Pediatrician in the Care of the Adoptive Child, continued

- Periodic surveillance
  - Examine children in sensitive and compassionate settings.
  - Repeat bloodwork for HIV, hepatitis B, and hepatitis C screening 6 months after arrival.
  - Perform developmental screening 2 or 3 times within the first year of arrival.

Abbreviations: CBC, complete blood cell count; HIV, human immunodeficiency virus; O+P, ova and parasites; PPD, purified protein derivative; TB, tuberculosis.

Adapted from Berman B, Weitzman C. Foster care and adoption. In: Rudolph C, Rudolph A, First L, Gershon A, eds. *Rudolph's Pediatrics.* 22nd ed. New York, NY: McGraw-Hill Education; 2011 and American Academy of Pediatrics Council on Foster Care, Adoption, and Kinship Care. *Adoption Medicine: Caring for Children and Families*. Mason PW, Johnson DE, Prock LA, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2014.

Parental Adjustment

Parents may experience post-adoption depression or even remorse.[32,40] Although this phenomenon is well described after the birth of a child, it is less well understood and may not even be accepted after an adoption. Parents are often reluctant to talk about this because they may feel shame, embarrassment, and doubt, particularly after all the effort and cost expended to adopt the child. Children may have greater medical, developmental, or behavioral issues than anticipated. They may behave in a rejecting manner to the adoptive parents, making them feel personally inadequate as parents. Parents may feel undeserving of parenthood and inadequate in their abilities to ease the child's transition. Mothers who gave up careers to raise the child, in particular, may feel conflicted and guilty that they lost a vital part of their lives.

Many adoptive parents are reluctant to discuss these feelings and often report that friends and family do not understand the complex feelings associated with adoption. Families may not wish to pursue counseling after so much scrutiny prior to adoption; they may just want to get on with being a family. Pediatricians can ask parents one of the following open-ended questions, which may help them feel comfortable exploring such topics: "In what ways has the experience of adoption differed from what you anticipated?" or "What is the most unexpected or challenging part of adoption?"

The Medical Evaluation

Many internationally adopted children are exposed to a number of infectious agents in their countries of origin, particularly if they were living within the crowded conditions of an orphanage. The AAP recommends

that internationally adopted children be evaluated within 2 weeks of arriving in the United States. US immigration law requires that internationally adopted children begin immunizations, if necessary, within 30 days of arriving in the United States.[41]

Box 18-4 displays the most common infectious diseases seen in internationally adopted children and recommended screening tests.[17] Even if children were screened for these diseases in their native country, it is recommended that testing be repeated after adoption. Screening to identify infectious diseases is important to promote the long-term health of the child and prevent transmission to family members and other close contacts. International adoptee transmission of vaccine-preventable diseases such as hepatitis A, hepatitis B, and measles to US caregivers and TB transmission to community contacts emphasizes the importance of screening and appropriate follow-up of test results after adoption.[42]

The AAP developed recommendations for screening internationally adopted children (Table 18-2).[41,42] In addition to these tests, urinalysis, thyroid stimulating hormone level, and vision and hearing screenings are also recommended.[17] Screening for cytomegalovirus is not indicated, as rates in adoptees are comparable to rates in US children in child care and screening does not distinguish between congenital infection and asymptomatic shedding.

Box 18-4. Screening Tests for Infectious Diseases in International Adoptees

- Hepatitis B virus serologic testing: hepatitis B surface antigen
- Hepatitis C virus serologic testing
- Syphilis serologic testing: nontreponemal test (rapid plasma regain, Venereal Disease Research Laboratories, or automated regain test); treponemal test (microhemagglutination test for *Treponema pallidum*; fluorescent treponemal antibody absorption; *T pallidum* particle agglutination)
- HIV 1 and 2 serologic testing
- Complete blood cell count with red blood cell indices and differential
- Stool examination for ova and parasites (3 specimens) with specific request for *Giardia intestinalis* and *Cryptosporidium* species testing
- Tuberculin skin test
- Children from countries with endemic infection: *Trypanosoma cruzi* serologic testing
- Children with eosinophila (absolute eosinophil count exceeding 450 cells/mm^3) and negative stool ova and parasite examinations: *Strongyloides* species serologic testing; *Schistomsoma* species serologic testing (for sub-Saharan African, Southeast Asian, and certain Latin American adoptees)
- Serologic testing for lymphatic filariasis (children from endemic countries who are older than 2 years)

Adapted from American Academy of Pediatrics. Medical evaluation for infectious diseases for internationally adopted, refugee, and immigrant children. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics;2015:194–201.

Table 18-2. American Academy of Pediatrics Recommended Screening Tests for Internationally Adopted Children

TEST	POPULATION TO BE SCREENED	ADDITIONAL TESTING OR CONSIDERATIONS
Tuberculin skin test	All adoptees	Repeat in 4–6 months or when nutritional status is improved if negative on initial screen. Retesting will also detect an evolving infection.
Hepatitis serology Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody	All adoptees	Repeat in 6 months if negative on initial screen to detect emerging infection.
Hepatitis C antibody	Adoptees from China, Russia, Eastern Europe, and Southeast Asia Adoptees with risk factors for infection	Repeat in 6 months if negative on initial screen to detect emerging infection.
Syphilis serology Non-treponemal test (RPR, VDRL, ART) Treponemal test (MHA-TP, FTA-ABS)	Non-treponemal tests for all adoptees	Children with positive test results and those diagnosed or treated in their birth country need additional testing, or if clinical signs or symptoms of syphilis are present. Treponemal tests if non-treponemal tests are reactive.
Stool examination for ova and parasites (3 specimens) Stool specimen with specific request for *Giardia intestinalis* and *Cryptosporidium* species testing (1 specimen)	All adoptees	Recheck after treatment to ensure resolution and no additional organisms.
HIV 1 and 2 ELISA (consider DNA PCR in infants)	All adoptees	Repeat in 6 months if negative on initial screen to detect emerging infection.

Abbreviations: ART, automated reagin test; ELISA, enzyme-linked immunosorbent assay; FTA-ABS, fluorescent treponemal antibody absorption; HIV, human immunodeficiency virus; MHA-TP, micro-hemagglutination test for *Treponema pallidum;* PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

Adapted from Barnett E. Immunizations and infectious disease screening for internationally adopted children. *Pediatr Clin North Am.* 2005;52(5):1287–1309. Copyright 2005, with permission from Elsevier.

Recommended Screening Tests for Internationally Adopted Children

Tuberculosis

Twenty-two countries have been identified as having 80% of TB cases globally; all 10 countries with the highest number of adoptees to the US are on the list, including Russia, Ethiopia, China, and India.[43] Rates of positive skin tests in international adoptees range from 3% to 19% due to the high rates of TB in countries from which children are adopted.[42] Most experts agree that an area of induration equal to or greater than 10 mm is considered positive for international adoptees, with 5 to 9 mm considered positive if a child is immunocompromised, had definite exposure to a person with TB, or has signs or symptoms of TB disease, including an abnormal chest radiograph. The risk of a false-positive purified protein derivative (PPD) skin test associated with prior bacille Calmette-Guérin (BCG) immunization is considered low if the skin test is placed at least 1 year following the vaccine.[44] In general, previous BCG immunization before placement should not be considered a contradiction to placement of a PPD; a positive PPD should never be assumed to be secondary to the BCG vaccine.

False-negative results may be caused by a number of factors, including malnutrition, concurrent inflammatory or rheumatologic disease, underlying immune deficiency, inactive antigen, or poor technique when placing the PPD test. Most TB cases in internationally adopted children are asymptomatic and classified as latent TB infection. Up to 20% of skin tests may be negative on initial testing but positive on testing 6 months later.[45] Therefore, retesting should be performed by 6 months after adoption, at which point some of the factors contributing to a false negative, such as malnutrition, may have resolved. In addition, if the child was exposed to TB shortly before adoption, retesting will detect an evolving profile.

Hepatitis B

Approximately 5% to 7% of international adoptees are infected with hepatitis B; this percentage may be higher if children are coming from countries that do not routinely immunize against hepatitis B. Recent adoptees who do not have hepatitis B surface antibody on the initial screen should undergo repeat testing for hepatitis B in 2 to 3 months to rule out infection immediately prior to adoption. Children with hepatitis B should be vaccinated against hepatitis A, will require further evaluation beyond routine screening tests, and should be referred to an expert in managing hepatitis. It is critical that family members and close contacts are immunized against hepatitis B to prevent infection.

Hepatitis C

Hepatitis C is rarely seen in internationally adopted children, although there are increasing numbers of women infected around the world. Current recommendations for testing include screening at the time of adoption and considering rescreening 6 months later.[42] The recommended test is hepatitis C antibodies. Maternal antibodies can persist up to 15 months; in these cases, confirmatory polymerase chain reaction (PCR) testing should be done.

Syphilis

Up to 3% of international adoptees were diagnosed with congenital syphilis after arriving in the United States despite undergoing screening and treatment for syphilis in their home country.[46–48] There have been rising trends in syphilis infections globally,[49–51] in part related to the passing of legislation that made prostitution illegal in South Korea and took away routine screening and treatment of sex workers. While syphilis remains a rare infection in internationally adopted children, there are severe complications if left untreated.[50] Most children with congenital syphilis are initially asymptomatic. Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are highly sensitive, although false-positive results may occur in individuals with rheumatologic or inflammatory conditions. All positive non-treponemal tests (VDRL or RPR) must be confirmed using the fluorescent treponemal antibody absorption test, which is more specific. Non-treponemal tests become nonreactive over time, whereas treponemal tests tend to stay positive for life. If the child is reported as being treated in the country of origin, he or she requires close follow-up to detect falling titers. Infected children should undergo lumbar puncture for VDRL testing of the cerebrospinal fluid to rule out neurosyphilis, as well as a complete blood cell count, liver function tests, long-bone radiographs, and vision and hearing screening.[17,42,52] Consider obtaining pediatric infectious disease consultation to guide treatment.

Human Immunodeficiency Virus

Although rates of HIV infection are quite high in some countries from where children are adopted, prevalence of HIV in international adoptees is quite low. In a study of international adoptees at 17 international adoption clinics, fewer than 1% of children had HIV infection.[53] This suggests that screening for this disease around the world is effective and, therefore, HIV does not represent a major risk for adoptees. Nevertheless, all newly adopted children should be screened for HIV infection because

reported results are not always reliable. Infants, who may have persistent maternal antibodies, need additional testing if it was not done in their country of origin. Two negative DNA PCR tests at or beyond 1 month of age and a third test performed at 4 months or older confirm a negative HIV status. When HIV antibody testing is used in children older than 6 months, 2 negative antibody tests performed at an interval of at least 1 month can confirm a negative HIV status.[54]

Hepatitis A

Up to 95% of children acutely infected with hepatitis A are asymptomatic[55] but can spread the infection to others who are more likely to be symptomatic. In one study of 279 international adoptees, antibodies to hepatitis A were detected in 29%, with rates highest in children older than 2 years and those from Africa, Latin America, Eastern Europe, and Asia.[56] In 2007 and 2008, numerous cases of international adoptees who infected members of their adoptive families and communities were reported.[57,58] Based on these cases, the Advisory Committee on Immunization Practices issued a new recommendation in 2009 to routinely vaccinate household members and close personal contacts of adopted children newly arriving from countries with intermediate to high hepatitis A endemicity.[59]

Intestinal Parasites

Intestinal parasite infections are common in children adopted internationally, with up to 27% having one or more pathogen(s) detected after arrival in the United States. *Giardia lamblia* is the most common parasite and has been identified in 19% of children.[46,60] All internationally adopted children should be screened on arrival with at least 3 stool specimens tested for ova and parasites, collected 2 to 3 days apart.[60] Treatment of *Giardia* and some parasites is recommended and especially important if the child is malnourished or symptomatic. Repeat testing for stool ova and parasites should be performed after treatment.[6]

Evaluating Immunization Status

There are a number of challenges in interpreting the vaccination records of children from other countries. Multiple studies show that many international adoptees have incomplete vaccination records, inappropriate timing of vaccinations, or inadequate protection against disease despite appropriate vaccination records.[18,61,62] The reasons for the latter might include

- Falsified records
- Improper vaccine storage

- Use of outdated vaccines
- Use of diluted vaccines
- Poor immune response because of reasons such as malnutrition

Based on these findings, the AAP recommends[41]

1. Repeat all vaccine doses when immunization records are assumed to be unreliable.
2. Accept as valid those immunizations for which there is documentation of vaccines doses administered according to current US vaccine schedules.
3. Judiciously use serologic testing to assess a child's immunity to vaccine-preventable diseases and make decisions about what vaccines to administer based on these results.

Determination of the most appropriate strategy toward interpreting vaccination records and planning immunizations need to be done collaboratively with parents. Obtaining multiple titers and delaying vaccination may not be cost-effective or practical, but many parents are wary of over-vaccinating their children. Careful discussion may be needed to contrast vaccination practice in the United States and the rationale behind it with the adoptive child's vaccination record. In addition, parents need to be made aware that an unrecorded vaccination given shortly before adoption could result in a transient elevation of antibody or titer to a specific vaccine but may not confer lasting immunity. The goal is to choose a route that minimizes distress for the child in obtaining multiple blood draws, is the most cost-effective, and, likely most importantly, confers the greatest assurance of long-term protection to the child and community from serious preventable illnesses.

Nutritional Screening

Nutritional history should be assessed, particularly with respect to iron, calcium, vitamin D, iodine, and other nutrients. It is also important to assess the child's current dietary habits and to determine if the child has any issues eating solid or textured foods. Exercise history is also important to obtain.[63] Table 18-3 provides guidance for monitoring growth and nutrition in international adoptees.

Oral Health

All children should be assessed for the presence of dental care or other oral health problems. Children older than 12 months should be referred for an oral health evaluation as well as younger children with evidence of caries and tooth decay.

Table 18-3. Growth and Nutritional Monitoring		
SCREEN	**WHO**	**RATIONALE/OTHER**
Measure length, height, weight (unclothed), and head circumference	All children.	Further work-up needed if there is not evidence of catch-up growth by 6 months after arrival in the home
CBC	All children	To evaluate for anemia, blood disorders
Hemoglobin electrophoresis	Selected children at risk for hemoglobinopathies	
Lead level	All children	Particularly important in children coming from countries with high environmental risk
TSH	All children	In some countries the soil is deficient for iodine
Newborn metabolic screen	For children up to age 2 years	
Iron, Calcium, Vitamin D	All children	To evaluate for micronutrient deficiency

Abbreviations: CBC, complete blood cell count; TSH, thyroid-stimulating hormone.

From American Academy of Pediatrics. A Healthy Beginning: Important Information for Parents of Internationally Adopted Children. http://www2.aap.org/sections/adoption/PDF/InternationalAdoption.pdf. Accessed June 4, 2015.

The Developmental Evaluation

Anywhere from 50% to 90% of internationally adopted children from many countries around the world exhibit developmental delays at the time of their initial evaluation, and a significant proportion are delayed in multiple areas (eg, language, cognition, motor skills).[64–66] It is often difficult to prognosticate a child's development based on early presentation shortly after adoption. Many children begin to show remarkable catch-up shortly after adoption, and many biological, genetic, and experiential influences on development are unknown. Approximately 4 to 6 weeks after adoption, when the child and family are recovered from jet lag and have had time to begin adjusting, it is useful to obtain a baseline assessment of the adopted child's current level of developmental functioning across domains, including social-emotional and adaptive skills. It is important to provide an interpreter who speaks the child's

native language during this assessment. The limitations to obtaining an accurate assessment include

- Using measures normalized on American children
- Administering tests in English
- Using materials that are unfamiliar and culturally unknown to the child
- Assessing the child during a period of intense adjustment

The value of assessing a child early is to help the family understand the child's baseline functioning, which may help interpret some of the behaviors displayed and obtain appropriate intervention services. It is important that pediatricians are cautious not to underreact or overreact to a child's developmental delays and behavior problems. It is equally harmful to prematurely intervene or become alarmed as it is to wait too long to refer a child for services with the belief that he or she simply needs more time to catch up. It is often helpful to refer children to an international adoption clinic or a developmental-behavioral pediatrician who is familiar with this population and skilled in assessing a child's behavior and development. During the developmental screening and assessment, it is important to prepare parents for the fact that the child is likely to show delays for a myriad of reasons and that these delays are not an indicator of long-term disability. Without this knowledge, parents' anxiety, uncertainty, ambivalence, and fear may be unnecessarily heightened.

LONG-TERM CONSEQUENCES

Adopted children are more frequently referred for mental health concerns[67,68] than their non-adopted peers; however, international adoptees have been shown to have fewer problems overall than domestic adoptees.[67] The higher adoptee referral rate may be attributed to a number of factors, including heightened vigilance for problems by adoptive parents with greater resources and awareness of mental health services and the effects of early toxic stress and genetic and biological risk factors. The BEIP, a longitudinal study that began in 2000 looking at children placed in institutions at or shortly after birth, provides much data about our understanding of adopted children's long-term consequences. The BEIP showed that removing young children from institutions and placing them in foster care resulted in improved attachment patterns, reduced signs of emotionally withdrawn or inhibited attachment, improved measures of positive affect, and reduced prevalence of internalizing disorders.[69]

Behavior and Emotion

Multiple studies indicate that international adoptees have a greater incidence of behavioral difficulties, including internalizing (ie, withdrawal, anxiety, depression, and mood disorders) and externalizing problems (eg, acting out, aggression, opposition), impairments in peer relations, and attention disorders.[35,67,70–74] However, a large meta-analysis that reviewed approximately 100 studies on adoption suggested that the effect size was small.[70] Many studies robustly indicate that the most important predictor of behavioral problems is the length of institutionalization and severity of early deprivation[67,75,76]; however, other studies do not demonstrate adoption age as an important predictor.[70] Many studies indicate that although many of the behavior problems improve, they also often persist long after adoption,[77] but considerable heterogeneity exists within adoptees. New information suggests that a threshold response may occur (particularly for children who experienced harsh and highly depriving early environments) in which, after a certain period of deprivation, there may be some damaging effects that become more difficult to reverse. Despite this robust evidence suggesting that internationally adopted children are at higher risk for behavior and emotional problems, a recent meta-analysis indicated that these children do not have poorer self-esteem.[78] Results from the BEIP confirm and extend previous findings on the negative outcomes of early institutionalization on mental health.

Motor Development

Recent evidence suggests that early deprivation has a negative effect on motor development that is not resolved by foster care placement and that this effect is mediated by the child's IQ.[79] As a result, it is important to monitor and address motor delays in children with a history of institutionalization, especially those with low IQ.[79]

Cognition

Similar to behavior and emotion studies, the length and severity of early deprivation is the strongest predictor of cognitive impairments in internationally adopted children.[66,67,75,80–82] Studies show that catch-up in cognitive skills can occur many years after adoption, although significant catch-up seen more than 2 years after adoption occurs, primarily in children who exhibited the greatest level of initial impairment.[81] Children who are adopted at young ages and female and who have been reared in foster care in their country of origin are most likely to show the least amount of delays at adoption and the greatest capacity for full

developmental catch-up. While children with signs of poor nutrition as measured by growth also have associated high rates of developmental delays,[83] studies suggest that early evidence of poor nutritional status does not predict later cognitive functioning.[82] Similar to findings related to behavior and emotion, there is some suggestion that a sensitive period in cognitive development or threshold may exist, after which it becomes more difficult to fully reverse the effects of severe early adversity.[80] Recent literature suggests that even in children functioning within the normal intelligence range, high rates of specific neurocognitive deficits in areas such as memory, executive function, and language may be seen, with length of early institutional care exerting the greatest influence.[73,84]

Executive Function

Executive function consists of components of inhibitory control, manipulation of information in working memory, and the ability to shift attention.[85] Significant impairments have been found among children experiencing early psychosocial deprivation on executive functions,[86,87] skills known to contribute to regulated and goal-directed behavior.[88] Specifically, institutionalization has been linked to disturbances in specific executive function skills such as inhibitory control,[89–91] conflict resolution,[87] and working memory.[86,89] Children who spent longer time in institutionalized care had more severe deficits in their executive functioning.[73,90] Less time with the birth family and lower quality of institutionalized care were also associated with poorer executive function in preschool-aged children 1 year post-adoption.[92] Exposure to adversity is believed to negatively affect the prefrontal circuitry that underlies executive functioning; this has been suggested by various imaging techniques, including event-related potentials,[87,91] positron emission tomography,[93] functional magnetic resonance imaging (MRI),[94,95] and diffusion tensor imaging.[96]

Attachment

Studies examining attachment in internationally adopted children echo the patterns seen in behavioral and cognitive domains where length of deprivation highly predicts the presence and persistence of an attachment disturbance.[67,75,97,98] However, once again there is considerable variability seen in attachment difficulties in internationally adopted children, with those with the longest institutional care having more atypical and disorganized attachment patterns. Recent evidence suggests that approximately 20% of currently institutionalized children have some attachment strategy, suggesting some coherent method of

gaining proximity and support from a preferred caregiver during times of stress and perceived threat; however, only a fraction of their strategies are well developed.[98,99] Recent evidence also showed that high-quality caregiving at 30 months predicted reduced functional impairment and psychopathology at 54 months, which was mediated by the security of attachment; as a result, this suggests that interventions for young children with a history of early deprivation may benefit from targeted caregiver-child attachment relationships.[100]

The most common pattern seen in internationally adopted children is indiscriminate sociability characterized by superficial relationships with others, approaching strangers without discrimination, a tendency to wander off from a parent without checking back, and a willingness to go off with a stranger. Indiscriminate sociability tends to be highly persistent over time, particularly in older adoptees, but is often not related to parents' assessments of attachment security.[101] Therefore, in 2013, the updated *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* renamed the diagnosis of disinhibited reactive attachment disorder as *disinhibited social engagement disorder* (DSED) to reflect this. Individuals with DSED need to be taught appropriate social boundaries, how to distinguish safe and unsafe social interactions, and how to read social cues, and this often requires intensive and sustained intervention.

Identity Development

Understanding adoption is an unfolding process that occurs over a lifetime and plays a role in the development of all adoptees' identity. Although each child and family will metabolize the experience of adoption differently, there are some predictable patterns (Table 18-4).[102,103] Adoption may come in and out of focus for children and families, particularly at nodal points such as life transitions or adoption anniversaries or as a child enters a new developmental stage. It is important that pediatricians continue to routinely ask about the role that adoption plays for the child and parent at different points so that intervention and support can be provided if necessary. Of note, a psychological or physical search does not necessarily imply psychopathology or distress, and the experience of mourning and loss may represent an important and healthy developmental step for a child. However, if a child is struggling with behavioral and emotional challenges, along with changes in functioning and school performance, this may represent more than a healthy component of identity development, and an evaluation and additional help by a mental health professional with experience in adoption may be warranted.

Table 18-4. Identity Development in Adoption

AGE	COMMON RESPONSES	RECOMMENDATIONS
Toddlers	Often enjoy adoption story but lack complex understanding of adoption	• Many books available to use as aids to discuss adoption • Adoption often viewed by children as highly positive during this period
Preschoolers	Children begin to notice differences and ask questions about these differences.	• Important not to over-interpret these questions as a marker of distress. • Children may have distortions in their understanding of adoption. • Older adoptees may have conscious memories of events but may be reluctant to talk about them.
School-aged children	Adoption may be first perceived as problematic even if adoption was years earlier.	• Begin to first understand experience of loss. • Problem behaviors may emerge. • Fantasies of reunion with birth parent may emerge. • Child may begin an "internal" search.
Adolescence	May see emergence of "identity crisis"	• May see prolongation of reunion fantasies • May blame adoptive parents and self for adoption losses • May experience fear of repeating adoptive parent's possible mistakes and desire to undo these mistakes • May initiate a physical search for birth parent(s)

BIOLOGICAL PROCESSES

Recent neuroimaging findings show distinct neurologic differences that contribute to increased rates of psychopathology in children with a history of institutionalization. For example, one study using MRI found diminished white matter connectivity in areas of the brain involved in higher cognitive and emotional function (ie, frontal lobe and amygdala) in adopted children who have been under institutional care.[96] Functional MRI has shown that altered activation of the amygdala plays a role in chronic behavioral problems in maternally deprived children who were later adopted.[104] A recent review also showed a pattern of decreased total brain volume linked to decreased amounts of white and gray matter across a number of regions in children with a history of maltreatment.[105] In the BEIP, institutionalized children had smaller cortical gray matter

volume compared with children who had never been institutionalized; however, placement into foster care intervention was associated with increased cortical white matter relative to children not randomized to foster care, implicating neural plasticity in white matter and a potential for catch-up to never-institutionalized peers.[106] Moreover, the BEIP showed that patterns of brain activity, as assessed by electroencephalogram (EEG), mediated the association between experience of institutionalization and attention-deficit/hyperactivity symptoms at age 5 years.[107] Similarly, specific changes in EEG power distribution among institutionalized toddlers have been linked to disinhibited sociability during the preschool age.[108]

Stress reactivity influences many biological processes that may be involved in adaptation for adopted children.[16] The stress system generates a neuroendocrine response that involves the hypothalamic-pituitary-adrenal (HPA) axis, which produces stress-related hormones, including glucocorticoids such as cortisol.[109] While activation and deactivation of the stress system is normal for typical functioning, in children experiencing early trauma, what begins as a protective body response to a stressor can ultimately trigger serious and lifelong issues in their development.[110] Recent evidence shows that post-institutionalized children also had higher levels of cortisol when interacting with their mothers compared with unfamiliar adults and that a history of more severe early neglect was associated with the highest basal cortisol levels, suggesting greater dysregulation of the HPA axis in institutionalized children.[111] Another study examined the effects of early institutionalization on oxytocin and vasopressin, hormones associated with positive and social behavior, and found that compared with children who had never been institutionalized, children with a history of institutional care had lower overall levels of vasopressin and, after interactions with their caregivers, lower levels of oxytocin.[112]

FOLLOW-UP VISITS AND SURVEILLANCE

The risks and rewards of international adoption can be great for families, and pediatricians can play a special role. Pediatricians need to follow internationally adopted children intensively over the first year after adoption to monitor development, health, growth, and family adjustment and adaptation. In addition, it is important to detect the emergence of atypical or maladaptive behaviors that may come into greater focus after an initial honeymoon period. Frequent visits will also ensure that children receive appropriate medical, developmental, and educational services and that families feel supported so they can develop into a cohesive and loving family.

KEY POINTS

- Approximately 127,000 children are adopted in the United States each year; approximately 5% to 25% of children are adopted from other countries.
- The overall number of children entering the United States from other countries is decreasing; a larger proportion of international adoptees have major or minor special health care needs.
- More than half of all international adoptees spent part or all of their early life in institutional care.
- Pre-adoption medical records are often scant but may provide important information about risks to health, development, and behavior.
- The length of time in institutional care is the greatest predictor of adverse cognitive, behavioral, developmental, and mental health outcomes.
- Shortly after international adoptions, it is common to see regulatory disturbances; mood instability; challenges in relationships, including indiscriminate sociability; and developmental regression.
- The AAP developed recommendations for screening international adoptees for infectious diseases and illness, which include obtaining assessments after adoption for TB, HIV, syphilis, and hepatitis.
- Nutritional history should be assessed, particularly with respect to iron, calcium, vitamin D, iodine, and other nutrients.
- Revaccination, acceptance of prior records, or serologic testing may be necessary to ensure that an adoptee's immunization status is appropriate.
- Between 50% and 90% of adoptees exhibit some developmental delay at the time of adoption.
- International adoptees may face long-term problems related to behavior and mental health, cognition, attachment, and social difficulties characterized by indiscriminate sociability.
- Most international adoptees do not show poorer self-esteem when compared with peers who are not adopted.
- Identity development is a lifelong task for adoptees and often follows some predictable patterns.
- Pediatricians are in a position to monitor the overall well-being of internationally adopted children and assess for the emergence of atypical or maladaptive patterns of behavior or development.

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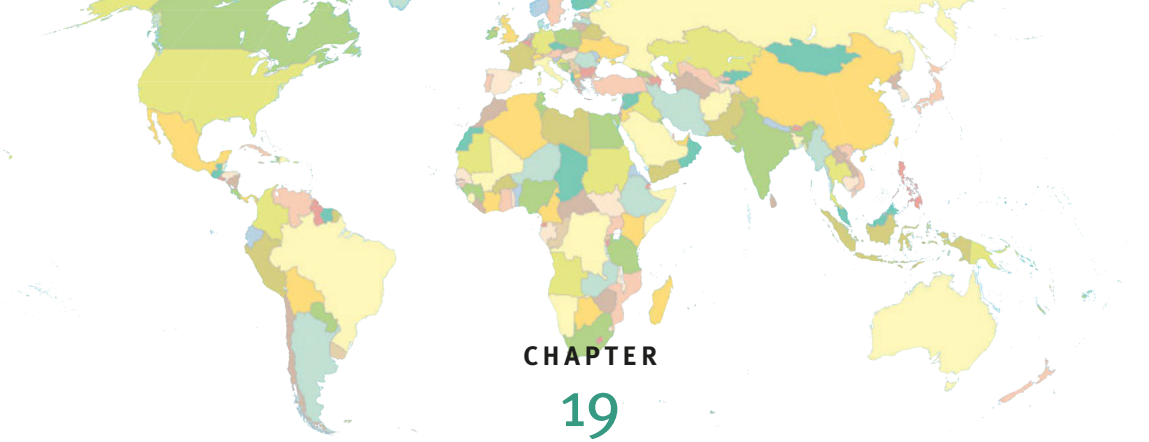

CHAPTER

19

Care of Immigrants

Elizabeth D. Barnett, MD, FAAP

INTRODUCTION

The number of foreign-born individuals in the United States has never been higher. Taking care of immigrant families is no longer an occasional event for pediatricians in the United States but rather a standard part of pediatric practice. Despite the prevalence of such patients, it is clear that health disparities continue to exist for foreign-born individuals. Caring for immigrant patients can be accomplished by acknowledging that there is a body of knowledge for the field of immigrant medicine and that best practices can be defined and put into practice. All immigrant patients should have access to medical care appropriate for the US-born population plus additional attention paid to migration-associated conditions that can be identified with appropriate screening and physical examination. Providing patient-centered care in a multicultural environment must also be accompanied by acknowledging and respecting cultural differences; this practice should be expected of every health care professional working in the 21st-century global health environment.[1]

IMPROVING THE HEALTH OF NEW AMERICANS

The Minnesota Immigrant Health Task Force, a 2-year citizen advisory group, developed a group of action steps to improve the health of new Americans.[2] These steps (summarized in Box 19-1) are worth reviewing, as they apply to any immigrant group and identify specific actions that can be taken to reduce health disparities in immigrants. Health care professionals cannot accomplish the action steps alone; input from policy

Box 19-1. Steps to Improve the Health of New Americans

1. Provide equal access to health care.
2. Improve health care organizations' capacity to provide care to immigrant populations.
3. Recognize different health care costs for immigrants and provide equitable payment.
4. Develop clinical guidelines and best practices for immigrant patients.
5. Diversify the health care workforce.
6. Use trained interpreters.
7. Use community health workers.
8. Train and educate health care professionals and immigrant patients.

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makers, administrators, academic researchers and educators, and advocates for immigrants and their families is also necessary for success.

ADDRESSING LANGUAGE AND CULTURAL BARRIERS

Health care professionals should be comfortable working with interpreters when taking care of immigrant families. Although the ideal situation is to have a bilingual or multilingual practitioner for every encounter, the reality is that too many languages are spoken and there are too few practitioners who are multi-lingual to ensure language-concordant practitioners for every encounter. Health care professionals are responsible for ensuring that children with limited proficiency in English and their parents or guardians have meaningful access to health services.[3] Health care organizations are also required to ensure the competence of the language assistance provided. Using family members, especially young children and friends, as interpreters is discouraged unless the patient specifically requests this and declines a professional interpreter. In many cases, patients who bring family members or friends to interpret will understand the need for professional interpreters when it is explained to them. These same patients may request that their friends be present during the encounter as an additional level of interpretation and support.

Linguistic access can be provided in many ways, such as through bilingual health care practitioners, professional in-person interpreters, and telephone interpreters. The number of medically trained telephone interpreters has increased substantially in recent years. Access to telephone interpreters is especially valuable in settings where a large number of immigrants are seen or many different languages, especially rare languages, are spoken.

Providing trained interpreters is, of course, just one part of culturally competent care. Health care professionals caring for immigrants must also be sensitive to and, ideally, knowledgeable about different concepts of healing systems outside the United States. General principles of cultural competence include awareness of one's own cultural beliefs, displaying attitudes that convey respect and engender trust, developing verbal and nonverbal communication skills that facilitate mutual understanding, and developing multicultural communication skills.[4,5]

Attending school is one of the first sustained activities immigrant children have within US culture. Health care professionals have a role in helping immigrant families access optimal education for their children. It is helpful if pediatricians understand the services that local schools provide for children with limited English proficiency.[6]

PUBLIC HEALTH ASPECTS OF MEDICAL SCREENING FOR IMMIGRANTS AND REFUGEES IN THE UNITED STATES

Foreign-born individuals arrive in the United States in many different ways and with highly variable exposure to medical services in their countries of origin or while in transit. US health care professionals must be prepared to face a wide spectrum of health problems. A pediatrician cannot assume that a specific process of screening or immunization was done prior to departure unless written or electronic documentation is available. Screening requirements vary depending on immigration status, and they change frequently. In reality, a small number of immigrants will have received comprehensive screening and immunization before entering the United States and be able to provide documentation of it. Additional information about the current screening requirements can be found at www.cdc.gov/ncezid/dgmq.

Individuals admitted to the United States as refugees are entitled to a health assessment on arrival, but there is no uniform national protocol, nor are refugees required to complete the assessment. Each state decides what it is able to provide to refugees, with some offering minimal screening and others providing comprehensive services including screening, immunizations, an introduction to the US health care system, and help transitioning to the US primary care health system.[7] Health care professionals are encouraged to find out what exists in their areas, states, or local health department to help immigrants with health care transition.

Medical Screening for Immigrants and Refugees

The goals of health screening on arrival to the United States include identifying contagious conditions (eg, infectious tuberculosis [TB]) that could pose a risk to the US population, providing a

comprehensive health assessment to identify symptomatic and asymptomatic health conditions, providing needed immunizations, and serving as an introduction to US health services. Box 19-2 lists health assessment components.[8]

Obtaining a complete history will depend on establishing rapport with patients and their families. Some immigrants may be disinclined to reveal aspects of their past until they are able to establish a degree of trust in the health care professional. Elements of the history should include details of the countries lived in, living conditions, and route to the United States. Specific attention should be paid to current health concerns, such as pain or chronic health problems. The health care professional should ask about symptoms of diseases that might be absent or less common in the United States, such as fevers with malaria, jaundice with hepatitis, itching with filarial diseases, or night sweats, cough, or weight loss associated with TB. Social history should include family structure, information about literacy and school attendance, languages spoken, and exposure to or witnessing of trauma or torture. Obtaining

Box 19-2. Components of Health Assessment for New Immigrants

- History
- Physical examination
- Hearing and vision screening
- Dental evaluation
- Mental health assessment
- Tuberculosis screening
- Laboratory screening
  - CBC with differential
  - Hepatitis B serology (testing for infection and existing immunity)
  - Lead level
  - Urinalysis
  - Stool for ova and parasites
  - Malaria smear or other testing (when indicated by history)
- Immunizations according to ACIP recommendations
- Other laboratory testing based on information gained from history and physical examination
  - HIV testing
  - RPR
  - Hepatitis C testing
  - Hepatitis A testing (those with hepatitis B or C infection; vaccine candidates where prevalence of hepatitis A is high enough in the country of origin so that testing may be cost-effective compared with cost of immunizing)

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CBC, complete blood cell count; HIV, human immunodeficiency virus; RPR, rapid plasma reagin.

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complete information may take a number of visits as the relationship develops between the practitioner and the patient and family.

The physical examination should be complete and include special focus on conditions that may be more common in certain immigrant groups, such as dental disease, untreated heart conditions, hepatosplenomegaly, ritual scarification, or growth or developmental problems. Growth parameters should be measured and plotted; particular attention should be paid to whether there might be a discrepancy between the patient's true age and what is reported on immigration documents. Pelvic examination is almost never appropriate during an initial health assessment unless there is a specific medical indication.

Mental health screening is an important aspect of a health assessment[9] but may not always be easy to accomplish in the first visit.[10] A family's initial priorities on arrival in the United States center around obtaining appropriate housing, enrolling children in school, finding employment, and learning English, if necessary; mental health counseling, even if conditions such as post-traumatic stress disorder (PTSD) or depression are present, may not be a priority. It is important, however, to ask about symptoms of hyperarousal, avoidance, and difficulties with sleep, memory, and concentration; more urgent attention may be needed if these symptoms interfere significantly with resettlement tasks. In some cases, these symptoms may not come to medical attention until the child enters school or another environment where the symptoms interfere with appropriate functioning.

Depression or PTSD in parents may affect children; evaluating and treating parents is critical in these circumstances. Assessing family function and the resettlement process can include asking if the adults in the family found employment or are learning English and if children are enrolled in school, as well as assessing general interfamily interactions during the encounter.

Laboratory Screening of New Immigrants

Tuberculosis

There is strong evidence to support screening all new immigrants for TB. An increasing proportion of TB cases in the United States are in foreign-born individuals; beginning in 2002, foreign-born individuals accounted for more than 50% of US TB cases.[11] The overseas screening process for refugees was enhanced recently to include TB skin tests (TSTs) and sputum cultures for individuals considered at increased risk (ie, high-risk groups, a family member with TB, signs or symptoms of TB); previously, only chest radiographs were done. One significant

challenge is ensuring that overseas screening records are available to the health care professionals seeing these patients on arrival in the United States. Currently, unless overseas records are available, a TST should be placed or, if appropriate, an interferon gamma release assay done on all new arrivals, even those with chest radiographs interpreted as showing evidence of prior TB.

Receipt of bacille Calmette-Guérin (BCG) vaccine is not a contraindication to screening for TB. If a TST is done, it should be interpreted without regard to BCG vaccination. Individuals with positive TSTs should be evaluated for any evidence of active TB, especially for manifestations of extrapulmonary TB. If none are found, the individual is a candidate for treatment for latent TB infection (LTBI) and should be managed by TB programs or health care professionals familiar with the management and follow-up of TB and LTBI and adverse events of antituberculosis medications. Some experts, particularly those who care for internationally adopted children, recommend repeating the TST 3 to 6 months after the first.[12] This may be especially important when the new arrival is malnourished or ill at the time of the initial health assessment or there is other reason to suspect that response to the initial TST may not be optimal.

Blood-based assays were developed in the past decade as an alternative to skin testing for diagnosing TB. These tests are based on the release of interferon gamma in response to TB antigens and have the advantage of being more specific for *Mycobacterium tuberculosis* than TSTs. They are recommended by the Centers for Disease Control and Prevention (CDC) as being interchangeable with TSTs for use in TB screening in most healthy individuals older than 5 years and are beginning to be used routinely for TB screening in appropriate immigrant patients when available. Data continue to accumulate about use of these assays in children and immigrants.[13]

Hepatitis B

All immigrants should be considered for testing for hepatitis B infection, and testing is recommended for those arriving from areas where prevalence of hepatitis B surface antigen is 2% or more (ie, parts of Asia, Africa, and Latin America). Identifying hepatitis B infection allows the individual to receive appropriate management and treatment and facilitates implementation of actions to reduce transmission to others, such as immunizing family members and close contacts and educating the individual about reducing transmission (eg, not sharing razors or toothbrushes, management of blood spills). Individuals infected with hepatitis B should be referred to an appropriate specialist for further evaluation of

infection status and assessment of treatment options. Individuals found to have hepatitis B surface antibody should have their immunization records reviewed, as it is common for immigrants to receive a single dose of hepatitis B vaccine prior to arriving in the United States to satisfy immigration requirements. The antibody test may be positive if tested on arrival, but immunity may not be durable unless the individual completes the 3-dose series. Use of hepatitis B core antibody is controversial when testing immigrant children but is felt to have value when assessing adults for prior hepatitis B infection.[14]

Complete Blood Cell Count

A complete blood cell count with differential can identify anemia, thrombocytopenia, and eosinophilia, all of which may have important implications in immigrants. Anemia may be caused by iron deficiency, hemoglobinopathy, or glucose-6-phosphate dehydrogenase deficiency. Thrombocytopenia may be associated with malaria. Eosinophilia is often associated with parasitic infection and should be addressed with appropriate serologic testing for parasitic diseases along with stool testing for ova and parasites or with empiric treatment for appropriate parasites.

Parasitic Diseases

Testing stool for ova and parasites is appropriate for many, but not all, immigrant populations. Stool testing alone is not sufficient for patients with eosinophilia; these patients also need an evaluation with serology or other appropriate tests for parasites, such as strongyloidiasis, schistosomiasis, or filarial diseases. The CDC recently published guidelines for evaluating refugees for parasites; these guidelines are available at www.cdc.gov/ncezid/dgmq. Routine screening for malaria is not indicated for most immigrants. Most clinicians would focus on signs and symptoms when taking the medical history and screen those with compatible findings (eg, fevers, splenomegaly, thrombocytopenia).

Sexually Transmitted Infections

Some experts recommend testing all immigrants for syphilis and HIV. Others limit their testing to those with compatible signs or symptoms. Some refugees and immigrants may be tested before arriving in the United States, but testing for HIV is no longer required as a condition of immigration. US-based health professionals may want to review documentation of these results and be aware that there may be additional exposure between testing and arriving in the United States. Testing for other sexually transmitted infections may be based on information obtained during the history and physical examination.

Hepatitis C

Routine testing for hepatitis C is not recommended at this time for all immigrants, although it is often performed for internationally adopted children. Screening guidelines for the US population may be used to assess whether immigrants are candidates for testing.

Immunizations

Immigrants should be immunized according to current US recommendations. In most circumstances, written documentation of immunizations given outside the United States may be accepted as valid if the vaccine name and month and year it was administered are listed. Immunization records of internationally adopted children are under increased scrutiny; the American Academy of Pediatrics (AAP) permits repeating all immunizations or using serologic testing for antibody to vaccine-preventable diseases to guide administration of needed vaccines. The AAP *Red Book* and yearly immunization schedules developed by the Advisory Committee on Immunization Practices are excellent references. Detailed discussion of immunization issues for immigrants can be found in the article, "Immunization for immigrants."[15]

Immunization records from outside the United States should be reviewed and the vaccines documented in the child's immunization record. Specific issues to look for include a measles-containing vaccine given before 1 year of age (these children need 2 additional doses after 1 year of age); reversal of day and year; and incomplete hepatitis B vaccine series (be sure to complete the series even if screening shows that the child has measurable hepatitis B surface antibody). For school-aged children, measuring antibody to varicella may be cost-effective compared with empiric immunization, especially if a history of varicella is obtained in the patient's child or sibling. For older children, screening for hepatitis A IgG antibody may be cost-effective compared with 2 doses of vaccine, especially if the child has a history of jaundice.

PREVENTIVE HEALTH CARE FOR IMMIGRANT CHILDREN

Immigrant children should receive the same preventive care as US-born children but may experience more barriers to getting this care. Immigrant children are less likely to have health insurance. Language barriers can make it more difficult for immigrant families to access care, learn about available services, understand recommendations, and navigate our complex health and health insurance systems.

The stresses of relocation, as well as those associated with uncertain or undocumented immigration status, may also affect ability to take advantage of what the health care system offers. Children of immigrant

families are the fastest growing segment of the US pediatric population. Outreach into communities as well as health care professionals' cognizance of immigrant children's needs are necessary for addressing the barriers to care for these children.[16]

KEY POINTS

- Be prepared to provide qualified medical interpreters and an introduction to the US health care system to families new to the United States.
- Be prepared to test new immigrants for TB and hepatitis B infection.
- Become familiar with common screening tests that may be beneficial for immigrant populations.
- Provide time during multiple visits with families new to the United States to develop a relationship that will lead to increased trust and sharing of health information.
- Become familiar with catch-up immunization schedules for children of all ages.
- Be prepared to hear stories of resilience, strength, and courage from immigrant families and to be rewarded by the experience of caring for new Americans.

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SECTION 3

Practicing Pediatrics in Resource-Limited Countries

CHAPTER

20

Newborn Care

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INTRODUCTION

Newborns account for approximately 40% of deaths in children younger than 5 years.[1] The vast majority of these 3.1 million neonatal deaths occur in the developing world.[1] The 3 leading causes of neonatal death are preterm birth complications, intrapartum-related complications, and sepsis or meningitis.[1] In addition, many newborns who survive to childhood experience lifelong problems. Many of these problems are potentially preventable by simple interventions and early treatment.

- Neurologic disability from severe perinatal asphyxia resulting from prolonged labor and a difficult delivery without a skilled attendant
- Deafness from neonatal jaundice in a neonate born near a clinic without phototherapy units and transport to a referral hospital
- Severe developmental delay after inappropriate treatment of neonatal meningitis with oral antibiotics after only 3 days of parental treatment
- Severe growth retardation in a premature newborn who is fed inappropriately diluted cow's milk

NEONATAL RESUSCITATION

The following section is adapted from Textbook of Neonatal Resuscitation, *6th Edition.*[2]

Neonatal resuscitation is one of the most important tools in saving newborn lives and preventing birth asphyxia and its sequelae. Numerous studies across the world demonstrate decreases in neonatal mortality or birth asphyxia with the introduction of neonatal resuscitation programs as well as fresh stillbirths that may be incorrectly coded as stillbirths. Fresh stillbirths are often classified as neonatal death, but these infants may, in fact, respond to appropriate neonatal resuscitation, even in low-resource settings. A recent study in Tanzania was associated with a significant reduction in neonatal death with the implementation of Helping Babies Breathe training (RR 0.53; 95% CI 0.43-0.65; $P \leq 0.0001$) as well as the rates of fresh stillbirths (RR 0.76; 95% CI 0.64-0.90; $P \leq 0.001$).[3] One study in China by Zhu and colleagues reported an almost 3-fold reduction in the perinatal neonatal mortality rate after a neonatal resuscitation program was introduced.[4] In Uganda, O'Hare et al reported significantly improved Apgar scores, decreased asphyxia incidences, and survival of newborns weighing more than 2 kg.[5] Deorari et al in India reported a significant decrease in asphyxia-related deaths.[6] Turkey saw a decrease in neonatal mortality rates of 41 to 29 per 1,000 live births between 1998 and 2003 after introducing the Neonatal Resuscitation Program (NRP).[7]

Other studies show that minimal neonatal resuscitation skills can be taught effectively to various health care practitioners in the developing world.[8–11] As so clearly pointed out by Singhal and Bhutta[12] and stated explicitly by Choudhury,[7] neonatal resuscitation needs to be carried out in "practically all settings where asphyxiated babies are born," which, as we know, includes homes, communities, churches, health centers, and hospitals providing all levels of care. The appeal of the current NRP is that it is possible to effectively teach the minimal steps of resuscitation at each of these levels.

Supplies and steps of neonatal resuscitation are adapted from *Textbook of Neonatal Resuscitation,* 6th Edition,[2] to be used in lower resource settings. Helping Babies Breathe[13] is a program for neonatal resuscitation in low-resource settings that includes a low-cost simulator (NeoNatalie) and a simple method to train all those involved in delivering babies, even in homes and villages. Helping Babies Breathe does not require that the birth attendant be literate; it focuses on the Golden Minute, which stresses the need for ventilation by 1 minute in any newborn without effective breathing by the end of that first minute. Interestingly,

in the study by Msemo et al in Tanzania, implantation not only led to improved survival, as noted earlier, but also a decrease in bag-mask ventilation, presumably from improved initial steps of resuscitation.[3]

Basic Supplies for Neonatal Resuscitation

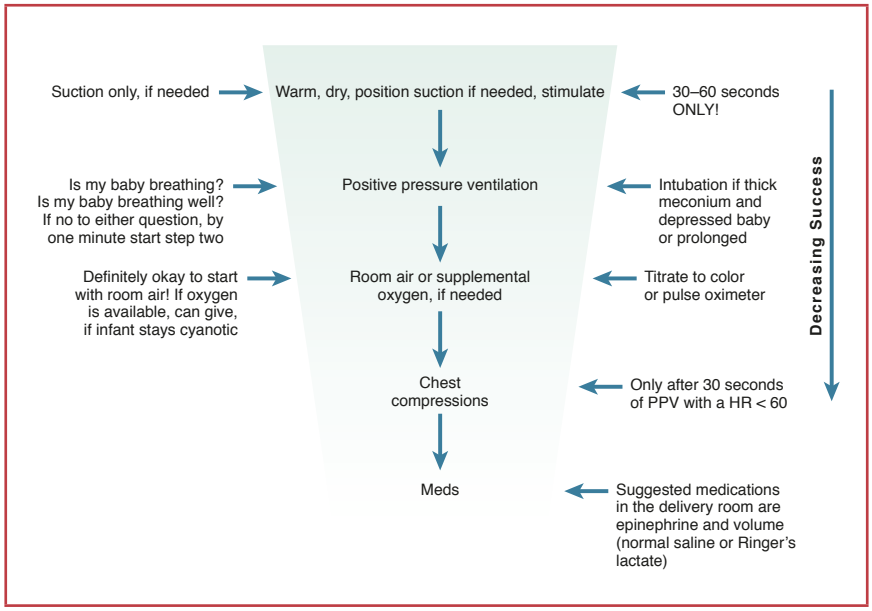
Neonatal resuscitation can be done with minimal equipment and supplies. Equipment, supplies, and instructions should be tailored to the clinic or hospital as well as to the training and experience of the facility's personnel. Basic supplies are limited to

1. A warm place for the newborn. This can be as simple as a warm room with closed windows and overhead fans turned off or a table under an overhead warmer or bulb.
2. Two clean cloths. One cloth is to dry the neonate and one is to wrap or swaddle the baby after drying. It is important to cover the newborn's head and leave his chest and abdomen exposed should he need active resuscitation.
3. Something with which to suction the baby's airway. This can be a simple bulb aspirator, a mucus extractor, a DeLee suction trap, or a suction machine powered by foot, battery, or wall electricity. A simple bulb aspirator often works better than a small suction catheter, especially if intubation is unnecessary or not possible. Any suction device needs to be cleaned effectively and appropriately between patients to avoid infection.
4. A self-inflating bag and mask. The bag and mask need to be checked after each use to ensure they are still functional and that all parts are clean and working properly. Mouth-to-mouth resuscitation by mothers or family members is sometimes appropriately taught in community-based resuscitation programs.[8] Concerns about health care practitioners acquiring infections limit the applicability of mouth-to-mouth resuscitation in clinic and hospital settings. Reusable bags are preferred over disposable bags and need to be cleaned according to directions.
5. A clock. Although a clock is not essential, one that is easy to read helps time interventions and making other time-related decisions.

Resuscitation Steps

The inverted pyramid (Figure 20-1) is a concise summary of resuscitation and helpful in teaching. It emphasizes the point that the first steps in resuscitation are the most likely to be successful and, therefore, are the steps on which teaching should be concentrated. Progress toward the apex of the resuscitation triangle will depend on resources and staff skill levels. Infection control should always be observed

Figure 20-1. Inverted Neonatal Resuscitation Pyramid



Modified from American Academy of Pediatrics, American Heart Association. *Textbook of Neonatal Resuscitation*. 6th ed. Kattwinkel J, ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011.

throughout resuscitation. Checking to make sure basic supplies are available and clean and in working order is a must at every shift and before every delivery.

At the time of birth, 3 questions should be asked: Is the baby term? Is the baby breathing? Does the baby have good tone? Term, healthy, vigorous newborns who are crying or breathing well do not need resuscitation and should be dried and placed on the mother's chest and covered with a clean, dry cloth or blanket.[14,15] These same newborns also do not need suctioning. Those newborns who are not crying or breathing well will need resuscitation. The first block of the resuscitation triangle includes

1. *Warm*. Place the newborn in the warmest place in the room that still allows access. Turn off fans and close windows.
2. *Dry* the newborn and get rid of the wet cloth. Leaving on the wet cloth makes the newborn colder, which can make resuscitation more difficult, especially if the newborn is premature.
3. *Position*. Position the newborn's head in a neutral or sniffing position, not hyper-flexed or hyperextended.

4. *Suction only if needed.* Vigorous term newborns do not need suctioning. Suction the baby's mouth first, then the nose. Suctioning the nose first increases the chance that the baby will get angry, attempt to cry, and aspirate what is in the mouth (eg, amniotic fluid, meconium). One tool that NRP uses to teach this is that M comes before N in the alphabet, just as *m*outh comes before *n*ose in neonatal resuscitation. Suction gently, preferably with a bulb syringe, and avoid suctioning too deeply, especially when using a suction catheter. If a physician or health care practitioner is not available during a resuscitation of a depressed newborn with thick meconium, the nurse or midwife should be instructed to suction the mouth and nose as best as possible with the device on hand (eg, bulb, mucus extractor, large suction catheter) and then proceed with resuscitation as usual. Suctioning can unnecessarily cause bradycardia and trauma and should therefore be avoided. See Indications for Intubation on page 435 for instructions about thick meconium in a depressed newborn when a skilled practitioner who can intubate is available.
5. *Stimulate.* Stress safe stimulation methods, which primarily include flicking the baby's feet and rubbing her back. Do not use unsafe methods, such as holding the baby upside down and slapping her bottom; putting alcohol, pepper, or other substances in her nose; putting her in cold water; or compressing her abdomen or chest. Emphasize limiting stimulation time, as the newborn with primary apnea will respond rapidly. Neonates in secondary apnea will not respond to stimulation regardless of duration. If stimulation is not immediately effective, proceed to positive-pressure ventilation.
6. *Emphasize the need to respond and work quickly.* The first 5 steps should take no more than 30 to 60 seconds. A newborn who is not breathing or not breathing well by 1 minute of life should receive positive-pressure ventilation. Practice the timing with obstetric and pediatric staff until it happens without thought. Emphasize that more than 1 step can be carried out simultaneously if more than 1 person is available to assist with resuscitation.
7. Emphasize teamwork when possible. Whenever possible, there should be at least 2 people available to help with resuscitation of the newborn. Team concept and roles should be stressed.

Ventilation is the most important step in newborn resuscitation and likely to be successful in any baby who still has a heart rate.[16] Heart rate comes up almost immediately in newborns who are immediately and adequately ventilated. Very few resuscitated newborns need chest compressions or medications. Teach and practice good hand position

creating a seal with the mask without obstructing the airway. If the chest is not rising or not rising well, quickly figure out the problem. Possibilities, in order of likelihood, include

1. Ineffective seal between the mask and face. This usually responds to repositioning the practitioner's hand on the mask or the newborn's face or repositioning the newborn's head or opening his mouth.
2. Secretions. Repeat suctioning.
3. Bad bag or mask. Replace.

Supplemental oxygen is not routinely needed at the beginning of a resuscitation. Most term neonates with respiratory depression at birth will respond to adequate ventilation with room air. Oxygen is toxic, especially in high concentrations when tissues become oversaturated, and may be harmful in neonatal resuscitation.[2,17,18] Current NRP training states that it is preferable to begin the step of resuscitation without oxygen.[2,16] If available, oxygen should be titrated to keep the neonate pink and oxygen saturations normal. Therefore, if the practitioner begins without oxygen and the neonate remains blue (or desaturated), oxygen should be added, if available. If the neonate is pink (or well saturated) and oxygen is being used, it should be weaned rapidly as long as the neonate remains pink (well saturated). It is normal for the pre-ductal oxygen saturation (ie, right hand) to take up to 5 minutes to get to 80% to 85% oxygen saturation and up to 10 minutes to get to 85% to 95% oxygen saturation.[2]

These oxygen instructions are for the delivery room; decisions addressing which newborns should be placed on oxygen in the nursery and what saturations are appropriate are made at the time of transfer to the nursery, when indicated.

Heart rate should be checked after 30 seconds of positive-pressure ventilation. Chest compressions should not be done until after 30 seconds of effective positive-pressure ventilation. Effective ventilation means the chest is moving—not too much and not too little. Heart rate can be estimated by counting the umbilical cord pulsations for 6 seconds or by counting heart rate for 6 seconds and multiplying by 10 (ie, if the 6-second heart rate is 4, the baby's heart rate is about 40 beats per minute [BPM]). An increasing heart rate is the best sign of effective ventilation in a newborn. Positive-pressure ventilation should be continued until the heart rate is greater than 100 BPM, the baby is breathing effectively, or resuscitation efforts are stopped.

Chest compressions are indicated if the heart rate remains below 60 BPM after 30 seconds of effective ventilation. They should be done at a rate of 3 compressions to 1 ventilation, compressing the chest

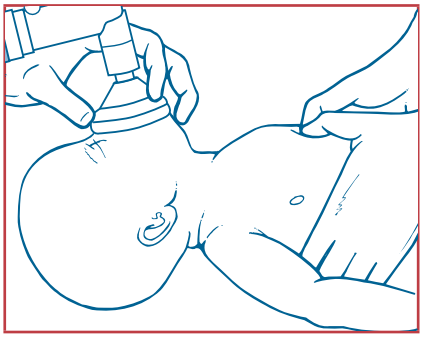
about one-third of the chest's diameter. Encircling the baby's chest with 2 hands, using fingers to provide a hard surface for compressions, is the most effective and preferred way for practitioners to perform compressions (Figure 20-2). However, the baby can be placed on a hard surface and compressed with 2 fingers (Figure 20-3); this method is best for single rescuers providing ventilation and cardiac compressions.

Medications are not generally needed in neonatal resuscitation and, according to Wyllie and Niermeyer, are "probably justifiable in less than 0.1% of births."[19] The single most important resuscitation medication is *epinephrine* (still called adrenaline in many countries). Epinephrine increases the strength and rate of cardiac contraction and may increase blood flow to the head and coronary arteries. The only concentration routinely available in many countries is 1:1,000, which is usually supplied in a 1-mL vial; this is too concentrated to give to a neonate by intravenous (IV) or intraosseous infusion and needs to be diluted 1:10 to make a concentration of 1:10,000 (Table 20-1).

An umbilical venous catheter (UVC) may be placed to facilitate medication and fluid administration. The procedure for placement includes

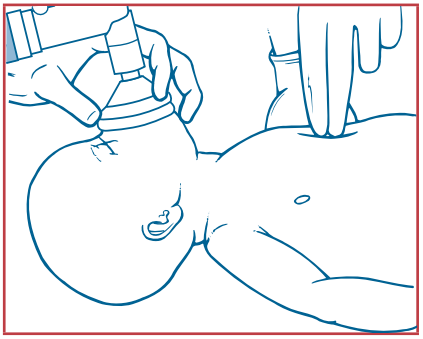
1. Retrieve needed supplies.
   a. A sterile tube that can be inserted into the umbilical vein; any sterile tube that is the correct size can be used (often a 5-6 feeding tube).
   b. A tie for the umbilical stump, which can be tightened if there is bleeding.
   c. A sterile blade or scalpel.
   d. Sterile cloth or drapes (the inside wrapper of a glove package can be used in an emergency).

Figure 20-2. Thumb Compressions



From American Academy of Pediatrics, American Heart Association. *Textbook of Neonatal Resuscitation.* 6th ed. Kattwinkel J, ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011:137.

Figure 20-3. Two-Finger Compressions



From American Academy of Pediatrics, American Heart Association. *Textbook of Neonatal Resuscitation.* 6th ed. Kattwinkel J, ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011:137.

Table 20-1. Dilution Options to Make 1:10,000 Epinephrine, Depending on Syringe Size

EPINEPHRINE 1:1,000	STERILE WATER OR NSS	TOTAL CONCENTRATION OF 1:10,000
0.1 mL	0.9 mL	1 mL
0.2 mL	1.8 mL	2 mL
0.3 mL	2.7 mL	3 mL
0.5 mL	4.5 mL	5 mL
1 mL	9 mL	10 mL

Abbreviation: BPM, beats per minute; IO, intraosseous; IV, intravenous; NSS, normal saline solution; UVC, umbilical venous catheter.

Epinephrine can be repeated every 5 minutes if the heart rate remains less than 60 BPM.

The dose for a neonate is 0.1 to 0.3 mL/kg IV/IO (weight is estimated to the nearest 0.5 kg to make math simpler). Follow dose with a flush of sterile water or NSS. If IV cannot be quickly started, consider a UVC or IO.

   e. Soap or cleaning solution for the cord and abdomen.
   f. Hemostat to hold the cord before cutting.
2. Elevate the cord off of the abdomen, clean the cord, and drape the abdomen.
3. Place the clean tie or umbilical tape on the skin at the cord's base and tighten slightly.
4. Cut the cord with a sterile blade or scalpel.
5. Insert the catheter into the larger umbilical vein just until there is good blood flow; if it is inserted more than 2 to 4 cm, it is probably in too far. Administering medication into the liver can be dangerous; it can be avoided by inserting the catheter just until good blood flow is obtained. If the UVC is to be left in, it can be replaced and positioned above the liver, confirming position with a radiograph as described in neonatal handbooks/textbooks.[20] There are several methods for determining the approximate length to insert a UVC that is going to be left in. One method is to determine the length in centimeters, which is done by measuring the distance from the shoulder at the distal end of the clavicle and multiplying the length obtained by 0.66.[20]
6. Medication can be administered and blood samples obtained through this catheter.

If bleeding is suspected and the newborn is not responding to resuscitation, a 10 mL/kg bolus of normal saline solution (NSS) or lactated Ringer solution can be given over 5 to 10 minutes and repeated if needed.

Other medications, such as sodium bicarbonate, calcium, atropine, and narcotic antagonists, are rarely indicated or effective in neonatal resuscitation in the delivery room.

Indications for Intubation

Intubation is indicated at the delivery of a depressed newborn with thick meconium when a practitioner is available who can effectively perform the intubation. In this situation, the practitioner should intubate and suction the newborn before stimulating or providing positive-pressure ventilation. It is best to suction with a device attached directly to the endotracheal tube (ETT) or to intubate directly with a large suction catheter (14FR). Small suction catheters inserted through small ETTs are ineffective in suctioning out significant amounts of thick meconium. Devices to attach a 3 or 3.5 ETT can often be made out of available tubing if commercial devices are not available. Intubation is not recommended for vigorous newborns with meconium-stained amniotic fluid.

Intubation is not necessary in a standard neonatal resuscitation, as ventilation can be provided even for extended times with a bag and mask. However, if the health care practitioner is skilled in intubation, the newborn may be electively intubated at any point, especially if resuscitation may be prolonged. If prolonged bag-mask ventilation is going to be provided, pass a small orogastric or nasogastric tube to keep the stomach deflated. It is possible to provide effective bag-mask ventilation with a small nasogastric tube in place.

Discontinuing Resuscitation Efforts

It is appropriate to discontinue resuscitation when a newborn has a heart rate above 100 BPM and good respiratory effort. If the heart rate is below 100 BPM, ventilation should continue regardless of the respiratory effort unless the decision is made to discontinue all resuscitation efforts.

It is not always clear when unsuccessful resuscitative efforts should be discontinued. Generally, if there are no signs of life at 10 to 20 minutes after delivery, it is appropriate to discontinue resuscitation. Sometimes the more difficult decision is what to do when a newborn's heart rate is greater than 100 BPM but there is no respiratory effort and the newborn is in a setting without a ventilator. In this situation, it is important to rule out reversible causes of apnea or agonal respirations, such as narcotic overdose. If there are no reversible causes identified and no mechanical ventilation is possible, it may be appropriate to stop resuscitation efforts at some point, which will vary depending on the specifics of the situation. This decision is made after carefully considering many factors, including the clinic's or hospital's resources and discussion with parents.

Preterm Birth

Each year, 15 million neonates worldwide deliver prematurely before 37 completed weeks' gestation. Approximately 12% of all births in low-income countries are preterm; more than 60% of these occur in Africa and South Asia. Most are late preterm neonates born at 34 to 36 weeks' gestation. Preterm neonates are at higher risk for virtually all neonatal problems, including hypothermia, hypoglycemia, respiratory distress, apnea, infection, feeding intolerance, jaundice, and brain injury. Surviving preterm neonates continue to be at higher risk during infancy, especially for infection and malnutrition.

Prematurity is the leading cause of neonatal death; most survivors in low-resource settings are born at later than 32 weeks' gestation. Although more than 1 million premature newborns die each year from complications related to their preterm birth, most could be saved with basic intrapartum and neonatal support using cost-effective interventions such as antenatal steroids, clean delivery, basic neonatal resuscitation, exclusive human milk feeding, continuous skin-to-skin (STS) mother care, and antibiotic therapy for suspected infection. The ability to provide IV fluids, phototherapy, oxygen, and noninvasive continuous positive airway pressure (CPAP) for respiratory distress further reduce morbidity and mortality.[21] In a recent report from South Africa, 75% of extremely low birth weight (mean 856 g) and gestational age (mean 27.7 weeks) preterm neonates survived in a limited resource setting given access to maternal antenatal steroids, delivery room support, and surfactant or nasal CPAP for respiratory distress.[22]

FLUIDS AND NUTRITION

Appropriate fluids and nutrition are extremely important for the survival of a sick and premature neonate. This can be especially challenging in environments without IV pumps, micro-drip (giving) sets, and total parental nutrition.

Fluid Requirements

Fluid requirements for term newborns are 60 to 80 mL/kg/day on day 1 of life and increasing by about 20 mL/kg/day thereafter, up to 120 to 160 mL/kg/day. Factors that increase fluid requirements, such as phototherapy and overhead warmers, or decrease fluid requirements, such as congestive heart failure and renal insufficiency, must be considered when calculating fluid requirements. Term newborns may lose 5% to 10% of their birth weight in the first week before caloric intake is adequate. Most healthy term newborns regain their birth weight by

day 7. Premature newborns generally require more fluid per kilogram per day. The more premature the baby, the higher the insensible fluid loss through the skin and the more total fluids required. Fluid requirements for the premature newborn start at the upper end of the fluid requirements for term newborns and also increase by about 20 mL/kg/day, with the maximum titrated to achieve adequate hydration without fluid overload. Generally, fluid requirements for premature newborns are a maximum of 150 to 160 mL/kg/day, but extremely premature babies with birth weight less than 1 kg may require more than 200 mL/kg/day to maintain hydration because of excessive insensible fluid loss through their thin skin. Keeping premature newborns inside a humidified incubator or placing them under a small tent of plastic wrap decreases their insensible loss and total fluid requirements. Premature newborns may lose up to 15% of their birth weight, which is proportionally more than term newborns, and take longer to regain their birth weight. It is helpful to plot their weight on a graph (Figure 20-4) every 1 to 3 days to ensure that initial weight loss and subsequent weight gain are appropriate.

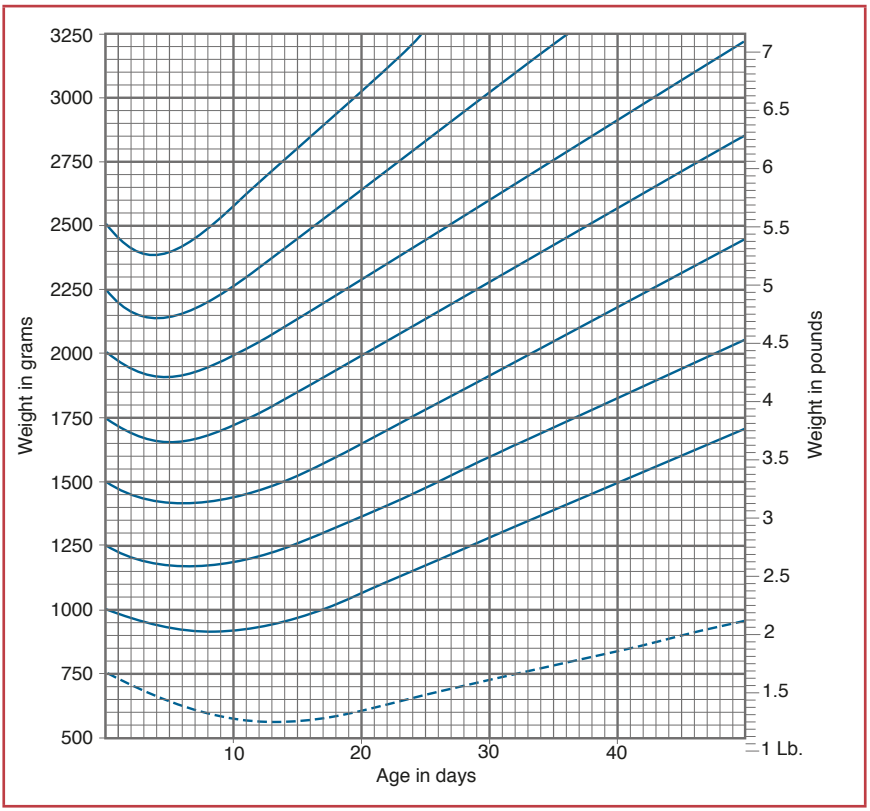
Types of Intravenous Fluids

The appropriate type of fluid also varies by day of life and birth weight or gestational age of the newborn. Dextrose 10% in water (D10W) is generally the recommended fluid on the first 1 to 2 days of life for newborns weighing 1 kg or more. Those weighing less than 1 kg should start on dextrose 5% in water (D5W). Neonates small for gestational age (SGA) and those of diabetic mothers may require a higher glucose infusion rate based on weight to maintain euglycemia (blood glucose >40–45 mg/dL). Fluid intake per day should be calculated based on birth weight until birth weight is regained.

Electrolytes in IV fluid (IVF) are usually not needed in the first 48 hours of life. Sodium (2–4 mEq/kg/day) should be added after 48 hours. Hyponatremia is unlikely in low-resource settings in the first few days of life. Hypernatremia is more common due to a variety of reasons (ie, hot environments; too little fluid given; excessive sodium loss in the urine, especially in extremely low birth weight [<28 weeks]). Neonates who are younger than 28 weeks and weigh less than 1,000 g may need considerably more sodium than other neonates and should have serum sodium levels monitored whenever possible. However, it is important to avoid administering excessive fluid, as this can lead to hyponatremia, even in term neonates.

Most hospitals are limited to standard IVF mixtures. An approximation can be obtained by adding 25 mL of NSS or Ringer solution (lactated

Figure 20-4. Expected Neonatal Weight Changes Based on Birth Weight



This growth chart is shown because it represents adequate growth without the availability of total parental nutrition, high-calorie formulas, or human milk fortifiers. Newer growth charts reflect nutritional support not available in most of the developing world.

From Dancis J, O'Connell JR, Holt LE. A grid for recording the weight of premature infants. *J Pediatr.* 1948; 33(11):570–572. Copyright 1948, with permission from Elsevier.

Ringer may be used if Ringer solution is unavailable) to 100 mL of D10W or D5W, which provides about 3 to 4 mEq of sodium per 100 mL. Another option is to add additional glucose to D5¼ NSS if available (Box 20-1).

Potassium (1–2 mEq/kg/day) should also be added around day 3 or 4 if the newborn is not tolerating enteric feeds and has adequate urine output. Adding 10 mEq of potassium per 1,000 mL of IVF and providing 1 mEq per 100 mL is practical and maintains normal serum potassium in most newborns. Deviation from this should only occur when clinically indicated. Add potassium to IVFs very carefully to avoid mistakes that can be fatal. Develop a check-and-balance system when adding

Box 20-1. Preparing Standard Glucose and Electrolyte Solutions

TYPES OF SOLUTIONS

Dextrose 50% in water (D50W)

Dextrose 10% in water (D10W)[a]

Ringer Lactate
Sodium: 130 mEq/L
Potassium: 4 mEq/L
Calcium: 2.7 mEq/L (equivalent number of Ca mEq as 0.6 mg/mL calcium gluconate)
Chloride: 109 mEq/L
Lactate: 28 mEq/L

Ringer Solution
Sodium: 147 mEq/L
Potassium: 4 mEq/L
Calcium: 4 mEq/L (equivalent number of Ca mEq as 0.9 mg/mL calcium gluconate)
Chloride: 156 mEq/L

D5¼ NSS (0.225% sodium chloride)
Sodium: 34 mEq/L
Chloride: 34 mEq/L

½ NSS (0.45% sodium chloride)
Sodium: 77 mEq/L

PREPARATION OF SPECIAL SOLUTIONS

To make D10¼ NSS from D5¼ NSS and D50W

1. Remove 50 mL from 500-mL bag of D5¼ NSS.
2. Add back 50 mL of D50W.

When infused at 100 mL/kg/d, provides
- GIR: 7 mg/kg/min
- Sodium chloride: 3.6 mEq/kg/d

To make D7.5¼ NSS from D5¼ NSS and D50W

1. Remove 25 mL from 500-mL bag of ¼ NSS.
2. Add back 25 mL of D50W.

When infused at 100 mL/kg/d, provides
- GIR: 5.2 mg/kg/min
- Sodium chloride: 3.8 mEq/kg/d

To make D7.5¼ NSS from D10W and NSS

1. Remove 62.5 mL from a 250-mL bag of D10W.[b]
2. Add back 62.5 mL NSS to the 250-mL bag of D10W.

Or

1. Remove 250 mL from a 1-L bag of D10W.
2. Add back 250 mL NSS to the 1-L bag of D10W.

When infused at 100 mL/kg/d, provides
- GIR: 5.2 mg/kg/min
- Sodium chloride: 4 mEq/kg/d

Box 20-1. Preparing Standard Glucose and Electrolyte Solutions, continued

PREPARATION OF SPECIAL SOLUTIONS, CONTINUED

To make D7.5 electrolyte solution

1. Remove 62.5 mL from a 250-mL bag of D10W.
2. Add back 62.5 mL of Ringer solution to the 250-mL bag of D10W.

Or

1. Remove 250 mL from a 1-L bag of D10W.
2. Add back 50 mL of Ringer solution to the 1-L bag of D10W.

When infused at 100 mL/kg/d, provides (rounded to the nearest whole number where possible)

- GIR: 5 mg/kg/min
- Sodium: 4 mEq/kg/d
- Potassium: 0.1 mEq/kg/d
- Calcium: 0.1 mEq/kg/d (equivalent to 86 mg/kg/d calcium gluconate—a small dose)
- Chloride: 4 mEq/kg/d

To make D10 lactated Ringer

1. Remove 200 mL from a 1-L bag of lactated Ringer.
2. Add back 200 mL of D50 to the 1-L bag of lactated Ringer.

The resulting solution will have 80% of the original lactated Ringer.

When infused at 100 mL/kg/d, provides (rounded to the nearest whole number where possible)

- GIR: 7 mg/kg/min
- Sodium: 10 mEq/kg/d
- Potassium: 0.3 mEq/kg/d
- Calcium: 0.2 mEq/kg/d (equivalent to 43 mg/kg/d calcium gluconate—a very small dose)
- Chloride: 9 mEq/kg/d
- Lactate: 2 mEq/kg/d

To make D10¼ NSS

1. Remove 200 mL of ½ NSS from a 1-L bag of ½ NSS.
2. Add back 200 mL of D50 to the 1-L bag of ½ NSS.

If infused at 100 mL/kg/d, provides

- GIR: 7 mg/kg/min
- Sodium chloride: 6 mEq/kg/day

Abbreviations: GIR, glucose infusion rate; NSS, normal saline solution.

[a] Other permutations using D5W instead of D10W will result in electrolyte solutions with dextrose concentrations less than 5%.

[b] Save removed D10W in sterile, capped syringes for later (eg, for D10 boluses or for "y-ing" into maintenance intravenous fluids to increase GIR), but it must be done carefully, as it invites contamination if not done in a sterile environment.

potassium, such as having 2 nurses check the amount added. In addition, unless it is absolutely necessary to alter the amount of potassium added, add exactly the same standard amount of potassium to the same volume of IVFs. If enteral feeds (by mouth or nasogastric tube) are being

advanced appropriately, consider not adding potassium to IVFs to avoid potential errors. Ringer and lactated Ringer solution have the advantage of providing an appropriate amount of potassium as well as a very small amount of calcium (see Box 20-1).

Other additives are generally not necessary. Calcium infiltrations can result in severe burns when given via peripheral IV line. If the newborn has symptomatic hypocalcemia with life-threatening conditions, such as seizures, arrhythmias, or hypotension, and a central line is not available, it is safest to slowly give diluted calcium boluses under direct observation in a newly placed peripheral IV line. Be sure the IV line is patent before beginning the calcium infusion. For nonlife-threatening situations, IV or oral calcium gluconate is preferable. *Give calcium by mouth whenever possible because it is the safest route.* The IV calcium gluconate preparation is well tolerated orally. Calcium carbonate antacid can also be given. Calcium glubionate syrup, an oral calcium preparation, is not recommended in newborns because it is hyperosmolar and often causes diarrhea. Although calcium chloride is preferred in life-threatening situations because it does not require conversion in the liver, calcium gluconate, the only form of IV calcium available in many hospitals, is also effective.

Nutrition

Total parental nutrition is seldom available in nurseries in low-resource settings; therefore, early enteral nutrition is essential and should be started as soon as possible after birth.

Term newborns generally require about 110 to 120 cal/kg/day (180 mL/kg/day) enterally to gain weight appropriately. Adequate weight gain is about 20 to 30 g/day or about 10 to 15 g/kg/day after the first 3 to 5 days.[23,24] Most healthy, term, breastfeeding newborns regain their birth weight by days 7 through 10. If a term newborn has not regained his birth weight by then, an explanation should be sought and the newborn followed closely. Changes in breastfeeding technique, higher calorie feeds, or supplementation may be needed. A newborn's stomach is small, holding only approximately 5 mL/kg immediately after birth; therefore, appropriate initial feeding volumes for term newborns are 5 to 20 mL per feed on the first day and 10 to 45 mL per feed on the second day after birth. Feeds in excess of this often result in emesis.

Premature neonates born before 35 weeks' gestation generally require about 120 kcal/kg/day to gain weight optimally. Adequate weight gain is 15 to 20 g/day or about 13 to 15 g/kg/day. As with term newborns, the optimal and best-tolerated feeding is maternal human milk. Because of weak suck, limited stamina, and incoordination, newborns born before

35 weeks' gestation are unable to take full nipple feeds or breastfeed exclusively. Although some will appear to be breastfeeding well, actual milk transfer is low. These newborns require some or all feedings every 2 to 3 hours by nasogastric gavage (5FR) tubes or, in more physiologically mature preterm newborns, by cup or spoon.

Feeding Advancement

In preterm newborns, begin feeds slowly at 20 mL/kg/day on day 1 if clinically stable. Intravenous fluids need to be given to maintain adequate hydration until 60 to 80 mL/kg/day of enteral feeding is reached. Advance feedings slowly by 20 mL/kg/day to reach full feeds at 7 to 10 days of age unless signs of feeding intolerance occur. One suggested systematic method of increasing feeds is included in Table 20-2. The gavage tube is aspirated and the gastric residual measured prior to each feed. Small residuals (≤2 mL) of clear gastric fluid or undigested milk are normal and can be refed without changing feeding volume or schedule. Red-brown–tinged residuals usually indicate old blood in the stomach, which may be swallowed maternal blood or the result of gastric irritation. In the absence of any other sign of gastrointestinal (GI) problems (see Necrotizing Enterocolitis on the next page), these secretions are not an indication to stop enteric feedings. This is important to emphasize to nursery staff because it is a frequent cause of stopping feeds for fear of necrotizing enterocolitis (NEC), but, in fact, if all else is well, it is better to feed maternal human milk than not to neutralize stomach acid. Steady weight gain of 15 to 20 g/day is a sign of adequate enteric intake. When newborns are taking oral feeds, IVFs need to be decreased proportionally as feeding volume is increased to avoid fluid overload.

Table 20-2. Premature Newborn Nutrition: Suggested Feeding

WEIGHT (g)	INITIAL VOLUME OF FEEDINGS (mL)	INTERVAL BETWEEN FEEDING (h)	VOLUME OF INCREMENT (mL)	FREQUENCY OF CHANGE
<1,000	0.5–1	2	0.5–1	Every 24 h
1,000–1,500	1–2	2	1–2	Every 12 h
1,500–2,000	2–3	2–3	2–4	Every 12 h
2,000–2,500	4–5	3	4–7	Every 8 h
>2,500	10	3	10–15	Every 3 h

Adapted with permission from Zlotkin SH, Perman M. Feeding the preterm infant. In: Jeejeebhoy KN, ed. *Current Therapy in Nutrition*. Toronto, Ontario, Canada: BC Decker, Inc; 1988.

Delay initial feedings if there is severe respiratory distress, shock with poor perfusion to the gut, or a condition requiring surgical intervention (eg, duodenal atresia, gastroschisis, omphalocele, or imperforate anus; diaphragmatic hernia; esophageal atresia or fistula), in which case surgical correction of the underlying problem is indicated before starting enteral feeds. Start feeding when the clinical condition is stable and when signs of GI motility have returned (eg, bowel sounds, passing stool, not excessive or bilious gastric residuals).

Feeding Intolerance

Signs of feeding intolerance include persistent or increasing gastric residuals, emesis, abdominal distention, and abnormal stool. Abdominal distention without any other abnormalities may resolve after stooling. Small but persistent non-bilious gastric residuals may indicate slow gastric emptying and, if so, will usually resolve after temporarily decreasing feeding volume. Consider decreasing feeding by about 25% of the previous amount and holding at that level for 2 to 6 feeds, then slowly increasing again. Sepsis is often associated with an ileus, increased residuals, decreased or absent bowel sounds, and abdominal distention.

Feeds should be held when signs of feeding intolerance occur. How long feeds are held depends on the clinical stability of the neonate and seriousness of the problem. Bilious emesis or gastric residuals, bloody stools, or a definitely abnormal bowel radiograph all indicate significant GI pathology, necessitating withholding feedings until several days after all abnormalities resolve.

Gastrointestinal bleeding that is not maternal in origin can be treated with ranitidine IV or enterally. Ranitidine[25] oral dose is 2 mg/kg/dose every 8 hours; IV dose is 0.5 mg/kg/dose every 12 hours slow push (premature) or 1.5 mg/kg/dose every 8 hours slow push (term). Any baby who is actively bleeding should get vitamin K_1 as soon as possible.

Necrotizing Enterocolitis

Persistent vomiting; gastric residuals that are bilious, progressively increasing, or greater than 20% of the preceding feeding volume; abdominal distention, especially if progressive and severe and with visible bowel loops; bloody stools; and clinical instability or acute deterioration are all signs of NEC. A brown or bloody gastric aspirate alone is not a sign of NEC. If a radiograph can be obtained, look for distended, thickened bowel loops; air bubbles in the bowel wall (pneumatosis cystoides intestinalis); portal air in the liver; and free air in the abdomen (pneumoperitoneum), which are all signs of NEC. Newborns with possible, presumed, or definite NEC or surgical abdomen will need to be placed

on nasogastric drainage and broad-spectrum antibiotics with close clinical follow-up, complete blood cell count (CBC), and serial abdominal films. Newborns with perforations are unlikely to survive without total parental nutrition and intensive care that is usually not available in many nurseries in the developing world. The decision to proceed with surgery will depend on available resources and prognosis with surgery.

Human Milk Feeding

Human milk feeding is optimal for almost all newborns. The World Health Organization (WHO) currently recommends exclusive human milk feeding (no other fluids, teas, or foods) for the first 6 months of life, after which complementary feeds are added to breastfeeding, which should continue for at least 18 to 24 months.[26] The many benefits of human milk include improved tolerance of feeds, fewer respiratory and GI infections, decreased incidence of sudden infant death syndrome, and lower infant and early childhood mortality.[27–32]

For the premature newborn, additional benefits include fewer infections, less NEC, and enhanced neurocognitive outcome.[28,33,34] The WHO and United Nations Children's Fund (UNICEF) strongly support exclusive breastfeeding through the Ten Steps to Successful Breastfeeding of the Baby-Friendly Hospital Initiative.[35] In many cultures, mothers discard colostrum, delay the first breastfeeding for hours or days, or give various fluids and teas in the first few days after birth, all of which increase the risk of neonatal morbidity and mortality.

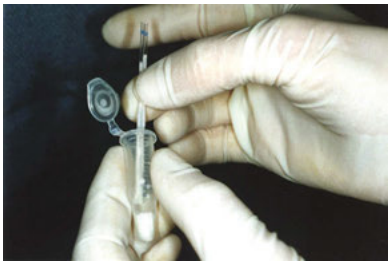
Stress the importance to medical staff and mothers about putting the newborn to the breast within the first hour after birth and giving colostrum, which contains a large amount of immunoglobulin (IgA), lymphocytes, vitamin A, and lactoferrin, all of which protect the baby from infection.[36,37] Many mothers are concerned that they have too little milk in the first few days after birth; reassure them that this is normal. A healthy, breastfed term newborn receives only 30 to 40 mL/kg/day on day 1. Volume gradually increases over the next few days as the mother's milk "comes in." Galactopoiesis may be delayed, especially if mothers are ill or after cesarean delivery. Newborns should breastfeed on demand every 2 to 3 hours (10 to 12 times a day) during the first week. Intake is adequate if the newborn is passing urine and stool several times per day by day 3. Stools should be soft and yellow by day 4. Newborns whose human milk intake is insufficient because of low milk volume or inadequate milk transfer in the first several days after birth often present with dehydration, fever, or jaundice.

The caloric density of human milk in normal healthy mothers varies from 14 kcal/oz to 35 kcal/oz, with a mean of 21 to 22 kcal/oz,[38]

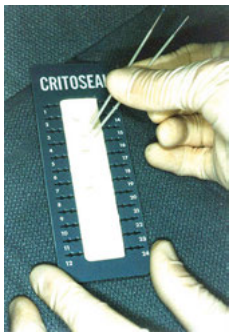
depending on fat content, which is largely independent of the mother's nutritional intake or status except in extreme circumstances. Healthy babies compensate for the caloric density of their mother's milk by altering the volume they consume. When caloric density is low, newborns compensate by feeding longer and more frequently, taking in more milk than newborns of mothers with high-caloric (high-fat) milk. It can be very helpful to determine the caloric content of the mother's milk by measuring fat and calculating the percentage of cream in a sample of the milk (creamatocrit). The creamatocrit can be easily determined, even in developing countries, by putting a sample of human milk in a capillary tube and spinning it in a centrifuge. When it spins down, a layer of fat or cream will appear at the top of the capillary tube, which can be placed on a hematocrit (HCT) reader to view the percentage of fat. The percentage of fat determines the caloric content of the sample (Figure 20-5 and Table 20-3).

Achieving adequate intake and weight gain in breastfed premature and sick newborns can be challenging. When babies cannot obtain adequate intake by directly breastfeeding, as is the case with sick term and many premature newborns, mothers must express their milk every 2 to 3 hours for each feed. Hand expression is the most widely used method in developing countries. Although newer hand pumps and battery or electric pumps may yield higher volumes, most mothers can produce adequate amounts of milk for premature newborns using hand expression frequently, as recently shown in Uganda.[39,40] Although these babies may take only a very small volume per feed from the breast in the first few weeks, it is important for mothers to express their milk frequently and completely empty their breasts at each expression to build up and maintain an adequate milk supply (at least 500 mL/day) as soon as possible after delivery. When volume cannot be increased to compensate for low caloric intake, higher calorie hind milk is one of the most practical and best-tolerated methods of improving weight gain without adding formula-feeding or supplements to expressed human milk in newborns who are unable to breastfeed. The first milk (foremilk) a mother expresses appears thin—low-fat or "skim" milk. As she continues to express milk during a pumping session, it becomes visually thicker as fat content increases—"whole" milk (hind milk). The last milk or "cream" expressed has the highest fat content. Hind milk is well tolerated even at a very high caloric content. The process of separating milk into foremilk and hind milk and using the proportion of hind milk the baby requires to gain adequate weight is called lacto-engineering and can even be done by mothers who have been taught to do so.[41] If hind milk is unavailable,

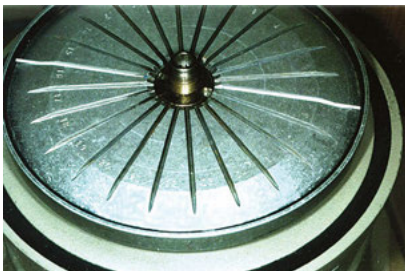
Figure 20-5. Creamatocrit Procedure



1. Mother empties her breast milk into container, which is shaken well for 5 seconds.
2. From this sample, pour about 0.5 mL into a sample cup.
3. Mix sample by shaking again for 5 seconds.
4. Fill 2 non-heparinized microhematocrit capillary tubes with milk.



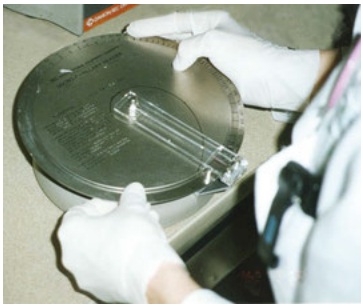
5. Seal capillary tubes at one end with Critoseal.



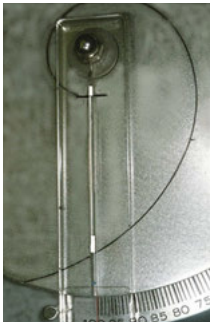
6. Place tubes with sealed end to the outside of the centrifuge, in a counterbalanced position.

7. Screw lid in place.
8. Close top of centrifuge.
9. Set timer for 5 minutes.
10. When spinning stops, remove tubes from centrifuge.

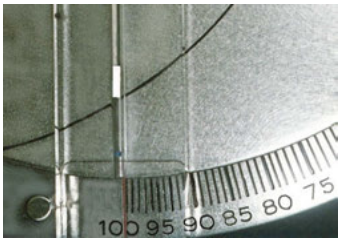
Figure 20-5. Creamatocrit Procedure, continued



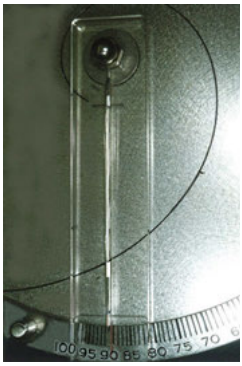
11. Place tubes on hematocrit reader with Critoseal end at top.
12. Place the intersection of sealant and milk at the cross point of the curved line.



13. Rotate upper disc so that bottom of curved line intersects *bottom* point of milk in the capillary tube.



14. Set lower percentage disc at 100%.



15. Rotate percentage disc until curve line intersects cream layer of milk.
16. Subtract this percentage (usually 85%–95%) from 100%. The result is the creamatocrit (usually 5%–15%).

Adapted from Griffin TL, Meier PP, Bradford LP, et al. Mothers' performing creamatocrit measures in the NICU: accuracy, reactions, and cost. *J Obstet Gynecol Neonatal Nurs.* 2000;29(3):249–257; *Br Med J.* 1978;1(6119):1018–1020; and © Rush Mothers' Milk Club Special Care Nursery, Rush Children's Hospital, 1653 W Congress Pkwy, Chicago, IL 60612.

Table 20-3. Nutritional Value of Human Milk Based on Creamatocrit Value

CREAMATOCRIT PERCENTAGE	3	4	5	6	7	8	9	10	11	12
g fat/mL	0.017	0.023	0.03	0.037	0.044	0.051	0.058	0.064	0.071	0.078
cal/mL	0.49	0.56	0.62	0.69	0.76	0.82	0.89	0.96	1.02	1.09
cal/oz	15.7	17.8	20	22.1	24.3	26.4	28.5	30.7	32.8	34.9
% of cal—fat	22	37	44	48.2	52.1	56	58.2	60.4	62.6	64

Based on regression equations in Lucas A, Gibbons JA, Lyster RL, Baum JD. Creamatocrit: simple clinical technique for estimating fat concentration and energy value of human milk. *Br Med J.* 1978;1(6119):1018–1020.

an alternative is adding small amounts of vegetable oil (eg, corn, sunflower, olive), which contains 8 kcal/mL, to fortify mother's milk.

Health care workers and mothers can be taught to modify the caloric content of human milk to achieve appropriate growth and weight gain. Mothers can also be easily taught to express and set aside the foremilk before collecting the hind milk.[41] If hind milk volume is too low for the newborn at a given feeding, it can be topped off with foremilk. Foremilk, which is not used immediately, can be frozen and given later as needed. If the mother is temporarily too ill to feed her baby at the breast or go to the special-care baby nursery to feed her baby, staff or her family can help her express milk, which can then be given to the newborn.

Low Milk Volume

Ensure good breastfeeding technique for healthy term newborns with proper positioning and latching. If the baby has a good suck and there is adequate milk transfer, the mother can breastfeed more frequently to increase her milk production. She can also try hand expression with breast compression, massage, and pumping to increase milk production, as described by Morton et al in premature newborns.[42] Sometimes mothers with an overabundant supply of milk may be feeding only low-fat foremilk. In this case, mothers can be instructed to express and discard some of the foremilk before feeding so the newborn receives more of the higher-fat hind milk, which improves feeding satisfaction and reduces intake and frequency of feeding, thereby reducing the mother's overabundant milk supply. For premature newborns who are being fed expressed human milk or term newborns with poor suck and milk transfer, the mother should be encouraged to completely empty her breast at

each expression or at each feed to increase her milk supply and include high-calorie hind milk during the feeding.

If all of these measures fail to adequately improve milk production, the mother, in conjunction with her physician, can consider beginning metoclopramide or domperidone tablets to stimulate milk production. Both drugs will double milk supply providing the mother pumps frequently (ie, every 2–3 hours). Mothers should discuss using these drugs with their physician before taking either. They should be screened for potential risks (eg, depression, prolonged corrected Q-T interval [QTc]), advised that these are off-label uses for these drugs, and made aware of possible side effects.

Metoclopramide increases prolactin, thereby increasing milk supply. One dosage regimen that decreases potential sleepiness in mothers is 10 mg once on day 1; 10 mg twice on day 2; 10 mg 3 times daily on days 3 through 10; 10 mg twice daily on day 11; and 10 mg once on day 12.[43] Another suggested dosing regimen is 10 mg 3 times daily for 7 to 10 days[43] and a subsequent taper of 10 mg per week until off the drug.[44] If the metoclopramide effectively increases milk supply but milk production drops off after stopping, the dosage regimen can be repeated. Metoclopramide is widely available, even in low-resource settings. It is occasionally associated with side effects, such as fatigue, dizziness, dystonia, seizures, and depression.[43]

Domperidone also increases milk production, probably by increasing prolactin levels.[45] It is available outside the United States, where it is the preferred medication prescribed for low milk supply because it appears more effective and has fewer side effects than metoclopramide.[43] Domperidone can be taken as three 10-mg tablets (30 mg total) 3 times a day for 3 to 8 weeks or until the mother's milk supply is adequate.[46] There is no need to slowly increase or decrease domperidone.

Encourage the mother to drink non-caffeinated fluids, rest, and eat well. Mothers should drink fluids when thirsty to replace fluid lost through breastfeeding; excess fluid intake does not increase milk volume. Milk composition and volume are little influenced by diet except in conditions of severe deprivation. Make mothers comfortable and decrease anxiety as much as possible. If these measures are unsuccessful in achieving a sufficient milk supply, milk may be supplemented with commercial formula or human donor milk that has been properly tested and stored in human milk banks, which are feasible in some low-resource settings.[47]

Feeding Options for Newborns Exposed to HIV

Newborns of mothers who are HIV positive have a high risk of dying of illness such as diarrhea, especially if artificial baby milk feedings are not "acceptable, feasible, affordable, sustainable and safe" (AFASS).[30,48] Because of the increased risk of dying of infection associated with replacement feedings in the developing world, breastfeeding is often the best option for many of these mothers. HIV-positive mothers of newborns in low-resource settings should be given the option to exclusively breastfeed or use replacement feedings with formula. However, per WHO and UNICEF recommendations, if replacement feedings with formula are not AFASS, exclusive breastfeeding for 6 months is the only viable option. Feeding options should always be discussed with the mother and her choice supported.

In the first 6 months of life, mixed feedings should be avoided because they are associated with the greatest risk of HIV transmission through human milk.[49,50] The mother should be counseled about the pros and cons of available feeding options so she can make the most informed choice for her baby's feeding. Cultural and social stigma can play a major role in determining which choice is appropriate for a mother. Whatever the mother's choice, she should be fully supported to make it as safe as possible for her baby. If the mother elects to breastfeed, duration of exclusive breastfeeding will vary depending on the mother's health, milk supply, and availability and adequacy of feeding alternatives. The baby should be transitioned any time alternate feeding is AFASS. Per WHO, Joint United Nations Programme on HIV/AIDS (UNAIDS), and UNICEF recommendations, if formula-feeding is still not AFASS at 6 months, complementary feeding along with breastfeeding should continue and the mother, baby, and situation should be frequently reevaluated.[51] Oral medications prescribed for any reason should still be given.

As supported by the Kesho Bora study,[52] WHO now recommends providing antiretroviral prophylaxis (to mother or child) for the entire duration of breastfeeding. Current recommendations from WHO on the use of antiretrovirals in mothers who are HIV positive and who do not meet criteria from treatment with antiretrovirals for themselves and choose to breastfeed are as follows: option A consists of daily nevirapine to the newborn; option B consists of triple antiretroviral drugs provided to a pregnant woman starting from as early as 14 weeks' gestation, continuing until 1 week after all exposure to human milk has ended, or option B+, which consists of lifelong antiretrovirals for all pregnant and

Table 20-4. Program Options for ART and PMTCT

NATIONAL PMTCT PROGRAMME OPTION	PREGNANT AND BREASTFEEDING WOMEN WITH HIV		HIV-EXPOSED INFANT	
Use lifelong ART for all pregnant and breastfeeding women ("Option B+")	**Regardless of WHO clinical stage or CD4 cell count**		**Breastfeeding**	**Replacement feeding**
	Initiate ART and maintain after delivery and cessation of breastfeeding		6 weeks of infant prophylaxis with once-daily NVP	4–6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)
Use lifelong ART only for pregnant and breastfeeding women eligible for treatment ("Option B")	**Eligible for treatment**[a]	**Not eligible for treatment**[a]		
	Initiate ART and maintain after delivery and cessation of breastfeeding[b]	Initiate ART and stop after delivery and cessation of breastfeeding[b,c]		

[a] CD4 count ≤500 cells/mm^3 or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.

[b] Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.

[c] In the case of breastfeeding stop ART one week after breastfeeding ends. In the case of replacement feeding stop ART after delivery.

From World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendations from a Public Health Approach June 2013*. Geneva, Switzerland: World Health Organization; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en. Accessed June 12, 2015.

breastfeeding women (Table 20-4).[53] In both options, the mother should receive antiretroviral therapy from 14 weeks' gestation through 1 week after delivery. If the mother chooses not to breastfeed, the baby should receive daily nevirapine or zidovudine (AZT) for 4 to 6 weeks after delivery. These recommendations are subject to change and should be verified on a regular basis with sources such as WHO.

Commercially prepared infant formula, diluted correctly, should be used when AFASS. Other options, especially if option A and B are not possible, might include heat-treated human milk.[51] Commercial formulas, not homemade formulas, are generally a safer option and recommended in infants younger than 6 months. In premature or sick babies, another option might be donor human milk, at least until babies are well and commercial formula is available. As previously noted, donor milk must be rigorously tested and storage conditions maintained if this option is to be safe and viable.

Feeding Methods and Transitioning to the Breast

Newborns weighing less than 1,200 to 1,500 g and those too weak or immature to effectively breastfeed should be given their mother's expressed milk via nasogastric tube. An alternative to nasogastric tube with gavage feedings would be a cup and spoon. However, if a cup and spoon are used, babies should be allowed to lap the milk up—the milk should not be poured down their throats. Before each feed, the practitioner should ensure that the tube is still in the stomach and gastric residual should be aspirated and measured. The appropriate feeding volume should be placed in a syringe and allowed to drip in by gravity. Because of the type of syringes available in some developing countries, feeds may need to be pushed slowly rather than dripped in. The tube should be flushed with 0.5 to 1 mL of sterile water after feedings. Healthy premature newborns between 1,250 and 1,500 g should be given the opportunity, if alert and interested, to "practice" breastfeeding at each feeding, recognizing that actual milk transfer is usually negligible and that growth will depend on receiving sufficient supplemental feeds with expressed milk. Some healthy newborns who are about 30 weeks' gestation and older can begin supplemental feeds with a cup.[54]

Babies who are neurologically intact and clinically stable may be offered feedings at the breast beginning at approximately 1,500 g. Almost all babies at this weight will also need to be supplemented with expressed milk unless they are more mature and growth restricted. If the baby is not sucking well or is losing excessive weight, supplement with expressed milk via a cup, spoon, or nasogastric tube. Initially begin supplementing with 25% of the newborn's required feeding volume and adjust to a supplemental volume that allows for a weight gain of 10 to 12 g/kg/day.

Newborns who weigh more than 1,800 g and are neurologically intact should begin feedings at the breast and be observed carefully for sucking adequacy and weight gain. If they fail to gain weight appropriately, they may need to be supplemented with expressed human milk using a cup or spoon as they learn to feed at the breast. Adequate weight gain is the best sign of adequate intake. Effectiveness of feeding in all methods and appropriateness of weight gain must be followed closely in these premature, low-birth-weight babies.

Holding the baby in STS care has numerous benefits, including increasing maternal milk volume and duration of breastfeeding.[55,56]

Iron, Multivitamin Supplements, and Blood Transfusion Recommendations

When the premature newborn is about 2 to 4 weeks of age and is tolerating near or full feeds, she should begin on supplemental iron at approximately 3 mg/kg/day of elemental iron. Iron preparations from different manufacturers and in different countries vary, so the actual elemental iron content of the preparation needs to be verified and the iron dosed accordingly. Multivitamins, including vitamin D (400 IU/day), should also be started with iron supplementation in all premature newborns. Check dosing recommendations on the package. About a one-half dose is generally suggested for term newborns until their weight exceeds 2 kg.

Hematocrit should be monitored every 1 to 2 weeks in the growing premature baby. Term and preterm newborns all become anemic after birth, reaching a nadir at 4 to 6 weeks of life. Hematocrit may be as low as 25% or less in preterm newborns. Anemia is physiologic because of decreased erythropoietin and red cell production (not iron deficiency) and is usually well tolerated by most babies. Supplemental iron does not correct anemia but rather increases iron stores and prevents iron deficiency anemia at 4 to 6 months after neonatal iron stores are depleted by increased red cell production. Transfusion is not routinely recommended to correct anemia unless the baby is symptomatic with acute blood loss, respiratory distress, or otherwise unexplained apnea and bradycardia, persistent tachycardia, tachypnea, or poor feeding (Box 20-2).

Breastfeeding and Medications

Almost all maternal medications are compatible with breastfeeding. In general, all maternal antibiotics are compatible with breastfeeding. Very few medications (eg, antimetabolites, radioactive compounds, drugs of abuse) are absolutely contraindicated in breastfeeding. Mothers should

Box 20-2. General Transfusion Guidelines

1. Transfuse if hematocrit is less than 35% in babies with severe cardiopulmonary disease.
2. Transfuse if less than 30% **and**
   - Mild to moderate cardiopulmonary disease
   - Significant apnea
   - Symptomatic anemia (weight gain <10 g/kg/d at full caloric intake and heart rate >180 beats per minute for more than 24 h)
   - Undergoing major surgery
3. Transfuse if hematocrit is less than 21%: asymptomatic associated with a low reticulocyte count.

Blood must be screened for at least HIV and hepatitis B, and if possible, hepatitis C.

From Gomella TL, Cunningham MD, Eyal FG, et al. Blood abnormalities. *Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs.* 5th ed. New York, NY: McGraw-Hill Education; 2004:332–353.

not breastfeed while on chloramphenicol but can, of course, resume breastfeeding 24 hours after completing the drug.[44] Most other contraindications are relative. In almost all circumstances, the benefits of breastfeeding in lower-income countries far outweigh any associated risks. Check reputable sources such as Hale (*Medications & Mothers' Milk*) recommendations for information if a mother is taking medication.[44] *Physicians' Desk Reference* is not useful in determining if a medication is compatible with breastfeeding.[57] If a medication is contraindicated but is only going to be needed for a limited time, have the mother express her milk while giving the baby formula and resume breastfeeding when the medication is stopped and metabolized. Formula-feedings may be indicated if the contraindicated drug will be needed long term.

Expressed human milk feeding is medically indicated in some mothers, such as those with untreated active tuberculosis (TB),[58] unless there are lesions on the breast or breast abscesses that preclude using human milk.[36,58] The baby can begin breastfeeding once therapy in mother and baby has begun.[36] Continued close observation of the newborn for TB is still recommended.[36] For detailed recommendations on breastfeeding and infection, check a source such as the American Academy of Pediatrics (AAP) *Red Book*.[58] Some medical conditions resolve over time, and it may be possible for the mother to formula-feed while she expresses milk and then resume with breastfeeding.

Mastitis is generally not a contraindication to breastfeeding. The mother should not breastfeed if she has herpes lesions on her breast.[36] However, if herpes lesions are not on the breast, the mother may carefully consider breastfeeding if she uses very good hand washing, covers the lesions, and does not touch the baby with the actual lesions.[36]

Some mothers choose to formula-feed even though they do not have a contraindication to breastfeeding. These mothers should be supported if they made an informed decision. Carefully explain the importance of cleaning feeding utensils well. Encourage cup feeding instead of bottle-feeding with nipples. Cups can be successfully used[24] and are safer and easier to clean than bottles, reducing the risk of bacterial contamination. The cup should be placed against the lower lip and milk should be lapped up from the cup; it should not be poured into the mouth.[24] Explain the need for clean water. Lastly, explain the importance of measuring formula carefully and not diluting it to make it last longer. Inappropriate formula dilution, whether to save money or out of ignorance about proper dilution, is a common problem in developing countries.

THERMAL REGULATION

Keeping neonates warm, especially premature neonates, is essential to their survival. This task can be challenging, even in warm climates. The incidence of hypothermia is high in developing countries, where up to 85% of normal newborns are hypothermic (axillary temperature <36.5°C) within the first 24 hours after birth because of excessive heat loss. Climate, seasonal changes, cultural and hospital practices, and place of delivery all influence this incidence.[59] Newborns lose body heat very quickly after birth from evaporation (because they are wet), conduction (from being placed on cold surfaces), convection (from being exposed to drafts), and radiation (from being placed in proximity to colder surfaces in the surrounding environment).[59–61] A newborn's body temperature is maintained by insulation from subcutaneous fat, heat generation from motor and metabolic activity, and metabolism of brown fat. The premature newborn has decreased subcutaneous and brown fat, limited energy stores, and larger head-to-body surface area; thus, the premature newborn can become hypothermic quickly without an external heat source. Hypothermia is also associated with sepsis in term and preterm neonates, especially when the initial occurrence is after 24 hours of age.[59] Knowledge and practices of thermal control by health care professionals in developing countries are often inadequate but are potentially remediable with education.[62]

Exogenous heat sources (eg, STS mother care, incubator, heat lamp, radiant warmer, warming blanket, warm mattress) are needed to rewarm hypothermic preterm newborns who cannot metabolically generate enough endogenous heat to raise their temperature.

Hypothermia

Normothermia is critical to maintaining physiologic stability. Normal temperature for neonates is 36.5°C to 37.5°C rectally. Axillary temperatures may be 0.5°C to 1.0°C lower. The WHO guidelines define hypothermia as mild (36°C–36.5°C), moderate (32°C–35.9°C), and severe (<32°C).[61]

Hyperthermia (>37.5°C) is also dangerous and is associated with over-wrapping, an excessively high ambient temperature, dehydration, or infection. The hyperthermic baby may be tachypneic, tachycardic, flushed, sweaty, and very warm to the touch. Severe hyperthermia is life-threatening (>42°C).[61] Hyperthermia is particularly deleterious in asphyxiated neonates with hypoxic ischemic encephalopathy and is associated with worse neurodevelopmental outcome.

Understanding the dangers of hypothermia and recognizing them promptly is vital to reducing this common, potentially life-threatening problem. Hypothermia is associated with multiple metabolic, cardiorespiratory, and neurologic derangements, including lethargy, poor feeding, poor weight gain, reduced motor activity, peripheral edema, cold skin, hypoglycemia, hypoxia, respiratory distress, apnea, bradycardia, acidosis, NEC, thrombocytopenia, coagulopathy, and death.[20,63–67] Although it may be beneficial to maintain a state of controlled hypothermia in some instances (eg, term newborns with hypoxic-ischemic encephalopathy [HIE][68,69]), hypothermia, especially when prolonged, is clearly harmful for a premature newborn.[70,71] Several standard neonatal textbooks provide useful information on hypothermia management.[72–74]

Presently, the only accurate way to detect hypothermia is with a thermometer; touch is not a reliable way to identify mild to moderate hypothermia.[75] A premature or sick baby's temperature must be read with a thermometer at least once a day to identify hypothermia and intervene appropriately. Ideally, a newborn's temperature should be measured at least every 4 to 6 hours.[61] The hypothermic neonate must be rewarmed and followed closely with frequent temperatures checks at least every 2 to 4 hours until normothermia is restored.[61]

Preventing and Treating Hypothermia

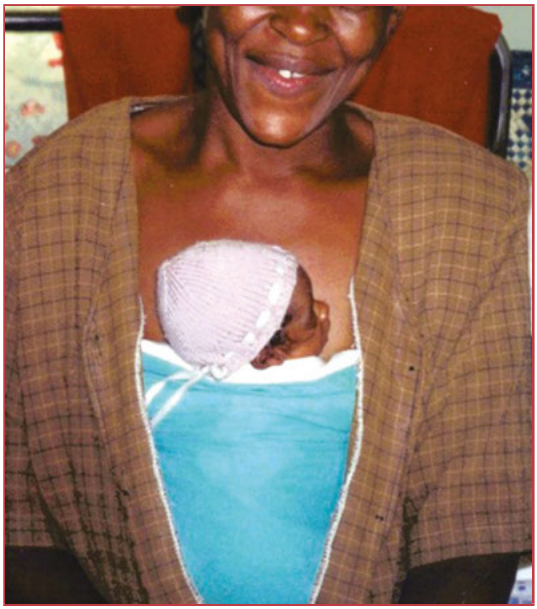
As highlighted in the WHO pamphlet, *Thermal Protection of the Newborn: A Practical Guide,*[61] preventing hypothermia is essential. Maintaining normothermia in a baby begins at birth; the delivery room must be kept warm and draft free. The newborn must be dried immediately on delivery, or wet wrappings should be removed as quickly as possible and the newborn rewrapped in a warm, dry cloth. Placing a hat (preferably wool) on the newborn will decrease heat loss from the head, which, being relatively large in the neonate, radiates a substantial amount of heat. Whenever possible, the naked baby should be placed in STS contact on the mother's chest and covered with a blanket immediately after birth. Skin-to-skin contact also facilitates early initiation of breastfeeding, which provides an energy source for heat production.

The first bath should not be given until at least 6 hours (up to 24 hours later) when the baby is stable and warm. The vernix caseosa has anti-infective properties and does not need to be removed.[63,76] The newborn can be cleaned quite thoroughly with clean, dry towels prior to 24 hours of age.

Hypothermia can further be avoided when the mother and her newborn are transported together in STS contact, versus transportation of mother and newborn separately or when the newborn is transferred

elsewhere for care.[61] The mother and her newborn should be cared for in a warm room. Premature newborns should be kept in continuous STS care before and after discharge whenever possible (Figure 20-6).

Figure 20-6. Skin-to-Skin Contact (Kangaroo Mother Care)



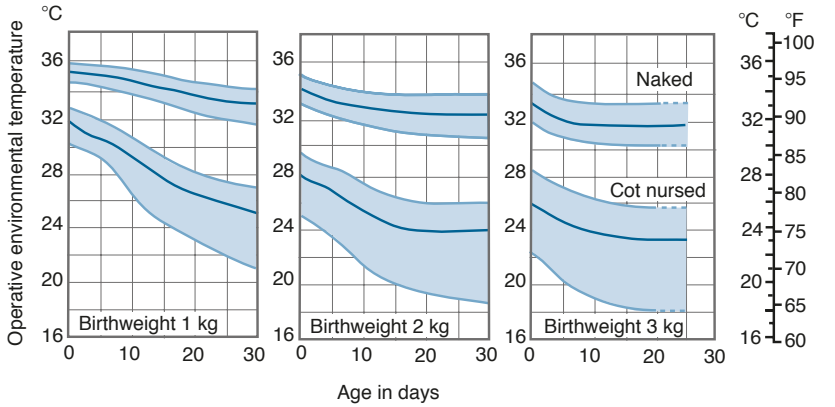
Courtesy of Tina Slusher, MD, FAAP.

Where STS care is not possible, additional options for keeping the newborn warm postdelivery include placing him in plastic wrap or plastic bags (which reduces evaporative heat loss[2,77]), on heated mattresses,[61] in homemade or commercial incubators, or under overhead warmers.[61] Local technology determines what resources are available. Maintaining normothermia in premature newborns is usually impossible without an external heat source. The ambient temperature required to maintain normothermia varies according to birth weight, postnatal age, humidity, and whether the baby is dressed (Figure 20-7).

Skin-to-Skin Care

Skin-to-skin care, also known as kangaroo mother care, involves placing the naked newborn prone, head upright, on the mother's (or other caregiver's) chest in direct STS contact. When in direct STS contact, the mother's body heat will keep the baby warm. It was found that very low birth weight (VLBW) newborns maintained their temperature better in STS care than in conventional incubators.[78] In Ethiopia, Worku and Kassie found that STS was associated with a much lower death rate than when conventional methods of care (usually including an artificial warming system) were used.[79] Place a hat on the newborn to prevent heat loss from the head and a wrapper or cloth around but not between the newborn and mother. Bergh et al state, "Integration of kangaroo mother care into routine newborn care services should be part of all

Figure 20-7. Neutral Thermal Environment



The usual ranges of environmental temperatures needed to provide warmth for newborns weighing 1 to 3 kg at birth in a draft-free uniform temperature surrounding at 50% relative humidity. Upper curves represent naked newborns. Lower curves represent swaddled, "cot-nursed" babies. Thick lines represent usual "optimal" temperature, and shaded areas are the angle within which to maintain normal temperature without increasing heat production or evaporated loss by more than 25%.

From Hey EN. The care of babies in incubators. In: Gairdner D, et al. *Recent Advances in Pediatrics*. 4th ed. London, UK: Churchill Livingstone; 1971.

maternal and newborn care initiatives and packages," in their article on implementation of this important intervention in facilities.[80]

Continuous STS care is at least as effective as an incubator in preventing and treating hypothermia.[81] Every hour the baby is kept in STS contact raises her temperature about 1°C. Advantages of STS care as a method of keeping premature newborns warm include increased exclusive breastfeeding, decreased nosocomial infections, improved weight gain,[59,82] and decreased apnea.[82] It is especially useful in health care facilities without consistent power and while transporting premature newborns to a higher level of care.[61] It is effective and often the only available method for rewarming hypothermic newborns.

Mild hypothermia is usually only identifiable by monitoring the body temperature. Moderately hypothermic babies may be lethargic, have a weak cry, and not feed well. Severely hypothermic babies (≤32°C) are very cold to the touch and have generalized marked erythema and edema of the extremities, which may become sclerematous if severe hypothermia is prolonged. They are bradycardiac and have very slow, shallow respiration; marked central nervous system (CNS) depression; and minimal spontaneous movement or response to stimulation. Complications of hypothermia in preterm newborns include abdominal

distention, emesis, NEC, coagulopathy, hemorrhagic pulmonary edema, hyperkalemia, acidosis, and death. Apnea, hypotension, and hypoglycemia may occur during rewarming. Hypothermic newborns may be rewarmed by 1°C to 2°C per hour using the aforementioned methods. Skin-to-skin maternal care is the most available and effective method of rewarming.

Homemade Incubators

Low-cost homemade incubators can be created from locally available materials and have the additional advantage of being easier to maintain and repair than commercial incubators. Ambient conditions inside the incubator should be continuously monitored; temperature can be controlled by adjusting the number of illuminated lightbulbs, and humidity is provided by placing a small bowl of water (changed and cleaned every 1–2 days) in the compartment containing the lightbulbs. Phototherapy can be installed on the top and sides of the incubator. Remember to position the phototherapy unit as close as possible to the incubator for maximum phototherapy. Glass can be substituted if Plexiglas is unavailable; however, Plexiglas should be used whenever possible (figures 20-8, 20-9, and 20-10) because glass can overheat or break.

Commercial Incubators

Commercial incubators are expensive and often costly to repair, but they have the advantage of more accurate ambient temperature control and the ability to servo-control the baby's temperature.

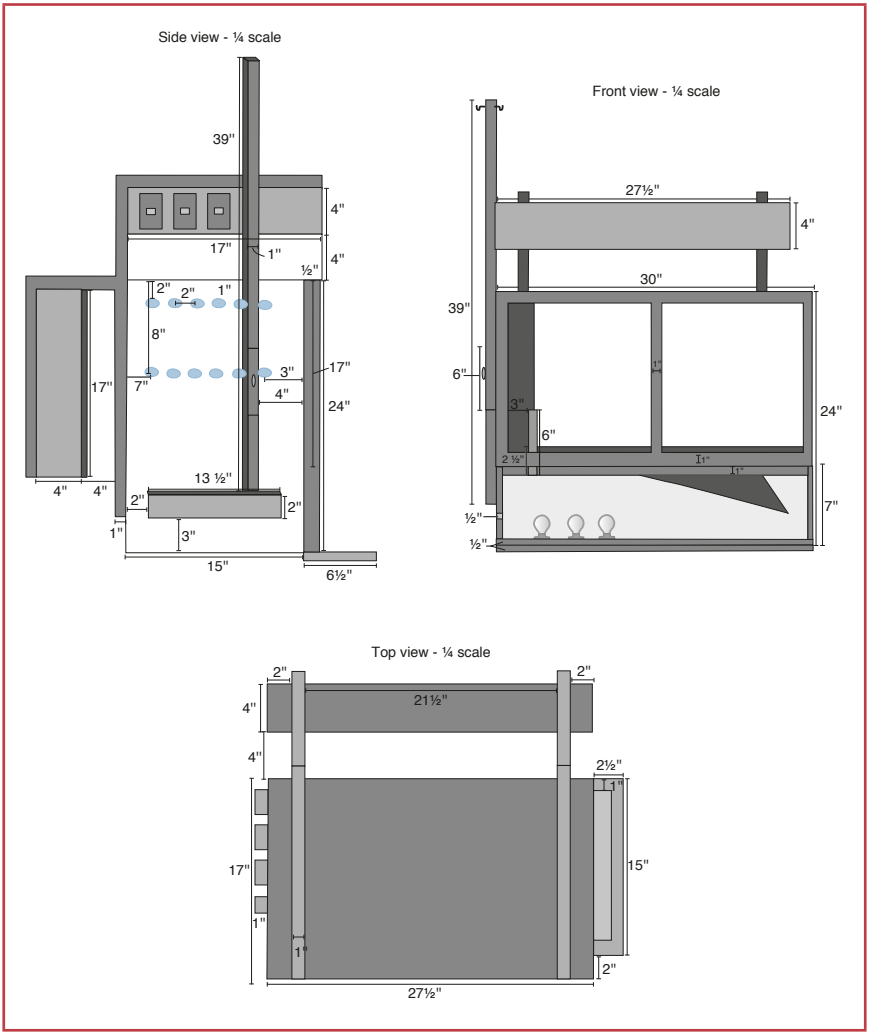
Commercial Overhead Warmers

Commercial overhead warmers, while effective at warming newborns, are expensive and costly to repair and increase water evaporation through the newborn's skin. Their primary advantage is to allow direct visualization and immediate access to the baby. An overhead warmer can be especially valuable when performing a procedure on the newborn or when the baby's condition requires frequent interventions (eg, positive-pressure ventilation for apnea). If a skin probe is not used, the newborn must be monitored frequently to ensure normothermia. Without a skin probe, the baby's temperature should be checked at least every 30 to 60 minutes.

Homemade Overhead Warmers

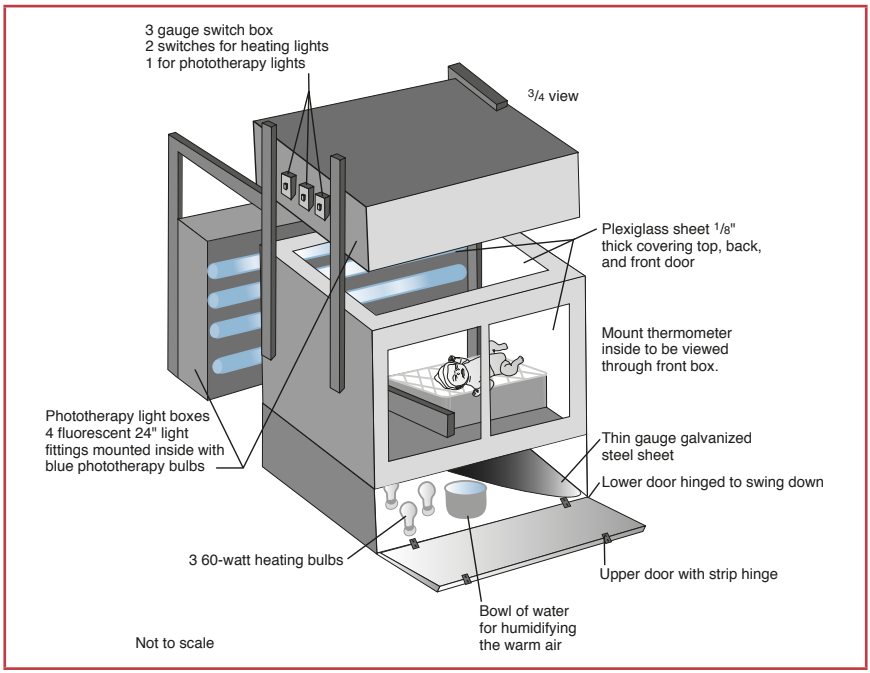
Homemade overhead warmers can be built using heat lamps, but the amount of heat generated is difficult to control.

Figure 20-8. Blueprints for Incubator



Adapted from Adrian Michael Slusher, BSME.

Figure 20-9. Components of a Homemade Incubator



Adapted from Adrian Michael Slusher, BSME.

Figure 20-10. Homemade Incubator

With permission of Carol Spears, MD.

Other Methods

Hot water bottles and warming pads should not be used, if possible, because the newborn can be burned by these devices. However, they may be the only means available to provide warmth.[61] If used, the newborn should be well wrapped in blankets to protect him from accidental direct contact with the heat source and to help retain warmth gained. Monitor the newborn's temperature closely to avoid hyperthermia. Unwrap the newborn frequently and check carefully for erythema or burns of the skin.

Encourage bundling the newborn loosely, allowing spaces for air between layers of cloth, because this practice actually increases heat retention; tight swaddling has the opposite effect and should be discouraged.[61] Keep the head covered, ideally with a wool hat.[59] Used alone, bundling and covering the head will not be effective if the baby cannot generate enough heat to maintain or increase body temperature, as is usually the case in premature, especially VLBW, newborns. An exogenous heat source, such as a warm incubator or STS care, is required to maintain normothermia.

PREVENTIVE CARE

Cord Care

Cutting the cord with a clean, sharp instrument, as well as clamping or tying it with a clean clamp or tie, are the first steps in appropriate cord care.[13] Studies in the developed world suggest that no cord care is actually necessary and that the cord separates quicker without antiseptics.[83] However, emerging studies from low-resource settings, reviewed by Karumbi et al,[84] suggest that cleaning the cord with 4% chlorhexidine may reduce the risk of neonatal sepsis and associated mortality.[84] If a mother insists on putting something on the cord or if the cord is soiled, it is better to choose a benign option, such as soap and water, instead of more dangerous practices, such as applying cow dung, plant material, or mentholated products. Alcohol is less optimal because it does not help dry the stump and delays cord separation.[83] The cord stump does not require covering with tight cloth/band.

Delayed Cord Clamping

Several studies support delay in clamping the cord until it stops pulsating or after about 30 to 180 seconds.[85–87] The practice of delayed cord clamping is recommended for the preterm newborn as a means of reducing anemia and increasing iron stores.[88] Delayed cord clamping is especially helpful in premature newborns. In addition to raising

the initial HCT, it reduces the need for transfusion and the risk for hypotension, intraventricular hemorrhage, late neonatal sepsis, and death.[89,90] Decreasing baseline anemia could be especially important in parts of lower-income countries where the incidence of malaria is high.[88] Cord milking in premature newborns has a similar result to delayed cord clamping.[90–92] In a recent study by Ranjit et al,[93] a longer duration of phototherapy was noted but not a higher incidence of significant jaundice. In a meta-analysis by McDonald et al,[94] more babies in the delayed cord clamping group required phototherapy; these authors felt that "delayed cord clamping is likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available."[94]

Eye Prophylaxis

Several different regimens are beneficial in reducing the incidence of ophthalmia neonatorum, a preventable cause of blindness most often caused by gonococcal or chlamydial infection. Predominant organisms have changed over time; thus, prophylactic regimens have also changed.

Eyelids should be cleaned immediately after birth and followed by applying one of several potential antimicrobials within 1 hour of birth.[95] Potential antimicrobials include 1% silver nitrate, 1% tetracycline ointment, 2.5% povidone-iodine, or 0.5% erythromycin ointment.[95–97] Povidone-iodine can be locally prepared.[90,95] Silver nitrate application may cause chemical conjunctivitis[95] with swelling, erythema, and a purulent discharge, which may be confused with infectious conjunctivitis.

Vitamin K

Vitamin K deficiency is a preventable cause of bleeding in the neonate.[98] Vitamin K_1 should be given to neonates at birth to prevent hemorrhagic disease, which is not infrequent in developing countries where vitamin K prophylaxis is not routinely given. Term newborns should receive 1 mg intramuscular (IM); preterm newborns weighing more than 1,000 g should receive 0.5 mg; and newborns weighing less than 1,000 g should receive 0.3 mg IM.[20,99] Vitamin K_1 may be given intravenously emergently in a newborn with coagulopathy or bleeding.[100] Anaphylaxis with vitamin K IV is rare[101] and extremely unlikely in the newborn having no prior antigen exposure and an immature immune system. Avoid vitamin K_3, as it is associated with jaundice in neonates.[102,103] Oral vitamin K may be given if parental form is not available or parents refuse it. The dose if given orally is 2 mg at birth with repeat weekly doses for the first 3 months.[99]

Hepatitis B Vaccination

Hepatitis B is a leading cause of preventable cirrhosis and liver cancer. It is primarily acquired by vertical transmission during delivery and child-to-child transmission.[103] The WHO now recommends that all neonates should receive their first dose of hepatitis vaccine as soon as possible after birth (preferably within 24 hours).[104] The neonate will then need 2 or 3 additional doses to complete the primary series.[105] All IM injections, including vaccinations, should be given in the upper outer thigh, *not* the buttock, to avoid sciatic nerve damage. Although hepatitis B immunoglobulin (HBIg) is rarely available in low-resource settings, it would be indicated, if available, in neonates born to mothers known to be hepatitis B surface antigen positive. When available, give HBIg if a mother's status is unknown and results cannot be obtained within 12 hours of birth. Make sure hepatitis B vaccine is given as soon as possible, preferably in the delivery room.

HIV Prophylaxis

HIV prophylaxis is extremely important in babies born to mothers who are HIV infected. Regimens vary from giving a single dose of nevirapine to the mother at presentation of labor and to the neonate immediately after birth to much more complicated treatment combinations. Studies are ongoing to determine which regimens are effective and affordable in resource-poor countries. Recommended regimens are in flux and vary from country to country. Practitioners should refer to the country-specific regimen, WHO,[53] or a similar source to determine what HIV prophylaxis to use and frequently check for updates.

Vitamin A

In its most recent guidelines, WHO does not recommend routine vitamin A supplementation in the first 28 days of life.[106]

NEONATAL DERMATOLOGY

Skin care is an under-recognized opportunity to positively affect newborn health. The skin is an important source of potential infection, especially in preterm newborns. There have been multiple studies looking at how barriers, oils, or lotions can be used as preventive skin care to reduce or increase the incidence of nosocomial infections and prevent potential nutritional conditions such as essential fatty acid deficiency. In addition, skin care may serve as a means to augment maternal-newborn bonding and reduce hypothermia.[107] These interventions appear to be

cost-effective, especially if the products are inexpensive and readily available. Appropriate skin care may prevent the need for more expensive treatments, such as prolonged antibiotics.

Newborn Skin

Vernix caseosa, the cheesy substance found on newborn skin, can be viewed by some cultures as "dirty," and usual practice may prompt immediate removal. However, recent evidence found vernix to be an excellent skin cleanser[108] with intrinsic antimicrobial properties.[76,109] Currently, WHO recommends delaying a healthy newborn's first bath until at least 6 hours of age.[110]

Skin care regimens can also be harmful to newborns; in Asian countries, for example, potentially toxic mustard oil is often rubbed on babies' skin. If a skin regimen is adopted, it is imperative that the substance does not harm the newborn. Studies done in higher-income and lower-income countries using a petroleum-based ointment show mixed results; some studies showed a reduction in infection, while others, particularly those done in the United States, demonstrated a trend toward more coagulase-negative *Staphylococcus* infection in premature newborns.[110] However, this may reflect the developed country's population bias with more access to central lines and, thus, a higher risk of infection.

Mentholated compounds found in many rubs and powders in lower-income countries cause hemolysis and are harmful to newborns with glucose-6-phosphate dehydrogenase (G6PD) deficiency, potentially causing severe neonatal jaundice and acute bilirubin encephalopathy.[111] Rubs containing these compounds should never be applied to babies in the neonatal period.

Applying antimicrobial solutions to a newborn's skin temporarily reduces skin colonization, potentially reduces infection, and appears to be safe. A randomized trial in Nepal demonstrated that cleansing a newborn's skin with chlorhexidine reduced mortality in babies with a birth weight less than 2,500 g. This effect has not been described in term newborns.[112]

A preterm newborn's skin, especially in an extremely premature newborn, differs from a term newborn's skin—it is less mature, thinner, and more prone to injury, with increased absorption of drugs and toxins and increased water loss.[113] In addition, increased water loss is substantial in the smallest neonates.[113]

Rashes

Common Benign Rashes

The neonatal period is a common time for benign skin eruptions throughout the world. The incidence of these very common rashes depends on the newborn's ethnic background. It is important that the clinician be able to differentiate these common rashes from more concerning rashes of diseases such as neonatal herpes.

Erythema Toxicum

Erythema toxicum is a common benign skin eruption that appears within the first few days of life and can occur intermittently within the first 1 or 2 weeks. It is characterized by white to yellow papules, measuring 1 to 2 mm, surrounded by erythema. It can be found on the entire body but is mainly seen on the head and trunk. The lesions are self-limited and treatment is not required. The hallmark characteristic of erythema toxicum is the intermittent migratory nature. If a lesion is unroofed and the fluid examined under a microscope, eosinophils are present; however, this is not necessary for clinical diagnosis. The etiology of this rash is not well understood.

Transient Pustular Melanosis

Vesicles or pustules appear in the first stage and are present for approximately 2 to 3 days, after which they rupture, leaving a central hyperpigmented macule with a peripheral "collarette of scale." The scale resolves, but the small central freckle persists, often for several months. Any stage, as well as multiple stages, of transient pustular melanosis may be evident at birth. Neutrophils predominate if unroofed in the pustular stage when examined under a microscope. The rash occurs most often in newborns of color.

Milia

Milia are very common small, white papules typically found on a newborn's face. These papules are caused by inclusion cysts and will exfoliate spontaneously. Milia are also often confused with sebaceous gland hyperplasia, which is classically found on the nose.

Sebaceous Gland Hyperplasia

Sebaceous gland hyperplasia consists of yellow papules on the nasal follicles from the effect of maternal androgens. These papules will resolve without treatment, usually within the first few months of life.

Epstein Pearls

Epstein pearls are commonly seen as white papules on the roof of the mouth caused by trapped epithelial cells. These are similar to milia, only vary in placement, are incidental findings of no clinical significance, and do not require treatment.

Neonatal Acne

Neonatal acne may be pustular or comedonal. Etiology is related to the effect of maternal hormones on the newborn's skin, as well as from occlusive skin products. Two weeks is the typical age of onset, with most lesions occurring on the face and chest. The course is self-limited and no treatment is required. Because of the risk of infection and scarring, lesion manipulation is discouraged.

Miliaria

Miliaria is a benign rash commonly seen in warm climates or on tightly swaddled babies. This rash appears as dew-like papules on the skin and should resolve quickly once the baby is removed from the warm environment.

Seborrheic Dermatitis

Seborrheic dermatitis is another benign rash of infancy that is characterized by a greasy scale on the scalp, posterior to the ears, and on the face. Like other lesions, treatment is not indicated. This condition will resolve over a period of months. If available, hydrocortisone may be applied to non-facial affected areas.

Pathologic Rashes

Herpes Simplex

Neonatal herpes simplex should be strongly considered with a newborn who has grouped vesicles on an erythematous base. Typically, onset of vesicles is approximately at 1 week of life, although babies can be born with these lesions. Not only is the skin involved, but the mucous membranes (eg, eyes, mouth, rectum) can be also involved. Risk of infection is highest if the mother had primary herpes outbreak during pregnancy or evidence of active lesions at delivery. However, the mothers of most infected babies do not have any history of herpes simplex virus infection. Herpes simplex virus infections typically have 3 presentations: localized to skin, eyes, and mouth; localized CNS disease (may not have vesicles); or widely disseminated disease. Herpes simplex is treated with IV acyclovir. Systemic disease is often fatal despite treatment. Severe

neurodevelopmental sequelae are common in newborns who survive herpes simplex infection involving the CNS. Because treatment with acyclovir is relatively benign, treatment should begin as soon as possible whenever herpes simplex infection is suspected.

Petechiae

Petechial lesions are often due to birth trauma and are usually confined to the presenting or traumatized part. Disseminated petechial lesions imply thrombocytopenia that may be associated with congenital infections such as TORCH (*t*oxoplasmosis, *o*ther [eg, syphilis], *r*ubella, *c*ytomegalovirus, *h*erpes). These newborns may also have hepatosplenomegaly or jaundice. Alloimmune thrombocytopenia should be considered as well.

Staphylococcal Pustules

Staphylococcal pustules are common in neonates in the developing world. They are generally diagnosed clinically; however, if there is doubt as to their etiology, a Gram stain will reveal gram-positive cocci. If the newborn is well, pustules can be treated by cleaning with clean soapy water, which ruptures the pustules, and short-course antibiotics. An oral antibiotic, such as cloxacillin, is appropriate if the newborn is nontoxic, afebrile, eating well, and not systemically ill. Methicillin-resistant *Staphylococcus aureus* should be treated with other antibiotics depending on sensitivities.

Syphilis

Congenitally acquired syphilis may be asymptomatic in the neonatal period. If symptomatic, newborns may have low birth weight, thrombocytopenia, petechiae, hepatosplenomegaly, nasal discharge, or respiratory distress. Skin findings may include desquamation, especially of the hands and feet; bullous skin lesions; or copper-colored maculopapular lesions.[114] Maculopapular lesions are typically found on the hands, soles, and diaper area. Skin lesions and nasal discharge are extremely contagious. Practice universal precaution, including wearing gloves and washing hands well. Congenital syphilis is treated with IV or IM penicillin for 10 to 14 days.

BIRTH ASPHYXIA

Worldwide, intrapartum asphyxia is responsible for approximately 1.2 million neonatal deaths, 1.6 million stillbirths, 25% of all neonatal mortality and stillbirths, and 8% of all childhood deaths.[115–118] The contribution of asphyxia to neonatal death is similar to prematurity or

infection. The incidence of asphyxia is much higher in lower-income countries. The true incidence of asphyxia is unknown because more than 50% of deliveries worldwide occur in the home, outside of the health care system. Morbidity and mortality data are usually based on hospital or health care center deliveries. Newborns who die shortly after a home birth due to asphyxia are less likely to be registered in the health system or have the reason for their death determined.[119]

Birth asphyxia is a clinical term denoting a series of antenatal and postnatal events that occur when there is significant tissue hypoxia and ischemia prior to delivery. In developed countries, the definition requires evidence of fetal distress, acidosis, and the need for resuscitation at birth and end-organ injury. A simpler definition often used in developing countries is "failure to breath at birth." This definition is less specific, as it includes all other causes of respiratory depression at birth, such as the effects of maternal medication or sepsis.

Asphyxia is associated with the depletion of energy supplies and increased production of cytotoxic free radicals, resulting in cellular injury or death and multiorgan dysfunction. The initial fetal response to hypoxia and ischemia is to redistribute fetal blood flow from nonessential (eg, skin, kidneys, GI tract) to vital organs (eg, brain, heart, adrenals). Reflex heart rate decelerations (fetal distress), decreased respiratory activity, body movement, and muscle tone reflect ongoing hypoxia and ischemia. Fetal hypoxia results in rapid gasping, followed by primary apnea, and then by slow gasping followed by secondary apnea, resulting in failure to breathe after delivery.

Whereas primary apnea responds quickly to resuscitation with stimulation, secondary apnea requires more vigorous resuscitation with positive-pressure ventilation. The duration of intrapartum asphyxia can be roughly judged from birth to the first gasp and the onset of regular respiratory effort (Table 20-5). The reflex passage of meconium into

Table 20-5. Time to Onset of Respirations After Resuscitation and Duration of Intrauterine Asphyxia

DURATION OF ASPHYXIA (min)	TIME TO FIRST GASP (min)	TIME TO REGULAR BREATHING (min)
10	2	10
12	9	21
15	14	30

Derived from Adamsons K Jr, Behrman R, Dawes GS, James LS, Koford C. Resuscitation by positive pressure ventilation and tris-hydroxymethylaminomethane of rhesus monkeys asphyxiated at birth. *J Pediatr.* 1964;65:807–818.

amniotic fluid before birth can be a sign of fetal hypoxia. An Apgar score of 6 or less at 5 minutes suggests compromised oxygen or blood flow to the fetal brain prior to delivery. Clinical problems caused by asphyxia evolve over several days and reflect the organs most often injured (ie, brain, kidneys, and lungs). These clinical problems include abnormal muscle tone, change in consciousness, seizures, oliguria or anuria, meconium aspiration, surfactant deficiency, pulmonary hemorrhage, persistent fetal circulation, hypotension, and NEC. Although most organ systems recover with time and appropriate medical support, brain injury is more likely to lead to permanent sequelae.

Preventing and Recognizing Intrapartum Hypoxia and Ischemia

Preventing and recognizing intrapartum hypoxia and ischemia is the key to reducing the incidence of birth asphyxia. Antepartum and intrapartum risk factors that predispose the fetus to birth asphyxia include a multitude of fetal or maternal problems that critically compromise placental function or blood flow to the fetus, thereby decreasing oxygen delivery (Table 20-6). Problems common to mothers in developing countries that contribute to an increased risk of asphyxia through an increased risk of prematurity and intrauterine growth restriction include

Table 20-6. Factors Predisposing to Birth Asphyxia

MATERNAL	PLACENTAL/UMBILICAL CORD	FETAL
Preeclampsia/ prehypertension	Infarction	Preterm/post-term
Diabetes	Intravascular thrombosis	IUGR/SGA
Trauma	Chronic bleeding	Multiple gestation
Chorioamnionitis	Previa/chorioamnionitis	Anemia/hemolytic disease/ infection/sepsis
Severe anemia	Prolonged/obstructed labor	Congenital/chromosomal abnormalities
Severe malnutrition	Abruption	Birth trauma
Chronic hypoxemia	Nuchal cord/cord prolapse	Abnormal presentation
Chronic infection (eg, HIV, malaria, TB)	Uterine rupture	Fetal hydrops

Abbreviations: HIV, human immunodeficiency virus; IUGR, intrauterine growth retardation; SGA, small for gestational age; TB, tuberculosis.

malnutrition, malaria, HIV, TB, syphilis, anemia, and living at a high altitude.[120–122] Recognizing fetal and maternal risk factors, treatment of maternal infection, obstetric intervention for fetal distress, emergent cesarean delivery, and maternal transfer to a higher level of care will all reduce the incidence of birth asphyxia.

When birth asphyxia occurs, it is essential to have the appropriate personnel and resources immediately available for resuscitation at delivery. Unfortunately, cost, transport difficulties, inadequate health center facilities, untrained staff, limited resources at health care facilities, and sociocultural barriers encourage delivery at home with unskilled birth attendants.[122] Even without advanced skills in resuscitation, vigorous drying and stimulating the apneic newborn are effective if the degree of depression is mild. More severely depressed term newborns with secondary apnea usually respond to effective ventilation using a self-inflating bag-valve mask and room air. Although resuscitation with oxygen has long been the accepted standard of care, resuscitation of term newborns with 100% oxygen delays onset of respiratory effort and is associated with lower Apgar scores and increased mortality.[123,124] Therefore, per AAP recommendations,[2] it is appropriate to begin initial resuscitation of term newborns with room air and titrate oxygen as needed to achieve adequate oxygen saturation, ideally using pulse oximetry. Because preterm newborns are more likely to have respiratory disease as well as depressed respiratory effort, beginning their resuscitation with 30% to 40% oxygen may be desirable.

Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy is the neurologic consequence of hypoxic-ischemic damage to the brain associated with birth asphyxia. Hypoxic-ischemic encephalopathy is usually the proximate cause of death in asphyxiated newborns and a major cause of lifelong neurologic disability for surviving babies. Disability is an especially serious problem in most lower-income countries where resources for care or rehabilitation of children with neurodevelopmental impairment are minimal or not available. Consequently, the entire social, economic, and emotional burden of impaired survival falls completely on the individual child's family.

The CNS response to asphyxia depends on the severity and duration of hypoxia and ischemia as well as gestational age of the fetus. Before 36 weeks, periventricular white matter is most susceptible to injury; after 36 weeks, deep gray matter of the basal ganglia and cortical gray matter are at greater risk. Abrupt, complete asphyxia (eg, placental abruption, cord prolapse) is more likely to injure the central gray matter (eg,

thalamus) and brain stem. Prolonged, partial asphyxia (eg, utero-placental insufficiency) is more likely to injure the white matter in watershed regions of the cerebral hemispheres.

Hypoxic-ischemic brain injury results in the release of excitatory neurotransmitters, secondary cytotoxic and vasogenic cerebral edema, and neuronal necrosis. These abnormalities are clinically reflected by an increased intracranial pressure manifest by increasing head circumference; a full, bulging fontanel; changes in levels of consciousness; increased or decreased muscle tone; changes in reflex activity; and seizures. Despite markedly increased intracranial pressure, newborns rarely develop brain stem herniation because they can decompress via their open fontanels and suture. Classification systems can be used to grade the severity of HIE as mild, moderate, or severe (Table 20-7). Mild HIE is characterized by a hyperalert or hyperexcitable state with normal motor tone; moderate HIE is characterized by a mildly depressed state with hypotonia; and severe HIE is characterized by stupor with flaccidity. Moderate and severe HIE are associated with electroencephalogram (EEG) abnormalities and clinical seizures.

Maternal Fever and Neonatal Hyperthermia

Maternal fever and neonatal hyperthermia exacerbate asphyxial brain injury. In developed countries, carefully controlled hypothermia is

Table 20-7. Severity and Outcome of Hypoxic-Ischemic Encephalopathy in the Full-term Newborn

SEVERITY	LOC	SEIZURES	PRIMITIVE REFLEXES	BRAIN STEM DYSFUNCTION	ELEVATED ICP	DURATION	POOR OUTCOME[a] %
Mild	↑irritability, hyperalert	Rare, jitteriness	Exaggerated	Rare	Rare	<24 h	0
Moderate	Lethargy	Variable	Suppressed	Rare	Rare	>24 h (variable)	20–40
Severe	Stupor or coma	Common	Absent	Common	Variable	>5 d	100

Abbreviations: ICP, intracranial pressure; LOC, loss of consciousness.

[a] Poor outcome is defined as the presence of mental retardation, cerebral palsy, or seizures.

From McDonald MG, Mullett MD, Seshia MMK. *Avery's Neonatology Pathophysiology & Management of the Newborn*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:1388, with permission.

recommended for treating HIE in moderately to severely asphyxiated term newborns with evidence of decreased mortality and improved neurodevelopmental outcome, particularly in newborns with moderate HIE.[125,126] Models of this are being explored in developing countries[127–129]; thus far, studies of therapeutic hypothermia in low-resource settings have not been successful in reducing mortality, perhaps due to selection bias, lack of infrastructure, or appropriate medical support.[128] Whether mild hypothermia (35.0°C–36.5°C) is beneficial is unknown. However, hyperthermia, which is associated with worse outcomes, should be avoided. Basic neuroprotective care includes treating the underlying condition whenever possible (eg, infection); maintaining physiologically normal levels of oxygen saturation (≥95%), glucose, and electrolytes; and maintaining an adequate blood volume and perfusion. Hypoglycemia should be avoided because it exacerbates brain injury.[130] Although cerebral edema is common, steroids are not indicated because there is no beneficial evidence in HIE. Use of dexamethasone, in particular, may worsen long-term outcome.[130]

Seizures

Asphyxia is the most common cause of neonatal seizures, which may be very difficult to control. Seizures, usually occurring within the first 48 hours after the hypoxic-ischemic insult, may be focal or generalized and take many different, sometimes subtle, clinical forms, including tonic posturing, clonic and myoclonic movements, eye deviation, repetitive sucking, tongue thrusting, eye blinking, purposeless movements, or apnea. Post-asphyxial seizures, unlike tremors or jitteriness, cannot be suppressed by gentle limb restraint or limb flexion. Intracranial bleeding, trauma, and metabolic abnormalities, such as hypoglycemia and hypocalcemia, can also precipitate seizures. Hypoxic-ischemic encephalopathy–induced seizures usually resolve within the first week as acute injury and the cerebral edema subside. Seizures are associated with worse long-term outcome. Clinical seizures should be treated aggressively; ongoing seizure activity may worsen brain injury. Phenobarbital is a very effective anticonvulsant and has the advantage of being inexpensive and widely available. The major risk at high doses is apnea. Other anticonvulsants, including phenytoin and fosphenytoin, and benzodiazepines, such as diazepam or other benzodiazepines, can be considered for persisting seizures if phenobarbital is ineffective. For dosing of phenobarbital and other anticonvulsants, see pages 504 and 505. The therapeutic level of phenobarbital for seizures is 15 to 40 mcg/mL. Seizures associated with HIE usually require doses in the higher end of the therapeutic range. Because the half-life of phenobarbital in the

newborn is very long (>96 hours) and the therapeutic level is directly related to the dose, the serum level of phenobarbital can be reliably estimated by adding the total mg/kg of phenobarbital (loading dose plus all additional doses) given over a 1- to 3-day period. Thus, a total of 20 mg/kg results in a serum level of 20 µg/mL, 30 mg/kg results in a serum level of 30 µg/mL, and 40 mg/kg results in a serum level of 40 µg/mL.

A newborn's neurologic status may be difficult to accurately assess until many days after phenobarbital is discontinued because the half-life of the drug is so long. Anticonvulsant medications for post-asphyxial seizures can usually be discontinued before discharge home. The newborn should be observed for recurrent seizures until the serum drug level is estimated to be subtherapeutic if any anticonvulsant medication is discontinued before discharge home.

Neurodevelopmental Sequelae

Neurodevelopmental sequelae of HIE include spastic cerebral palsy, mental retardation, seizures, microcephaly, and hearing deficit. Apgar score alone is a poor predictor of long-term outcome, although newborns whose Apgar scores are 3 or less throughout the first 20 minutes after birth are much more likely to have long-term disability. Although neonates with low Apgar scores at 1 and 5 minutes but without evidence of neonatal encephalopathy usually develop normally; a large cohort study reported that term newborns who required resuscitation at birth but were asymptomatic thereafter did have an increased risk of lower IQ scores at 8 years of age.[131] Long-term outcome does correlate with the time until onset of spontaneous respirations, as the magnitude of delay in breathing reflects the severity of the underlying brain injury. Prolonged apnea associated with perinatal asphyxia for more than 30 minutes after delivery in term newborns is associated with irreversible brain damage.[130]

Using the severity of HIE as a guide, newborns with mild HIE survive and generally recover fully. About 10% of newborns with moderate HIE die, and 30% of survivors with moderate HIE develop mild to moderate long-term neurologic sequelae. Those without neurologic sequelae generally have IQ scores slightly lower than healthy newborns but are still within normal range.[132] Almost all newborns with severe HIE die in the neonatal period without intensive care. Virtually all those who do survive have severe neurodevelopmental disability. Despite the advent of sophisticated neuroimaging, neurologic examination at the time of discharge remains the best predictor of neurologic outcome. Neonates who have normal neurologic examination results by 7 to 10 days of age

can be expected to develop normally. Neonates who have persistent poor feeding due to difficulties coordinating their suck and swallow are very likely to have significant long-term impairment.

HYPOGLYCEMIA

Definition

Hypoglycemia is most likely to occur in the first few hours after birth. In the otherwise healthy term neonate, the physiologic nadir of blood glucose typically occurs 2 to 3 hours after delivery. This normal process reflects the transition from dependence on maternal glucose delivery in the uterine environment to dependence on the newborn's own ability to mobilize glucose stores and stimulate glucose production. Blood glucose levels of 40 to 50 mg/dL (2.2–2.7 mmol/L) in the first few hours of life are normal. Levels below 35 mg/dL (approximately 2.0 mmol/L) are generally regarded as abnormally low.[133] Newborns with low glucose stores in utero (eg, SGA) or whose stores were depleted during the delivery process (eg, fetal distress, asphyxia) are especially prone to early hypoglycemia. The level or duration of hypoglycemia resulting in neurologic injury is unknown; it is preferable to err on the side of caution with early treatment and close follow-up.

Incidence

Incidence of hypoglycemia in higher-income countries is estimated to be approximately 10%. It is likely that the incidence of neonatal hypoglycemia is substantially greater in lower-income countries because of factors such as low glucose stores or glucose depletion associated with fetal malnutrition, fetal distress, prematurity, cold stress, infection, or low intake due to illness or delayed breastfeeding. In Nepal, approximately 58% of uncomplicated deliveries had evidence of hypoglycemia when screened.[134] Independent risk factors associated with hypoglycemia included hypothermia, young maternal age, low birth weight, and sampling soon after birth. Incidence of hypoglycemia is higher in sick or premature newborns. Small for gestational age newborns (more common in developing countries) are more likely to become hypoglycemic than their normally grown counterparts due to reduced in utero glucose and glycogen storage. Studies in India[135] found that 25% of SGA newborns became hypoglycemic, especially when feeding was delayed. Mothers who received dextrose-containing fluids during labor had an increased incidence of delivering a newborn with hypoglycemia. Babies fed early had less hypoglycemia.

Screening and Prevention

Screening glucose measurements in otherwise healthy, asymptomatic term newborns (without risk factors for hypoglycemia) is not recommended, as it may capture the physiologic nadir and lead to unnecessary treatment and interfere with maternal-newborn bonding and breastfeeding. Early (within 30 minutes of birth) and frequent breastfeeding every 2 to 3 hours on demand is the most important intervention to maintain normal blood glucose levels in healthy newborns. However, many cultures delay breastfeeding and give nonnutritive teas and other liquids for 1 to 3 days after birth. Small for gestational age babies whose feeds are delayed are at especially high risk for hypoglycemia.[135] Hypoglycemia can also be prevented by reducing cold stress (see Hypothermia on page 455).

Risk Factors and Signs and Symptoms

Risk factors for transient hypoglycemia are shown in Table 20-8. Newborns may or may not demonstrate nonspecific signs of hypoglycemia (Box 20-3). Screening at-risk or symptomatic newborns for hypoglycemia with test strips is generally not available in developing countries. Therefore, treatment is usually empiric, based on clinical setting and presentation.

Treatment

There are several options for treating suspected or documented hypoglycemia depending on the newborn and supplies available. Early breastfeeding within 1 hour of birth (preferred) or formula-feeding is the first step. Fat and protein from the enteral feed provide substrate for ongoing glucose production. Oral sugar water (D5W [5 g/100 mL] 10 mL/kg) may be used if breastfeeding or formula is not available but should not be used routinely. Frequent breastfeeding on demand should be encouraged. If oral feeding is not feasible, cup or gavage feeding (orogastric or nasogastric tube) of expressed human milk or formula may be used. The feeding target for the newborn on the first day of life is approximately 40 to 60 mL/kg/day, which can be divided into small bolus feeds every 2 to 3 hours.

Immediate treatment is indicated if glucose is very low (ie, <25 mg/dL) or if the neonate is symptomatic. If IV glucose is available, give a small initial bolus of 200 mg/kg (2 mL/kg of D10W or 4 mL/kg of D5W) followed by a glucose infusion rate of 5 to 7 mg/kg/minute (approximately 80 to 100 mL/kg/day of D10W), which can be calculated using the following formula:

Table 20-8. Risk Factors for Transient Neonatal Hypoglycemia	
MATERNAL	**FETAL/NEONATAL**
Diabetes mellitus	Hypothermia
Excessive intrapartum glucose delivery	Birth asphyxia
Maternal medications (eg, terbutaline, oral hypoglycemic agents)	Infection
	Prematurity
	Intrauterine growth restriction Small for gestational age
	Large for gestational age
	Polycythemia, hyperviscosity

Box 20-3. Clinical Signs Associated With Hypoglycemia[a]	
Abnormal cry	Irritability
Jitteriness/tremors	Hypotonia, limpness
Lethargy, stupor	Seizures
Apnea, cyanotic spells	Grunting, tachypnea
Poor feeding	Hypothermia
Tachycardia, sweating	Pallor

[a] Clinical signs should be alleviated with concomitant correction of plasma glucose levels.

Glucose infusion rate (mg/kg/minute) = (% dextrose concentration × total mL/kg/day)/144

Dextrose is typically supplied as D50W, which must be diluted to make a concentration of D10W (ie, 2 mL of D50W added to 8 mL of sterile water or NSS). Hyperosmolar D25 or D50 should not be used in neonates.[136] Hyperosmolar glucose in neonates has increased potential for rebound hypoglycemia, risk of sclerosing vein, and risk of intracranial hemorrhage in premature newborns.[136]

As enteral feeds are established, persistent hypoglycemia should not be an issue unless there is an underlying metabolic problem such as hyperinsulinism, endocrine abnormality, or inborn errors of metabolism.

JAUNDICE

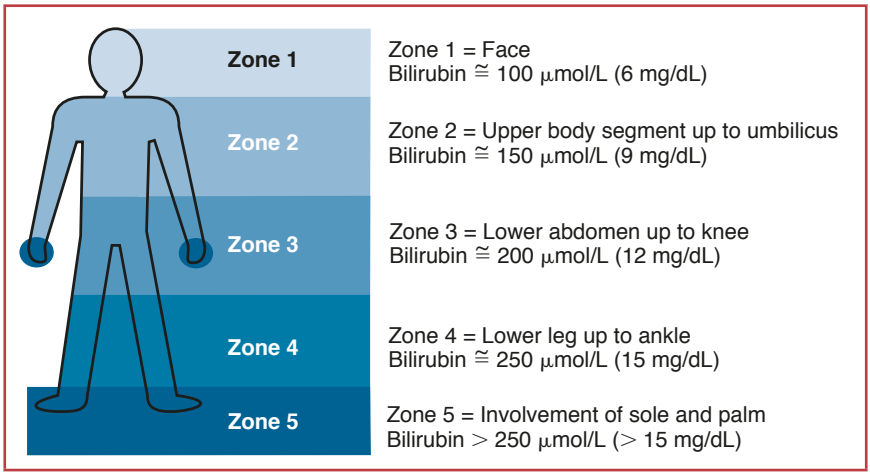
Neonatal jaundice is common, affecting more than 60% of term and almost all premature newborns. Generally, neonatal jaundice is benign and does not need specific treatment other than observation and follow-up if it worsens. However, it may be associated with significant morbidity. Although appropriate population-based studies have not been done to determine true incidence of severe jaundice, acute bilirubin encephalopathy, and kernicterus, these conditions are leading causes of neonatal morbidity and mortality in many nurseries in the developing world.[137–144] According to AAP recommendations, *acute bilirubin encephalopathy* is defined as acute changes seen in the neonatal period secondary to severe jaundice, such as tone abnormalities, opisthotonos, and abnormal cry, while *kernicterus* is reserved for chronic sequelae seen beyond the neonatal period, such as choreoathetoid cerebral palsy, deafness, and dental enamel dysplasia.[139] These long-term sequelae are devastating.[145]

Diagnosis

Every newborn should be monitored for jaundice while in the hospital.[139] A definitive plan should be in place to appropriately assess and follow up with jaundiced newborns.[139] A transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) should be checked if the newborn is jaundiced in the first 24 hours of life or more jaundiced than appears appropriate for her age, or if the level of jaundice is difficult to ascertain.[139] A TSB should be done if the TcB is elevated or no TcB is available. Ideally, every baby will have bilirubin checked before discharge from neonatal hospitalization.[146] The natural cephalocaudal progression of jaundice and tools, such as the Kramer scale (modified) (Figure 20-11) and icterometer, have been used to try to quantify the degree of jaundice, especially in low-resource settings without access to TcB or TSB.[147–150]

All these measures would be helpful in community health centers. However, these tools are best used as screening tools, as any clinical assessment of jaundice is fraught with inaccuracies, even among expert health care professionals.[151] Whenever possible, visual assessment of more than mild to moderate jaundice should be followed by a TcB or TSB to determine if or what treatment is needed. A TcB or TSB is always indicated for any jaundice noted in the first day of life and for jaundice involving the newborn's palms or soles because levels are highest when jaundice reaches these areas.[149] If possible, micromethods for determining serum bilirubin concentrations should be used. Standard laboratory equipment often requires large blood samples, and this can be a problem when obtaining multiple samples in small neonates. The cost

Figure 20-11. Kramer Scale (Modified)



Modified from Kramer LI. Advancement of dermal icterus in the jaundiced newborn. *Am J Dis Child.* 1969;118(3):454–458, with permission. Copyright © 1969 American Medical Association. All rights reserved.

of the device and disposables, durability, and accuracy of the results in pigmented newborns must be considered when choosing a device for measuring TcBs in developing countries.

Any newborn presenting with severe neonatal jaundice should be evaluated for acute bilirubin encephalopathy, looking for the stages noted per Volpe[152] (Box 20-4) and further modified and scored using the bilirubin induced neurologic dysfunction score (BIND II) or similar scoring systems.[153] In addition, neonates with severe acute bilirubin encephalopathy will often display a characteristic *kernicteric facies* (Figure 20-12) even after jaundice resolves. As noted by Slusher et al, kernicteric facies consists of paresis of upward gaze, often referred to as the setting sun sign; eyelid retraction; facial dystonia that makes the newborn appear "stunned, scared, or anxious"; and sometimes dysconjugate gaze.[154]

Etiology

Etiology of moderate to severe jaundice should be determined. Whenever possible, the workup should include total and direct bilirubin, a CBC with peripheral smear looking for hemolysis and evidence of infection, maternal and newborn blood type, direct Coombs test, and G6PD deficiency screening in populations with significant rates of G6PD deficiency.[20] A sepsis evaluation should also be done if clinically indicated and is likely a more common cause or at least cofactor in low-resource settings. The etiology of jaundice may be increased production

Box 20-4. Major Clinical Features of Acute Bilirubin Encephalopathy

INITIAL PHASE
Slight stupor (lethargic, sleepy)
Slight hypotonia, paucity of movement
Poor sucking, slightly high-pitched cry

INTERMEDIATE PHASE
Moderate stupor—irritability
Tone variable—usually increased, some with retrocollis-opisthotonos
Minimal feeding, high-pitched cry

ADVANCED PHASE
Deep stupor to coma
Tone usually increased, pronounced retrocollis-opisthotonos
No feeding, shrill cry

From Volpe JJ. Bilirubin and brain injury. In: *Neurology of the Newborn*. 4th ed. Philadelphia, PA: WB Saunders; 2008:635–637. Copyright 2008, with permission from Elsevier.

Figure 20-12. Kernicteric Facies

Courtesy of Tina Slusher, MD, FAAP.

of bilirubin (eg, hemolytic disease, polycythemia) or a decreased rate of excretion (eg, newborn of a diabetic mother, prematurity, poor feeding and intake).[20]

Etiology alone does not determine the need for treatment but can help guide decisions about the frequency of bilirubin checks, likelihood of the neonate progressing to severe jaundice with an increased risk of acute bilirubin encephalopathy, and risk to future siblings. Unless clinically indicated, direct bilirubin does not need to be repeated if it is not elevated on the initial bilirubin check.

Treatment

Treatment should be based on guidelines such as the one published by the AAP for newborns with a gestational age of 35 weeks or older in which the age of the newborn and associated risk factors, such as ongoing hemolysis, sepsis, asphyxia, and prematurity, are taken into consideration.[139] Clear guidelines are not yet determined, and there is more clinician variability in determining the level at which treatment is needed for newborns younger than 35 weeks' gestation (Table 20-9).

Newborns with significant jaundice should be treated with effective phototherapy. The most effective or intensive phototherapy available should be used. Intensive phototherapy per AAP guidelines involves irradiance levels of at least 30 μW/cm^2 per nm in the visible blue-green

Table 20-9. Guidelines for the Use of Phototherapy and Exchange Transfusions in Low Birth Weight Neonates Based on Birth Weight

TOTAL BILIRUBIN LEVEL (mg/dL[a])		
BIRTH WEIGHT (g)	**PHOTOTHERAPY[b]**	**EXCHANGE TRANSFUSION[c]**
≤1,500	5–8 (85–140)	13–16 (220–275)
1,500–1,999	8–12 (140–200)	16–18 (275–300)
2,000–2,499	11–14 (190–240)	18–20 (300–340)

Note that these guidelines reflect ranges used in neonatal intensive care units. They cannot take into account all possible situations. Lower bilirubin concentrations should be used for newborns who are sick (eg, sepsis, acidosis, hypoalbuminemia) or who have hemolytic disease.

[a] Consider initiating therapy at these levels. Range allows discretion based on clinical conditions or other circumstances. Note that bilirubin levels refer to total serum bilirubin concentrations. Direct or conjugated bilirubin levels should not be subtracted from the total.

[b] Used at these levels and in therapeutic doses, phototherapy should, with few exceptions, eliminate the need for exchange transfusions.

[c] Levels for exchange transfusion assume that bilirubin continues to rise or remains at these levels despite intensive phototherapy.

From Maisels M. Jaundice. In: MacDonald M, Mullett M, Seshia MMK, eds. *Avery's Neonatology Pathophysiology & Management of the Newborn*. 6th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2005.

(430–490 nm) range.[139] As noted by Jirapaet,[155] many things can and should be done to maximize phototherapy even when newer phototherapy devices are not available. Lights should be placed as close as possible to the newborn without overheating him (<15–20 cm above the baby [unless the baby overheats at this level] or stated differently by the manufacture).[139,156] Bulbs in conventional phototherapy units should be changed at least every 2,000 hours. Neonatal nurseries should be encouraged to get irradiance meters and measure irradiance of their phototherapy units periodically.[157] If bulbs are covered with a plastic shield, it should be clean and clear.[155] These plastic shields filter out ultraviolet light, not the wavelengths of visible light necessary for phototherapy.[156]

A phototherapy unit can be constructed using blue or white florescent bulbs. A blueprint for building homemade phototherapy devices is included in Box 20-5 and figures 20-13, 20-14, 20-15, and 20-16. These devices are intended for use in centers that do not have access to commercial phototherapy devices. As with all commercial units, irradiance should be checked; if it is not possible to check irradiance, bulbs should be changed as noted previously. Double phototherapy can be used by making lights that can be placed over the top of and beside or under the newborn's bed. Efficacy can be increased by using a white sling (cloth) over the bed or cot and phototherapy unit as a tent or canopy

Box 20-5. Local Construction of Phototherapy Devices

Phototherapy devices can be constructed with locally available resources. The size of the device and orientation of the lamps are determined by the space in which the baby is to be treated. Incubators and cradles (40 × 80 cm) need 7 to 8 tubes oriented parallel to their length. Cribs (80 × 140 cm, not shown) need 8 or more tubes (depending on the number of babies to be treated simultaneously) oriented parallel to the crib width (figures 20-13–20-16).

A. SUPPLIES AND TOOLS

1. Frame lumber. Obtain soft wood from a lumberyard or sawmill; cut it 7 cm wide × 3 cm high and up to 5 m long depending on the device to be constructed.
2. Cut 2 *device support bars* (Figure 20-13) to the width of the crib or bassinet *plus* 2 × 5 cm extensions.
3. Cut 2 *spacing bars* (Figure 20-13) to length of the lamp fixture *plus* 2 cm.
4. Obtain, from a lamp shop, a sufficient number of single or dual tube fixtures with 1 or 2 blue light fluorescent lamps each (20 W, 240 V alternating current [AC]), usually 59 cm long × 2.5 or 3.5 cm diameter. Do *not* use tubes that are painted blue. White tubes are not as effective as blue tubes, but if no blue lamps are available, white light is better than no light. Daylight tubes are more effective than cool white.
5. Wood saw.
6. Tape measure.
7. Marking pen(cil).
8. Screwdriver (Philips or blade).
9. Screws, 1 to 2 cm long, preferably sheet metal with approximately 8 mm in diameter Philips head, for mounting lamp fixtures (2 each per fixture).
10. Screws or nails, 4 cm long, to function as support bar stops (4 each per device frame).
11. Steel square.
12. Hammer.
13. Nails, thin, 1.0 to 1.5 mm, 4 cm long, 12 each per frame.
14. Wood glue.
15. Power cord, at least 200 cm long, with 240 V AC plug (Figure 20-14a).
16. Vinyl electrician tape.
17. Power cord lock or restraint clamps (a strip of triple-folded aluminum cut with scissors from a soft drink can and bent as shown in Figure 20-14a will do).

B. FRAME CONSTRUCTION

The following instructions are for making a wooden frame; however, aluminum frames are lighter and easier to move. They may also be made using the same dimensions or those needed to fit your incubators, cradles, cribs, or cots (Figure 20-14b).

1. Mark 5-cm sections from each side of the center corresponding to the total number of lamp fixtures to be used (1–6, 1–7, or 1–8 or more tubes for incubators, cradles/cots, or cribs respectively).
2. Turn the device supporting bars over onto a flat surface and align the spacing bars with the outer markings of the first and seventh tubes (Figure 20-14a).
3. Apply glue to the joints and connect the bars with one nail at each end of the spacing bar.
4. After using a steel square to verify that all the joints are square, apply a second and third nail to each joint, far enough from the edge to make sure that the wood does not split. The frame should now be square and sturdy.
5. When the glue has hardened, paint the frame with white latex or oil-based paint, making sure that you can still see the section markings. *Do not use lead-based paint.*

Box 20-5. Local Construction of Phototherapy Devices, continued

C. LAMP FIXTURE MOUNTING AND WIRING

1. Mount each of the lamp fixtures with one screw at each end, in the center of the sections marked 1 to 8 or fewer; make sure that on one of the support bars, a 2-cm space is left for mounting electrical wire connections. For the same reason, make sure that the power leads of the fixture exit toward this lamp support bar. A hole may need to be punched with a drill or hammer and nail 3 cm from each end of the fixture. The fixtures should be mounted with 0.5-cm spaces between them to allow for air circulation. In the case the device is to be used with a crib, it may be desirable to mount more than 8 tubes on the support bars.
2. It is recommended that a qualified electrician connect each of the lamp fixtures to the power cord. If such a person is not available, enlist the services of a person who understands how to make safe and effective electrical connections.
3. Start the process by making sure the lighting fixtures and lamps you obtained are in working condition. Test each lamp and fixture combination separately by connecting it to a power cord, insulating the junction, and making sure the lamp lights when the cord is plugged into a wall power socket.
4. There are 2 ways to make the electrical connections.
   (a) Using a so-called buzz wire connection or cord (Figure 20-14a) is neater looking but a more complicated and less reliable method.
   (b) The simpler and more reliable method (not shown) is to take one lead from each of the fixtures (same color, if the leads have different colors) and one of the power-carrying wires (not the ground wire) of the power cord and twist them firmly together. Then, preferably, fix them securely together with a so-called wire nut, if available. Do the same with the remaining fixture leads and power cord wires. Insulate each wire connection carefully with electrician tape. If the power cord has a ground wire, run separate wires to each of the light fixture frames.
5. For safety reasons, it is important that the power cord, as well as the fixture leads, be trimmed so that the wiring can be closely secured to the wood frame with one or more wire clamps (Figure 20-14a).
6. The phototherapy device is now ready for testing on an empty bassinet or crib for fit and proper functioning of all lamps. The device is intended to be suspended upside down from the top rails of the cradle (Figure 20-15) or bassinet (Figure 20-16) with the lamps hanging down. The distance between the lamps and the baby should be minimized for maximum efficacy of the light but should be no more than 20 cm unless the baby overheats or other heights are recommended by the manufacturer of the bulbs. You may need to limit or increase the number of mattresses beneath the baby or increase or decrease the height of the mattress support frame of a crib. If able to get high-intensity bulbs, such as some LED bulbs or tubes, you may need to increase the distance to limit the irradiance to safe levels, especially for premature babies. Again, the bulb manufacturer's instructions regarding distance should be followed whenever they are available. An irradiance meter can also be invaluable when making determinations regarding height above the baby and number of bulbs and phototherapy units to use.
7. For use with a crib, the device support bars should be fitted with stops at each of the 4 extensions through installation of a screw or nail (approximately 0.5 cm) outside the crib's side rail so that the device remains solidly in place between the side rails of the crib and will not slide inside the crib when bumped.
8. Plug the power cord into an operating power socket and make sure all lamps are lit.

Box 20-5. Local Construction of Phototherapy Devices, continued

D. TROUBLESHOOTING

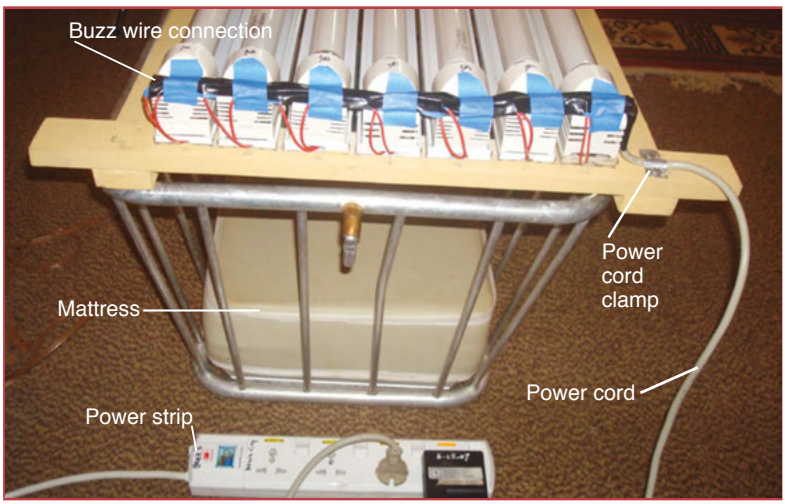
1. A lamp may not light up because it is defective or improperly placed into its sockets or the fixture may have failed wiring. Test the lamp by placing it in a working fixture. If the lamp works, return it to its original socket. If it still does not light, try twisting the lamp gently in its sockets to make sure that the lamp pins connect with the socket connectors. If this does not light the lamp, you may have a faulty fixture or faulty wiring. To determine what is going on at this point, you may need to acquire a volt-meter or replace the fixture with a working one.

With permission of Hendrik J. Vreman, PhD.

Figure 20-13. Assembling a Locally Made Phototherapy Device

With permission of Hendrik J. Vreman, PhD.

Figure 20-14a. Locally Made Phototherapy Device Inverted Over a Cradle to Display Fully Assembled Device



With permission of Hendrik J. Vreman, PhD.

Figure 20-14b. Aluminum Frame Homemade Phototherapy

With permission of Fidelia Bode-Thomas, MBBS.

Figure 20-15. Phototherapy Device in Use With a Cradle

With permission of Hendrik J. Vreman, PhD.

Figure 20-16. Phototherapy Device Constructed for Use With a Bassinet (Note Extended Spacing Bars for Protection of Lamps)

With permission of Hendrik J. Vreman, PhD.

or aluminum foil on either side of the baby.[156] White cloth is safer if there are any concerns about the electric wiring of the unit; however, make sure the cloth is not touching anything that can catch fire.

The newborn's eyes should be covered. Expose as much of the baby to the lights as possible, using only a small diaper, if needed.[139,157] Adequate hydration is important; however, routine supplementation is not advised in breastfed late preterm and term newborns unless the baby is dehydrated.[139] Premature neonates on IVFs need an extra 0.5 to 1 mL/kg/hour while under phototherapy.[20]

Bilirubin should be checked at least every day in newborns receiving phototherapy. Bilirubin should be checked every 4 to 6 hours in newborns nearing exchange levels and less often (every 12–24 hours) in those whose bilirubin is stabilized or declining. Hematocrit or packed cell volume should be checked on a neonate admitted with jaundice and at least daily if the baby is hemolyzing or appears pale.

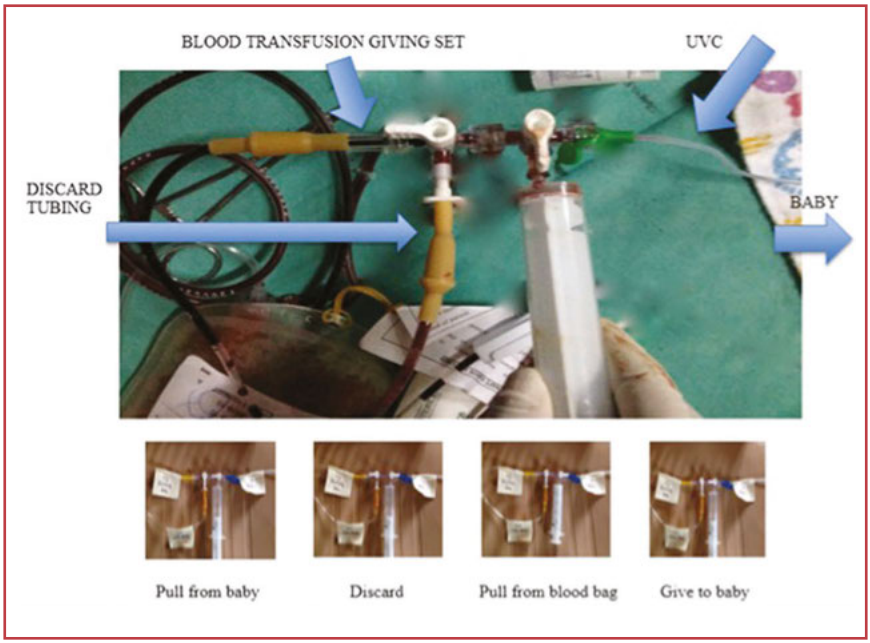
If a newborn's bilirubin rises to exchange blood transfusion levels based on age and weight, or the newborn demonstrates signs of acute bilirubin encephalopathy, an exchange transfusion should be done

as quickly as possible with fresh (<72 hours old) type O, Rh-specific, blood that is cross-matched to the mother and baby.[20] A double volume exchange requires approximately 160 mL/kg plus blood for the tubing. Hold the exchange transfusion at 1 unit if the amount in the unit or blood bag is slightly less than that required for a double volume exchange; this decreases the potential increased infectious risk from using multiple units. Blood should be warmed before beginning the exchange. Because commercial blood warmers are rarely available in lower-income countries, other methods, such as water baths at 37°C, or simply placing it directly on the caregiver's skin to warm are most practical. Care should be taken not to overheat the blood because this can lead to hemolysis.

Most transfusions can be done through a single UVC. Sterile feeding tubes in size 5, 6, or 8FR are generally used when umbilical catheters are not available. The exchange transfusion tubing should be set up so that blood is drawn from the newborn and discarded. Blood should then be drawn from the blood bag and infused into the newborn. The procedure should be repeated in a circular pattern without breaking the circuit. A 4-way stopcock is ideal, but, when not available, two 3-way stopcocks in tandem can be used. Ensure that all stopcocks and tubing are in the correct order before placing the catheter in the newborn; the cord is prepped and sterilely draped and a tie is placed on the skin at the base of the cord, minimally tightened, and left in place to tighten further if needed to control bleeding. The cord is then cut, leaving about a 1-cm stump. The feeding tube or catheter is inserted until good blood flow is noted (usually 2–4 cm) and not advanced further; further insertion can lead to placement in the liver, which can lead to liver damage (Figure 20-17).

The exchange blood transfusion begins after the catheter is inserted. Use 5 to 10 mL aliquots in premature newborns and 15 to 20 mL aliquots in near-term and term newborns. Exchanges are done over 90 minutes. Blood must be periodically agitated to prevent red cells from settling. Slowing the exchange leads to an increase in bilirubin withdrawal. Some clinicians give calcium gluconate 10% (1 mL)[20] after each 100 mL of blood exchanges via slow push to prevent bradycardia. Other clinicians suggest only giving calcium if the newborn develops signs or symptoms of hypocalcemia or if serum calcium levels are low. However, because calcium levels are seldom checked in laboratories in lower-income countries, many clinicians favor giving calcium prophylactically. Check the bilirubin immediately before and after exchange transfusion and then every 4 to 6 hours depending on the bilirubin level. If

Figure 20-17. Exchange Setup



Photographs courtesy of Ashley Bjorklund, MD.

hemolysis is ongoing, as it often is in newborns with G6PD deficiency or Rh incompatibility, a second or, rarely, third exchange transfusion may be needed.

Intravenous immunoglobulin (IVIG) (0.5–1 g/kg) decreases hemolysis and is indicated for treating hemolytic anemia associated with Rh or other blood group incompatibilities, if available.[139] Older drugs, such as phenobarbital, are generally not beneficial in unconjugated (indirect) hyperbilirubinemia because it takes about 48 hours to induce liver enzymes that increase the rate of bilirubin excretion. However, one study suggests that phenobarbital use in low birth weight newborns may reduce the need for phototherapy and exchange blood transfusions when given as prophylaxis.[158] Although maternal phenobarbital given prophylactically is controversial in hemolytic disease,[159] maternal phenobarbital administration can be considered in subsequent pregnancies of mothers whose prior babies had acute bilirubin encephalopathy, especially if appropriate and timely therapy for the newborn's jaundice is likely to be unavailable. Trevett et al recommend giving phenobarbital 30 mg per dose 3 times daily beginning at least 1 week before expected delivery.[160] It may be more practical to begin phenobarbital 2 to 3 weeks prior to the expected due date because ultrasounds are less common

in lower-income countries and there is less accuracy in predicting due dates. Newer drug treatments may have a place in the future treatment of hyperbilirubinemia; some of the porphyrins currently being researched are especially promising.[139,161]

Figure 20-18 demonstrates the threshold for initiating phototherapy based on a newborn's age, serum bilirubin, and risk factors. Risk factors include jaundice in the first 24 hours, prematurity, previous sibling(s) with jaundice, cephalhematoma, bruising, breastfeeding, and racial groups known to have a high incidence of G6PD deficiency.[139]

Figure 20-19 demonstrates the threshold for performing an exchange transfusion based on a newborn's age, serum bilirubin, and risk factors.[139]

RESPIRATORY DISEASES

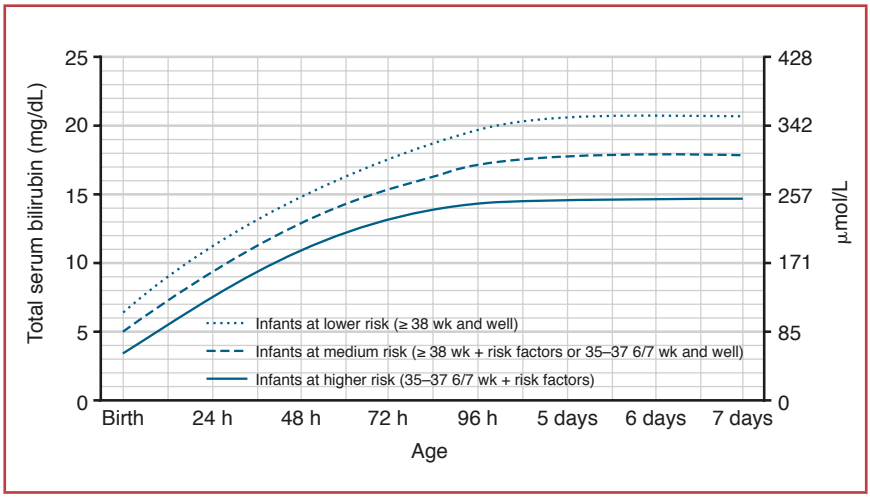
Respiratory distress is a common newborn problem worldwide. In India, a prospective study of more than 4,500 births was conducted to identify incidence of various causes of respiratory distress in a birth cohort. The overall incidence of respiratory distress was 6.7% in all births, with preterm births having the highest incidence at 30% of all premature births.[162]

The differential diagnosis of neonatal respiratory distress in term and preterm newborns includes transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS) (surfactant deficiency), pneumonia, sepsis, and pneumothorax, as well as congenital abnormalities such as diaphragmatic hernia, tracheoesophageal fistula (TEF), and heart disease. Although surfactant deficiency (RDS) is more common in the preterm newborn and TTN in the term newborn, there is considerable overlap in diagnoses. Other non-pulmonary diagnoses to consider include neurologic injury, heart failure, choanal atresia, and TEF.

There are multiple signs of respiratory distress in the neonate, most commonly including tachypnea (respiratory rate >60 BPM). Of note, it is important to count for a full 60 seconds, as newborns will normally vary their rate of breathing intermittently. Counting for less time may not accurately identify abnormalities. Other signs of respiratory distress may include nasal flaring, grunting, tracheal tugging, retractions, and cyanosis. Grunting is an end-expiratory noise created when a newborn breathes against a partially closed glottis in an effort to create positive end-expiratory pressure (PEEP) to splint open airways. It may sound like the baby is saying, "EEEE."

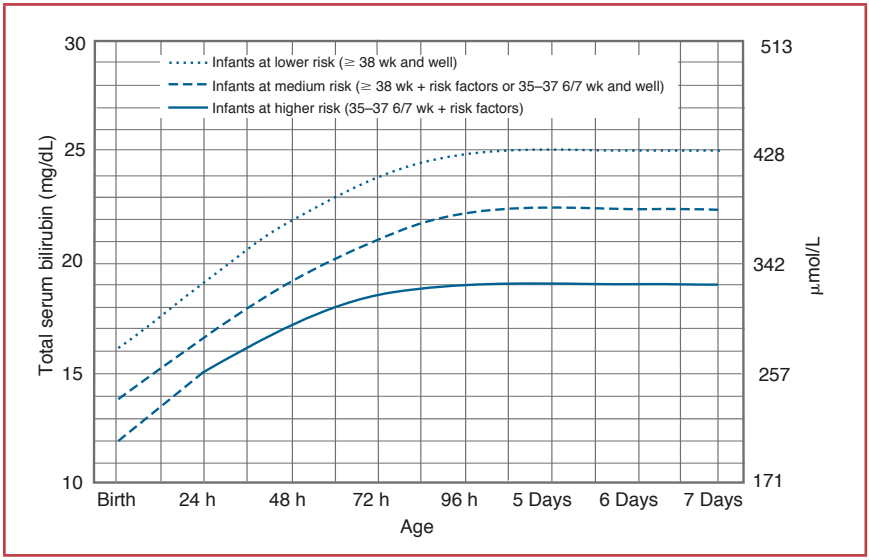
Apnea, cessation of breathing effort for a minimum of 15 to 20 seconds usually reflects brain stem immaturity in the preterm newborn but can also occur as a manifestation of severe respiratory distress or sepsis.

Figure 20-18. Guidelines for Phototherapy in Newborns 35 Weeks' Gestation or Older



From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297–316.

Figure 20-19. Guideline for Exchange Blood Transfusions in Newborns 35 Weeks' Gestation or Older



From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297–316.

It is important to distinguish prolonged apnea from normal immature respiratory patterns, such as periodic breathing. In the healthy term newborn, normal oxygen saturation in room air is achieved by 15 to 20 minutes after birth. Cyanosis is not readily apparent to the eye until oxygen saturation is less than 70% due to characteristics of fetal hemoglobin. If possible, use an oximeter to determine the level of oxygen saturation.

Evaluating the Newborn With Respiratory Distress

Diagnosis and treatment of respiratory distress in the newborn are completely empirical in many lower-income countries with limited resources. Maternal and perinatal history, physical examination, time course, and response to treatment may be the only information available to establish a diagnosis.

The evaluation should include

- *History.* Ask about maternal history, pregnancy complications, and delivery history, including prolonged labor, prolonged rupture of membranes, Apgar scores, presence of meconium, history of a difficult transition, or need for resuscitation at birth.
- *Vitals.* Check heart and respiratory rates and temperature; include blood pressure and oxygen saturation if available.
- *Physical examination.* Look for increased work of breathing, including retractions, nasal flaring, grunting, tachypnea, and cyanosis.
- *Tests.*
  - Complete blood cell count with differential to look for anemia or evidence of infection. A blood culture or C-reactive protein (CRP) may be helpful if infection is suspected or respiratory distress does not resolve within 4 to 6 hours of birth.
  - Consider a chest radiograph if available. This is not routinely done for most newborns because of cost and availability. However, a chest radiograph should be obtained if at all possible if the newborn is not responding to therapy as expected or has an atypical presentation.
  - Arterial or capillary blood gas, if available, may be indicated, especially if ventilator support is possible.
  - Oximeter, if available, to check or monitor oxygen saturation. Oximeters can also serve as cardiac monitors.

Specific Respiratory Conditions

Transient Tachypnea of the Newborn

Kumar and Bhat[162] noted that TTN was the most common cause of respiratory distress overall, occurring in approximately 43% of all newborns with respiratory distress. Although TTN is more common in term newborns, it occurs in preterm newborns as well. This generally benign condition, caused by delayed reabsorption of alveolar fluid, resolves without treatment within the first 48 to 72 hours after birth. Transient tachypnea of the newborn is more likely to occur following cesarean delivery, especially in the absence of labor; after precipitous vaginal delivery; in newborns of diabetic mothers; in males; and in late preterm newborns.

Physical examination should reveal a tachypneic baby in respiratory distress, which is typically mild but can be moderate. Persistent tachypnea may be the only sign. Lungs may be clear or sound wet with crackles. If available, chest radiograph may confirm this, but it is not required for diagnosis. Typical chest radiograph patterns may include diffuse pattern of opacification, increased vascular markings, fluid in the fissures, hyperinflation, and an overall homogeneous "wet" appearance to the lungs.

Treatment of TTN is largely supportive; there is no known treatment to hasten the reabsorption of fluid into the lungs. Oxygen should be provided if saturation is less than 90%. Typically, patients with uncomplicated TTN will not require more than 40% oxygen.

Respiratory Distress Syndrome

Respiratory distress syndrome, formerly called hyaline membrane disease, occurs primarily in preterm newborns and is caused by surfactant deficiency. Surfactant reduces surface tension in the lungs. As the newborn takes his first breaths, surfactant is needed to help maintain alveolar expansion and lung volume during respiration. The incidence of RDS is inversely proportional to the gestational age. Risk factors for RDS include prematurity, maternal diabetes, asphyxia, and male gender.

On physical examination, newborns with RDS have tachypnea, increased work of breathing, nasal flaring, retractions, and expiratory grunting. There are no specific findings on physical examination that will confirm RDS; one must rely on history and risk factors. The onset of this condition is typically immediately after birth with progressive increase in severity of respiratory distress and oxygen requirement. The characteristic chest radiograph shows a diffuse ground glass opacity, air bronchograms, and hypo-inflation due to diffuse alveolar collapse.

A relatively simple and inexpensive gastric shake test can help identify newborns with surfactant deficiency. This qualitative test is done at the bedside by mixing together an aliquot (0.5 mL) of gastric aspirate collected within 30 minutes after birth and an equal volume of normal saline for 10 seconds. One mL of 95% ethanol is then added and the mixture agitated for another 10 seconds. After resting for 15 minutes, the mixture is examined for stable bubbles, which indicate that surfactant is present. The absence of bubbles (ie, a *negative* test) indicates the absence of surfactant and a high probability of developing RDS. However, there can be false-negative results due to other substances in the gastric aspirate. On the other hand, a positive test result does rule out RDS.

The natural history of RDS is clinical worsening over the first 48 to 72 hours, followed by gradual improvement, which is heralded by a spontaneous diuresis. Newborns with RDS may benefit from the use of nasal CPAP (4–6 cm water) when possible. Oxygen should be administered by tent, nasal cannula, or nasal CPAP to maintain saturation between 88% and 94%. Several artificial and natural surfactants are commercially available for surfactant replacement. No one surfactant has demonstrably better long-term outcomes than another. Surfactant replacement is usually given through an ETT; trials of administrating by a laryngeal mask are currently underway but still not large enough to recommend routinely giving surfactant by laryngeal mask airway.[163–165] The use of surfactant replacement is limited by cost, difficulties in storage (mainly refrigeration), and need for administration via intubation. If prolonged ventilation is not possible, surfactant can be administered via the ETT, which is then removed, after which the newborn is placed on CPAP via nasal prongs. Interestingly and potentially very helpful in settings were surfactant is not available or affordable is a study published by the SUPPORT group suggesting the use of early CPAP (of 5 cm) as an alternative to surfactant in preterm infants.[166]

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension is the pulmonary vasculature response to hypoxia, acidosis, asphyxia, and sepsis, as well as various causes of respiratory compromise, such as meconium aspiration, pneumonia, pneumothorax, and TTN. Sometimes an underlying cause cannot be found. Essentially, this is persistence of the fetal pattern of circulation with continued right-to-left shunting through the patent ductus arteriosus (PDA) due to high pulmonary vascular resistance. These newborns present with tachypnea and cyanosis; they may not have increased work of breathing if there is no underlying lung disease. In developing countries, treatment is typically limited to oxygen administration via nasal

cannula, which acts as a pulmonary vasodilator. If possible, saturation should be kept at 95% or more. Nasal CPAP is also helpful if there is underlying lung disease associated with persistent pulmonary hypertension. Magnesium sulfate infusion has also been used in developing countries with some success; however, hypotension is a risk and vasopressors or inotropic agents may be required.[167] A Cochrane review[168] did not recommend this treatment because of lack of evidence.

Meconium Aspiration

The incidence of meconium aspiration syndrome (MAS) in the developing world is likely substantially higher than in the developed world because of the much higher incidence of asphyxia and post-term delivery. A retrospective study in the West Indies found that 8% of admissions requiring ventilation were due to MAS.[169] In one study in India, 4.6% of all term neonates admitted to the neonatal intensive care unit had a diagnosis of meconium aspiration.[170] The newborn's history typically includes being term or postdates with fetal distress or difficult labor. Most meconium aspiration occurs before birth when the fetus reflexively gasps in response to intrapartum asphyxia and inhales amniotic fluid filled with meconium, which was passed in response to hypoxemia. If a neonate, born through meconium-stained fluid, is depressed at delivery and a skilled birth attendant is present, intubation may assist in suctioning out meconium from the proximal airway. Meconium aspiration syndrome often leads to pulmonary hypertension. These patients require support with face mask, hood, nasal cannula oxygen, or CPAP.

Pneumothorax

Pneumothorax may be spontaneous at birth because of the large negative intrathoracic pressures needed to initiate breathing or an associated underlying pulmonary disease (eg, RDS, pneumonia, TTN, MAS) or by overdistension of the lung by aggressive ventilation (including CPAP), especially in newborns with RDS or MAS. Signs include tachypnea, desaturation, and, when very large, decreased breath sounds on the affected side. Small pneumothoraxes resolve on their own. Symptomatic pneumothoraxes can be aspirated by inserting a needle just over the rib at the second or third interspace at the midclavicular line. This may be done with a 20- or 22-gauge IV catheter, a small-gauge needle, or a 23-gauge butterfly needle attached to a 3-way stopcock and syringe. The butterfly tubing can be placed in sterile water after aspirating air; this will serve as a water seal to see if the pneumothorax has resolved. Persistent bubbling indicates that the air leak is ongoing and insertion of a chest tube is probably necessary; however, chest tubes are often not available in low-resource settings.

Tracheoesophageal Fistula

Tracheoesophageal fistula is another cause of respiratory distress in the neonate. In the most common type (85%),[20] the distal esophagus communicates with the posterior trachea and the esophagus ends in a blind hypopharyngeal pouch. It is often suspected in a newborn who is not swallowing secretions well from birth. It can be diagnosed clinically by attempting to pass a nasogastric tube that, on anteroposterior chest radiograph, is found to be curled in the hypopharynx. The only treatment is surgical, which is often complicated or unavailable in low-resource settings.

Infection (Pneumonia/Sepsis)

Infection, such as pneumonia, sepsis, or meningitis, may present with respiratory distress. Typically, early onset pneumonia may be caused by gram-negative bacteria such as *Escherichia coli* or gram-positive bacteria such as group B *Streptococcus*. Later in infancy, the most common cause is gram-positive organisms, such as *Staphylococcus*. Other infections to consider are *Treponema pallidum,* HIV, *Chlamydia,* and *Listeria*. Pneumonia is often impossible to distinguish clinically from noninfectious causes of respiratory distress such as TTN; therefore, newborns with respiratory distress should be treated promptly with broad-spectrum antibiotics. Ampicillin and gentamicin are generally used as first-line agents for empiric treatment of neonatal infection. However, drug-resistant organisms (eg, *E coli*, methicillin-resistant *S aureus*) are becoming more common. If at all possible, a blood culture should be obtained prior to beginning treatment and repeated if there is no clinical improvement within 48 hours to ensure the appropriate choice of antibiotic therapy.

Congenital Heart Disease

Congenital heart disease (CHD) may present with respiratory distress, cyanosis, or a heart murmur in the newborn period. Physical examination, chest radiograph, and electrocardiogram (ECG) can help determine the type of heart disease. Administering oxygen can help distinguish cyanotic heart disease from respiratory causes of cyanosis in the newborn. When 100% oxygen (hyperoxia test) is administered, the blue baby with a fixed right-to-left intracardiac shunt due to cyanotic CHD will remain cyanotic without any rise in oxygen saturation or improvement in color. Newborns with non-cyanotic heart disease or lung disease will usually have a rise in oxygen saturation and become pinker. Oxygen

saturation greater than 95% to 100% generally rules out cyanotic CHD. Echocardiography, which may be available in referral centers, is the most cost-effective way to diagnose CHD in low-resource settings. There is little treatment available in the developing world because of the complexity of the repairs required for most of these conditions. Depending on the type of lesion, life expectancy can be hours, weeks, months, or years.

Patent Ductus Arteriosus

Patent ductus arteriosus is a common problem in preterm newborns. A systolic murmur, hyperactive precordium, and bounding pulses (especially palmar or posterior tibial pulses) are typical signs. When a large left-to-right shunt occurs across the ductus, it results in pulmonary overcirculation and congestion, increased oxygen requirements, tachypnea, increased work of breathing, and apnea; hepatomegaly may become evident. Treatment includes diuretics (furosemide, 1 mg/kg/dose every 12–24 hours), fluid restriction (≤120 mL/kg/day), and administration of oxygen to maintain 90% to 95% saturation. If anemic, transfusion will help improve tissue oxygenation. If these measures are unsuccessful in closing the PDA, oral ibuprofen is a very effective treatment; this includes an initial dose of oral ibuprofen solution of 10 mg/kg nasogastric or orally followed by 5 mg/kg each at 24 and 48 hours after the initial dose. The regimen can be repeated once or twice if the PDA fails to close with the first 3-dose course.[171]

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia should be considered in the term newborn with respiratory distress and a scaphoid abdomen, as the abdominal contents are herniated into the chest. On examination, there are diminished breath sounds on the side of the herniation and cardiac impulse is deviated to the right if, as is more often the case, the hernia is in the left chest. It is possible to make this diagnosis by prenatal ultrasound. Most newborns present at birth with respiratory distress and cyanosis. After birth, diagnosis can be confirmed with a lateral chest radiograph demonstrating bowel in the chest. Diaphragmatic hernias are very difficult to manage under the best of circumstances because of lung hypoplasia and severe pulmonary hypertension, often requiring inhaled nitric oxide, high-frequency ventilation, and extracorporeal membrane oxygenation in addition to surgical repair. The prognosis is extremely poor for these newborns in developing countries without access to sophisticated neonatal intensive care.

Apnea of Prematurity

Apnea of prematurity, secondary to immature brain stem control of breathing, is very common in premature newborns, especially those who are younger than 34 weeks' gestation. These babies have irregular (periodic) breathing with intermittent periods of central apnea that results in bradycardia and oxygen desaturation when prolonged. The definition of *apnea of prematurity* is cessation of airflow for a minimum of 20 seconds. These apneas are typically central in origin, although airway obstruction can lead to hypoxia and central apnea. Care must be taken to avoid obstructive apnea by carefully positioning the newborn's head and neck so the airway remains patent. Typically, apneic or bradycardiac spells improve with tactile stimulation and usually resolve completely by term-adjusted age. Infection should be suspected as the cause of apnea when there is a sudden onset of apnea in a previously healthy premature newborn or if there is a marked increase in the severity or frequency of apnea in a preterm newborn with apnea of prematurity. Apnea in a term newborn is abnormal, and the possibility of infection or neurologic injury should be investigated.

Methylxanthines (ie, aminophylline, theophylline, or caffeine), which stimulate the respiratory drive, are used to treat apnea of prematurity. Dosing suggestions for theophylline and caffeine are included in Table 20-10. Caffeine citrate, which is commercially available in the United States for this purpose, is expensive and may not be readily available. However, whenever possible, caffeine citrate should be used instead of methylxanthine therapy because it is safer and has a much wider therapeutic index. In addition to pharmacologic stimulant therapy, some newborns require intervention with a nasal cannula or nasal CPAP, if available, to provide stimulation.

Table 20-10. Drugs Used for Apnea of Prematurity

DRUG	THEOPHYLLINE	AMINOPHYLLINE[a]	CAFFEINE CITRATE
Loading dose	Orally: 5 mg/kg	IV or orally: 5–6 mg/kg	IV or orally: 10–20 mg/kg
Maintenance dose	Orally: 1–2 mg/kg/dose every 6 h, up to 6 mg/kg/d	IV or orally: 1–2 mg/kg/dose every 6–8 h	IV or orally: 5–10 mg/kg once daily beginning 24° post–loading dose

Abbreviation: IV, intravenous.

[a] Typically, aminophylline is available in IV solution at a concentration of 250 mg in 10 mL. This can be diluted with sterile water or normal saline (1 mL aminophylline plus 9 mL sterile water), which will be a concentration of 2.5 mg/1 mL. This can be given orally or intravenously.

Oxygen

Oxygen should be considered a drug and used with caution. If available, a blender should always be used to minimize oxygen toxicity. Premature newborns can develop retinopathy of prematurity if administration of oxygen results in high oxygen levels in the blood. If saturation monitors are available, oxygen should be titrated to keep saturation between 88% and 95% in the absence of heart disease or other conditions that would require higher or lower oxygen saturation goals. Oxygen is most easily administered via nasal cannula. The amount of oxygen delivered is proportional to the flow rate, size of the nasal cannula, and whether room air is being entrained through the mouth or around the nasal cannula. High oxygen concentrations can be administered to preterm newborns if the mouth is closed and the baby is not crying. As seen in Table 20-11, in contrast with the adult patient who gets about 24% oxygen from a nasal cannula running off 100% oxygen supply, a neonate can get around 66% from the same flow. Non–re-breather masks with a reservoir are needed if 100% oxygen is required for larger term newborns. Regular face masks entrain room air and substantially reduce delivered oxygen concentration.

Continuous Positive Airway Pressure

Continuous positive airway pressure is indicated for mild to moderate respiratory distress and apnea of prematurity. It will not be effective for severe respiratory distress but can be lifesaving in less-severe disease. Continuous positive airway pressure has shown to decrease the need for mechanical ventilation in VLBW newborns with respiratory distress.[172]

Table 20-11. Nasal Cannula Conversion[a]

	F_{IO_2}			
FLOW RATE (L/min)	**100%**	**80%**	**60%**	**40%**
0.25	34%	31%	26%	22%
0.50	44%	37%	31%	24%
0.75	60%	42%	35%	25%
1.00	66%	49%	38%	27%

Abbreviation: F_{IO_2}, fraction of inspired oxygen.

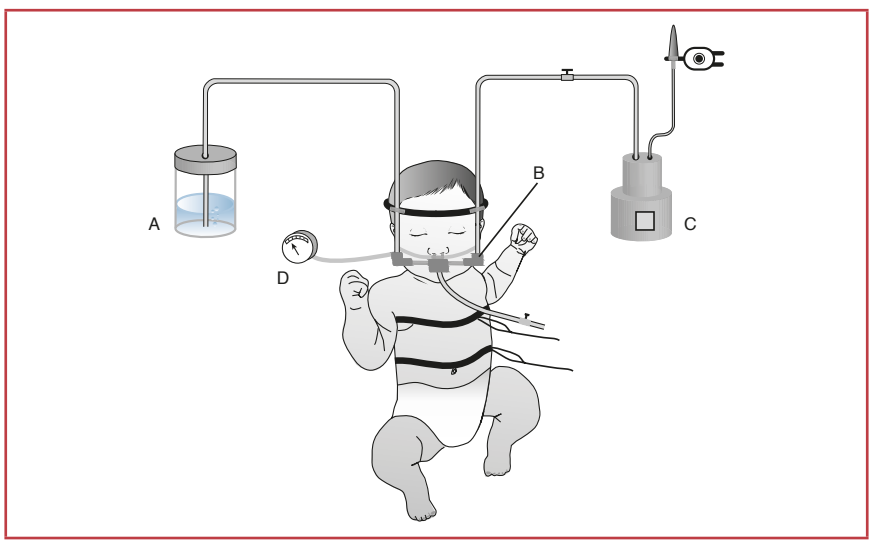
[a] Guideline only; F_{IO_2} provided via nasal cannula is approximate.

From Gomella TL, Cunningham MD, Eyal FG, Tuttle DJ, eds. *Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs*, 7th ed. New York, NY: McGraw-Hill Education; 2013.

Continuous positive airway pressure can be delivered via nasal prongs, an ETT placed in the newborn's oropharynx, or an ETT placed in the trachea. Intubation is rarely done in low-resource settings because of the risk of the tube becoming dislodged or occluded.

Simple components needed for bubble CPAP include an oxygen source, an oxygen flowmeter, oxygen tubing, a container of sterile water, a humidifier device, and a device to deliver CPAP to the neonate. Most commonly, CPAP is administered through commercially available nasal prongs, which come in different sizes and should be snugly fitted in the newborn's nose with as little leaking as possible (Figure 20-20). If commercial prongs are not available, an ETT can be shortened to decrease the likelihood of displacement and placed through the nose into the posterior oropharynx and the circuit attached to the ETT. Diligent observation to be sure the ETT is not obstructed with secretions is critical. Another option includes modifying a nasal cannula (Figure 20-21). An adult nasal cannula (for larger neonates) or pediatric nasal cannula (for small neonates) can be adapted for use if commercial prongs are not available. Sometimes it is necessary to cut and shorten the piece between the 2 nasal prongs to make the nasal cannula fit (see figures 20-21 and 20-22).

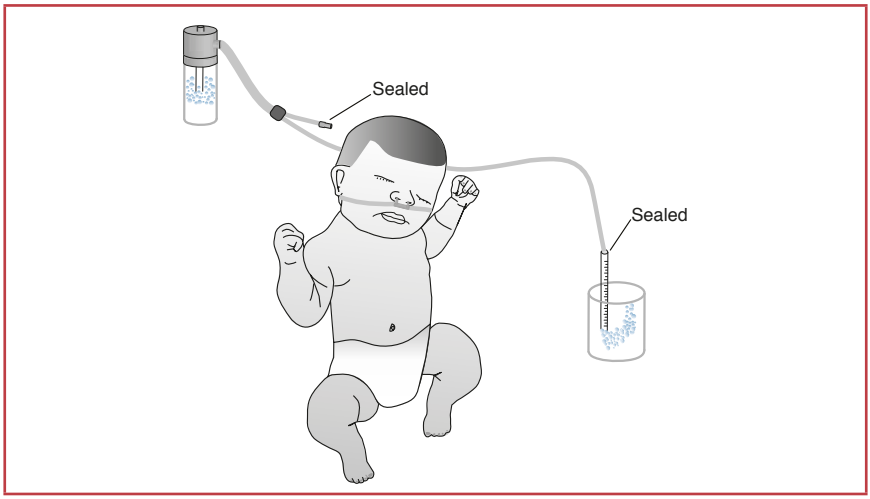
Figure 20-20. Schematic of Bubble Continuous Positive Airway Pressure Using a Commercially Available Circuit



A, Underwater bubble chamber. B, Nasal continuous positive airway pressure prongs. C, Heated humidifier attached to oxygen blender and flowmeter. D, Manometer.

Modified from Liptsen E, Aghai ZH, Pyon KH, et al. Work of breathing during nasal continuous positive airway pressure in preterm infants: a comparison of bubble vs variable flow. *J Perinatol.* 2005;25:453–458, with permission from Macmillan Publishers Ltd.

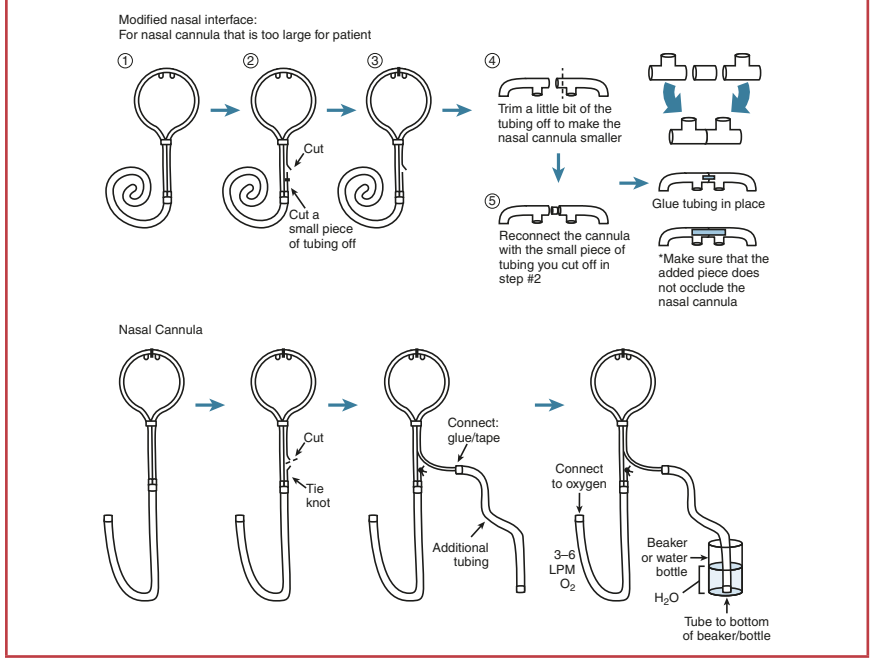
Figure 20-21. Schematic of Bubble Continuous Positive Airway Pressure Using a Modified Nasal Cannula



Begin liter of blended oxygen/oxygen flow at 3–4 L/min and increase up to 5–6 L/min if needed to compensate for small leaks at the nostrils.

Adapted from Adrian Michael Slusher, BSME.

Figure 20-22. Bubble Continuous Positive Airway Pressure Drawing



Compliments of Ashley Bjorklund, MD, and Adrian Michael Slusher, BSME.

Typically, CPAP is started on 5 cm of water pressure, but this can be increased if the patient requires additional pressure. The range of pressure needed is generally between 5 and 8 cm of water. To administer the desired level of CPAP, the water container must be maintained securely in an upright position and the tube securely held in the desired position underwater below the level of the baby. The level of CPAP can be titrated on the basis of oxygenation improvement, work of breathing improvement, or expansion of ribs on chest radiograph (goal of distending approximately 8–9 ribs), if available.

Continuous positive airway pressure can also be delivered with a pressure-limiting PEEP valve (eg, Accu-Peep) that delivers a fixed (5 cm) amount of PEEP. This device is attached to the distal CPAP tubing and taped securely horizontally to the edge of the bassinet. While the amount of CPAP delivered cannot vary, 5 cm is high enough to be therapeutic in most circumstances and low enough to minimize the risk of air leak. Flow needs to be at 6 to 8 L or greater to use this device.

In addition, continuous positive airway pressure can be delivered by a high-flow nasal cannula with flows of 1 to 6 L per minute. However, the amount of CPAP delivered cannot be monitored and depends on variables (eg, baby size, cannula size, magnitude of air leak, flow rate) and is not consistent.[173] Depending on the circumstances, the CPAP actually delivered may be more or less than expected.

Although CPAP is typically safe, too much distending pressure may cause pneumothorax, pneumomediastinum, or overdistension of the lung, which reduces venous return. Medical staff need to frequently monitor neonates on CPAP, as it is easy for the delivery device to dislodge, the apparatus to disconnect, or the prongs to become obstructed with secretions. In addition, the delivery device may cause trauma to the nares or oropharynx; patients must be examined frequently to ensure that there is no necrosis. Continuous positive airway pressure can also cause gaseous distension of the abdomen. Typically, this is not harmful, and an orogastric tube should be placed to decompress the abdomen. Infants with poor motility may develop gaseous distention of the GI tract. Gastric/GI perforation has been described in synchronized noninvasive ventilation of the neonate but has not been described in those with CPAP only. One good source for training staff in the use of CPAP is a manual by Ammari et al.[174]

SEIZURES

Because neonatal seizures occur for treatable and untreatable reasons, determining the cause is of utmost importance. Generally, the causes of neonatal seizures can be classified as infectious; neurodevelopmental,

which includes HIE and cerebral dysgenesis; acute metabolic and rare inborn errors of metabolism; traumatic or cerebrovascular; iatrogenic; or toxicologic.

Treatable causes of neonatal seizures include metabolic and electrolytic derangements, such as hypoglycemia, hypocalcemia or hypercalcemia, hyponatremia or hypernatremia, hypomagnesemia, and pyridoxine deficiency. Treating the underlying problem in these instances usually eliminates the seizure without the need for anticonvulsants. Neonatal seizures secondary to herpes encephalitis, bacterial meningitis, and polycythemia require cause-specific treatment in addition to anticonvulsant therapy. Other causes of seizures, such as HIE, intracranial hemorrhage, stroke, congenital malformations of the brain, and developmental and non-herpetic TORCH infection, may require anticonvulsants, but care of these neonates is otherwise largely supportive.

Theophylline toxicity must be entertained as a cause in the neonate, especially if the possibility of incorrect dosing exists or there are signs of theophylline toxicity, such as vomiting and tachycardia. Rarely, withdrawal from illicit drugs (ie, opiates) can cause seizures in the neonate. In these instances, although therapy is primarily supportive, the newborn may require temporary narcotic replacement and anticonvulsant therapy.

Clinical Manifestations

Diagnosis is usually based on observation of normal and abnormal movements in the newborn. Jitteriness and uncoordinated, random movements may be present in a normal neonate. The more premature the neonate, the more nonspecific the movements, which may be mistaken for seizures. Because the newborn brain is still developing, one does not see classic manifestations of seizures as in a more organized cortex. Moreover, there is a greater risk for seizures in the premature than term newborn, with an inverse relationship between degree of prematurity and risk for seizures. Seizures may present as

1. Rhythmic twitching (focal or multifocal), tonic or clonic movements that cannot be interrupted by grasping the affected extremity
2. Stereotypic, slow rhythmic movements, such as chewing motions, slow blinking, or posturing
3. Persistent horizontal or vertical deviation of the eyes or nystagmus
4. Autonomic instability (tachycardia, elevation of blood pressure, changes in color), pupillary changes[20,175]

In contrast with older infants, focal seizures in a neonate are not necessarily caused by focal lesions.

Diagnosis and Treatment

If a treatable cause of the seizure is identified, such as hypoglycemia, and the seizure resolves with that treatment, no further treatment is likely needed. The newborn will need to be observed closely for recurrence of the underlying cause (eg, hypoglycemia). Idiopathic seizures and seizures that persist despite specific treatment of underlying cause require anticonvulsant therapy.

Hypocalcemia is best diagnosed using serum tests for free ionized calcium. Because ionized calcium is not affected by the albumin level, it is preferable to total calcium. If serum calcium is not available but an ECG strip can be run immediately, probable hypocalcemia can be diagnosed by prolonged QTc (see formula on page 506). If serum calcium or ECG strip are not available and hypocalcemia is clinically suspected, such as in post–exchange blood transfusion or an SGA newborn, a trial of an IV calcium dose can be given. Ideally, hypocalcemic seizures are treated with IV calcium gluconate, 100 to 200 mg/kg/dose.[20] When administering calcium through a peripheral IV, it is crucial to verify that the IV is patent, preferably through a newly placed IV line. Intravenous calcium causes severe burns if it infiltrates, which may require skin grafting or an extended time to heal with marked scarring. Intravenous calcium should not be given through a scalp IV because these veins tend to be more fragile and prone to infiltration. The calcium dose should be diluted in 10 mL of sterile water or normal saline and given slowly over 10 minutes or longer with close observation for infiltration.

Rarely, severe hypercalcemia can cause seizures. Hypercalcemic seizures are treated by increasing fluids by about 25% and using diuretics such as furosemide (1 mg/kg/dose every 12 hours) and phosphate, administered IV or enterally 30 to 40 mg/kg/day.[20]

Hypernatremia and hyponatremia can be associated with seizures. The diagnosis of sodium abnormalities requires confirmation by serum testing and the neonate may require anticonvulsants alone until electrolyte abnormalities are corrected. Hyponatremic seizures should be treated with 3% saline. Normal saline can be used when hypertonic saline is not available. To determine the proper amount of sodium, use the formula on page 505 (see Fluids and Nutrition on page 436 for prevention). Six mL/kg of 3% saline is approximately equal to 20 mL/kg of NSS. Normal saline contains 0.154 mEq/mL of sodium. Three-percent hypertonic saline contains 0.513 mEq/mL.

Hypernatremic seizures are often associated with dehydration and therefore should be treated with increased free water (water without added sodium [eg, D5W]) and gradual reduction of serum sodium over 48 hours or more.[20]

Hypomagnesemia may be suspected clinically because testing serum levels for magnesium is largely unavailable in developing countries. Hypomagnesemia associated with seizures should be treated with magnesium sulfate (25–50 mg/kg/dose) given over at least 20 minutes IV every 8 to 12 hours[20] until symptoms resolve. Magnesium given orally is often associated with diarrhea and would not raise serum magnesium quickly enough to treat seizures.

Herpes encephalitis is difficult to diagnose definitively in the developing world. If available, an EEG showing abnormalities in the temporal lobe may help support the diagnosis. An EEG is helpful in the neonate but is not diagnostic in herpes simplex CNS infection. Term and late preterm neonates with the presumptive diagnosis of herpetic encephalitis should be treated with IV acyclovir (20 mg/kg/dose) every 8 hours until herpes can be confirmed or ruled out.[176] Treat for at least 21 days if CNS infection is confirmed or strongly suspected. Herpes encephalitis will require anticonvulsants in addition to acyclovir. These seizures may be difficult to control.

Bacterial meningitis requires high-dose antibiotic therapy in addition to anticonvulsant therapy. Seizures may occur at many different points in the course of meningitis.

Seizures associated with polycythemia (central HCT >65% if symptomatic) are treated with a partial exchange transfusion. Anticonvulsant therapy may be needed while waiting to perform a partial exchange transfusion. Normal saline is generally recommended for a partial exchange transfusion instead of blood products because of the lower infectious risks associated with its use. The procedure for doing a partial exchange for significant polycythemia is the same as described on page 486 for doing a double-volume exchange; however, the volume of normal saline needed to reduce the HCT appropriately is calculated using the following formula[20]:

$$\text{Volume exchanged} = \frac{(\text{weight [kg]} \times \text{blood volume}^{a} \times [\text{patient's HCT} - \text{desired HCT}])}{\text{patient's HCT}}$$

[a] Blood volume ≅ 80 mL/kg.

Pyridoxine deficiency may be the cause in newborns who have difficult-to-control seizures. A trial 50- to 100-mg dose of pyridoxine, ideally with concurrent EEG monitoring, is reasonable in a neonate who continues to have seizures of undetermined etiology despite adequate anticonvulsant therapy. If the newborn is responsive to the test dose with resolution of seizures within 30 minutes, begin maintenance therapy with pyridoxine, 50 to 100 mg by mouth, daily. If an EEG is not available, a trial of pyridoxine alone may clarify the underlying

cause but should be reserved as a last resort in refractory seizures[176]; the newborn should be monitored because apnea and hypotension can occur.[176]

Seizures may be associated with intracerebral hemorrhage or birth trauma. The diagnosis of intraventricular hemorrhage can be made with cranial ultrasonography. Other signs of clinical instability, such as hypotension, bulging fontanel, posturing, and apnea, may point toward intraventricular hemorrhage, especially in the premature newborn. These seizures should be treated with anticonvulsants. Subdural, subarachnoid, cerebellar, brain stem, and peripheral parenchymal hemorrhage require other imaging techniques, such as magnetic resonance imaging or computed tomography (CT) scans.

Anticonvulsants

(Note: Unless otherwise stated, all recommended loading doses for anticonvulsants are from the same source.[20])

First-line therapy for neonatal seizures without a specific treatment continues to be phenobarbital (also called phenobarbitone in many developing countries).[20,176,177] The loading dose for the neonate is 20 mg/kg IV followed by a maintenance dose of 3 to 5 mg/kg/day (given as 1 or 2 doses per day depending on available dosing formulations). For many health care practitioners in low-resource settings, the only long-term option is 30-mg phenobarbital tablets, which can be divided in halves or quarters, limiting dosage options to 7.5 or 15 mg per day. In an actively seizing neonate, phenobarbital doses can be repeated in 5 to 10 mg/kg doses every 15 to 30 minutes up to a total dose of 40 mg/kg.[20,176]

Although up to 80 mg/kg/day in sequential cumulative doses has been used in children,[178] a cumulative dose above 40 mg/kg is associated with apnea requiring ventilator support. Availability of this support should be considered before giving excessively high doses. The therapeutic effect seems to plateau at 40 µg/mL, which corresponds to a total loading dose of 40 mg/kg.[179]

If seizures persist despite treating the cause and giving adequate phenobarbital, the next line of therapy is usually phenytoin[20,176] or fosphenytoin.[20] Both are given as a loading dose of 20 mg/kg IV and then in a maintenance dose of 5 to 8 mg/kg/day divided in 1 to 2 doses per day. In the neonate, phenytoin needs to be given intravenously because levels with oral dosing are totally unpredictable and variable without changes in dosage form or dosage. Phenytoin must be given slowly in non–glucose-containing fluids, such as NSS or sterile water (maximum of 1 mg/kg/minute) due to the risk of cardiac arrhythmia. Fosphenytoin

may be given with glucose-containing fluids and is not as caustic to the vein as phenytoin; if available, it is preferable over phenytoin in neonates. Fosphenytoin should be refrigerated, which limits its use in some resource-poor settings.

Consider benzodiazepines if seizures still persist.[20,176] Their disadvantage is hypotension and respiratory depression, which may be hard to manage in resource-poor settings without ventilator support. Diazepam is the most commonly available; it can be given in a dose of 0.3 to 0.75 mg/kg every 15 to 30 minutes up to a maximum of 2 to 5 mg.[175] Although it is rarely practical in resource-limited settings without ventilator support, it can be used by continuous infusion in refractory seizures. More recently, because of its short half-life, midazolam has gained more acceptance and has been more widely used for neonates with refractory seizures as a bolus followed by a continuous infusion. An effective response may occur within 1 hour.

Some neonatal intensive care units are now using IV levetiracetam (100 mg/mL) as an initial therapy for neonatal seizures. The liver does not metabolize the drug and it is excreted unchanged in the urine. It does not interact with other drugs. The initial dose is 10 to 30 mg/kg given in 2 divided doses with maintenance doses of 45 to 60 mg/kg/day.[20]

If seizures persist and are resistant to first-line and second-line therapies, refer the newborn, if possible, to a center at which a pediatric neurologist, special-care baby unit, EEG, cranial ultrasound, and CT scans are available, or consult with a pediatric specialist or pediatric neurologist if available.

The recommended duration of seizure treatment depends on the cause, resources available, and recommendations of the neurologist or attending physician. Anticonvulsants may be stopped before discharge if the underlying cause has been corrected or abnormalities associated with the diagnosis have resolved (eg, cerebral edema due to HIE). If not, most physicians recommend slowly tapering the infant off anticonvulsants between 3 and 6 months of age at the latest.[180] However, because of concerns about adverse effects of anticonvulsants on neurodevelopment, some physicians may choose to discontinue anticonvulsants sooner. Observe closely for recurrent seizures.

Correction of Hyponatremia

(Desired sodium minus newborn's sodium) × weight (kg) × 0.6

The desired sodium is usually around 130 mEq/L. Half the calculated correction is given over 12 to 24 hours.[20]

Measuring Corrected Q-T Interval

QTc = Q-T (seconds)/square root of the R-R interval (seconds)

For a 3- to 4-day-old newborn, 0.44 seconds is the 97th percentile.[175]

INFECTIONS

Neonatal sepsis is still one of the most common causes of morbidity and mortality in neonates in the developing world.[181] Untreated sepsis is rapidly fatal in the neonate. Sepsis can be very difficult to diagnose. Pending accurate cultures, sepsis must be suspected in almost any neonate who deviates from normal, necessitating prompt evaluation and treatment. Signs of sepsis in the neonate are nonspecific and include almost any variation from normal in temperature, respiratory rate and effort, blood glucose level, feeding, activity, color, and mental status.[20,182] A study by Weber et al that looked at possible sepsis in more than 3,000 babies in lower-income countries showed that clinical signs alone could predict severe disease in neonates with a sensitivity of 87% and a specificity of 54%.[183] Investigators looked at signs of altered mental status and activity, feeding problems, respiratory distress, and decreased perfusion. However, requiring more of these signs significantly lowered sensitivity.[183]

Although viral and fungal sepsis are important in the neonatal population, these are likely to be untreatable in most low-resource nurseries and, therefore, are not covered in this chapter.

There are many risk factors for neonatal sepsis, including prematurity (<37 weeks); prolonged rupture of membranes; maternal fever or infection around the time of delivery; foul-smelling, purulent, or meconium-stained amniotic fluid; and need for resuscitation at birth.[20,182] Early onset group B streptococcal infections in neonates are associated with more frequent maternal vaginal examinations during labor and maternal intrapartum fever.[184]

Common bacterial causes of sepsis during the first week of life among home-born neonates in the developing world include gram-negative enteric organisms such as *Klebsiella* (25%) and *E coli* (15%), in addition to gram-positive organisms *S aureus* (14%) and group B *Streptococcus* (12%).[185] After the first week of life, 4 organisms caused most community-acquired neonatal infections, including *S aureus,* group B *Streptococcus, Streptococcus pneumoniae,* and non-typhoidal *Salmonella,* each causing 12% to 14% of the disease.[183]

Prevention is always the best treatment of neonatal sepsis. Clean deliveries, including good hand washing and clean instrumentation, are crucial in decreasing the incidence of neonatal sepsis. These principles are incorporated into safe motherhood training throughout the

world.[65,186,187] It is important to identify mothers at risk of delivering an infected newborn and to consider treatment with appropriate intrapartum antibiotics for the mother and her newborn.

Early recognition and treatment are important because septic neonates often die very quickly and have such nonspecific signs of infection. Equally important is minimizing the duration of treatment in newborns who are not infected. This can be especially challenging in situations in which diagnostics are very limited and cultures are unavailable, unreliable, or expensive.

Diagnosis

Reliable cultures are the gold standard for diagnosing sepsis,[182,188] although a single blood culture may miss 10% to 15% of positive blood culture results.[182,188] Multiple blood cultures are generally not recommended in the neonate because difficulty in obtaining multiple specimens may delay treatment. The minimum recommended volume for a blood culture is 1 mL.[20] However, in much of the developing world, even a single blood culture is unavailable[189] or unreliable, necessitating reliance on other methods to diagnosis and treat presumed sepsis. Ancillary tests are especially helpful where there are no reliable cultures available. No single laboratory evaluation, including total leukocyte counts, differential leukocytes counts, absolute neutrophil count, ratio of immature to total neutrophil (I:T ratio), leukocyte morphology, platelet counts, or acute phase reactants such as CRP, can be relied on to confirm or exclude sepsis in the newborn. Therefore, no laboratory test should be used as a reason not to start empiric coverage for sepsis in any neonate in whom sepsis is suspected. Antibiotics should be started emergently in any neonate with signs or symptoms consistent with sepsis regardless of laboratory value. Laboratory tests can be helpful in determining the duration of therapy. These tests are particularly insensitive indicators of infection during the first hours of early onset (within 48 hours of birth) neonatal sepsis. However, a total or absolute neutrophil count outside normal range for gestational age (high or low) will point toward sepsis in the symptomatic neonate. Neutropenia with respiratory distress is particularly associated with early onset (<48 hours) sepsis from group B *Streptococcus*[190] as well as other bacterial pathogens such as pneumococci[191,192] and gram-negative organisms.[193] A CBC with indices (Table 20-12) is more helpful if followed over time. A combination of abnormalities is useful (Table 20-13). Like most other screening tools, it is better at predicting the absence of sepsis than the presence of it. Per Rodwell et al (Table 20-13), a score of 2 or less predicted the absence of

Table 20-12. Neonatal Neutrophil Indices Reference Ranges (Per mm³)

VARIABLE	BIRTH	12 h	24 h	48 h	72 h	>120 h
Absolute neutrophil count	1,800–5,400	7,800–14,400	7,200–12,600	4,200–9,000	1,800–7,000	1,800–5,400
Immature neutrophil count	<1,120	<1,440	<1,280	<800	<500	<500
Ratio	<0.16	<0.16	<0.13	<0.13	<0.13	<0.12

From Gomella TL, Cunningham MD, Eyal FG, Tuttle DJ, eds. *Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs*, 7th ed. New York, NY: McGraw-Hill Education; 2013.

Table 20-13. Rodwell Hematologic Abnormality Scoring System

HEMATOLOGIC ABNORMALITY	SCORE
Immature to total neutrophil ratio ↑-	1
Total PMN/neutrophil count ↑ or ↓	1
Immature to mature neutrophil count >0.3	1
Immature PMN/neutrophil count ↑ (if no mature PMNs seen, score 2 rather than 1 for abnormal total PMN count)	1
Total white blood count abnormal	1
Degenerative changes in neutrophils (>3 + vacuolization, toxic granulations, or Döhle bodies [graded 0–4+])	1
Platelet count ≤150,000/mm³	1

Abbreviation: PMN, polymorphonuclear cell.

From Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. *J Pediatr.* 1988;112(5):761–767. Copyright 1988, with permission from Elsevier.

sepsis 99% of the time[194]; thus, discontinuing antibiotics would usually be appropriate.

C-reactive protein is a marker of acute tissue inflammation and injury and plays a role in classic complement pathway activation and regulation of leukocyte function and phagocytosis. Many studies of neonatal sepsis have shown elevations of CRP at the time of neonatal symptom onset, with sensitivity between 35% and 94%.[195–198] Unfortunately, its elevation is not always indicative of bacterial infection, and CRP levels may be elevated in viral infections and noninfectious conditions of the

newborn, including fetal distress, birth asphyxia, meconium aspiration, intracranial hemorrhage, and trauma.[196,198]

Because it is difficult to tell these conditions apart from serious bacterial infections, elevated CRP values are limited in their specificity and positive predictive value for infection. Thus, similar to absolute neutrophil count values, CRP determinations are most helpful in ruling out sepsis (negative predictive value) and should be followed over time whenever possible. Two CRPs less than 1 mg/dL obtained 24 hours apart and 8 to 48 hours after presentation indicate that bacterial infection is unlikely.[196,198]

A small study in Pakistan of 28 babies with culture-proven sepsis found that combining CRP values with absolute neutrophil count led to 100% sensitivity and 86% specificity in culture-proven sepsis.[199] Combining a positive gastric acid cytology, defined as greater than 5 polymorphonuclear cells per high-power field,[199] with an elevated CRP led to 100% sensitivity and 92% specificity. In an older study,[200] the combination of CRP plus a positive gastric acid cytology was also considered the best combination among the tests studied for differentiating between septic and non-septic babies. Additional studies[201,202] also suggest that a positive gastric acid cytology is helpful. The cost of CRP has decreased so that it may be affordable in low-resource settings and is easier to perform with a faster turnaround than blood cultures.

Using clinical presentation, clinical course, and a combination of available tests to determine the workup and duration of treatment is the most practical approach in situations in which blood cultures are unreliable or unavailable. Table 20-14 contains the uses and limitations of screening tests often done to screen for or rule out neonatal sepsis, including those mentioned previously. When no laboratory studies are available, the diagnosis of sepsis must be empiric, based only on the newborn's clinical presentation and course. Treatment should be directed against the most likely organisms depending on clinical setting and specific country. Initial treatment is broad-spectrum antibiotics and parenteral. In many low-resource settings, the course of antibiotics may be completed using oral antibiotics. The efficacy of this approach is unknown but presents a significant risk for newborns in whom sepsis is likely.

Duration of treatment depends on the infection being treated and the newborn's response to treatment. In general, pneumonia is treated for 7 days, sepsis for 10 days, and meningitis for 14 to 21 days. It is equally important to discontinue treatment promptly in newborns who are not likely infected. This may be a difficult decision, especially if laboratory

Table 20-14. Screening Tests for Septicemia: Uses and Limitations

TEST FINDING	FINDING SUPPORTING POSSIBLE INFECTION	COMMENT(S)
Total white blood cell count (cells/mm^3)	<5,000 or >20,000	<50% of those with finding have proved infection.
Total neutrophil (PMN) count (cells/mm^3)	<4,000	Particularly useful in first hours of life
Total immature PMN count (cells/mm^3)	>1,100 (cord blood) >1,500 (12 h) >600 (>60 h)	Relatively insensitive; finding unusual in uninfected newborns
Ratio of immature PMNs to total PMNs	>0.2	Sensitivity 30%–90%; good negative predictive value
Platelet count (cells/mm^3)	<100,000	Insensitive, nonspecific, and late finding
C-reactive protein (mg/dL)	>1.0	Sensitivity 50%–90% at onset
Interleukin-6 (pg/mL)	>15	Sensitivity >80%; cutoff points vary; serial determinations may be required.
Procalcitonin (ng/mL)	>0.5	Promising for early- and late-onset infection
Erythrocyte sedimentation rate (mm/h)	>5 (1st 24 h) >Infant's age in days +3 (through age 14 d) >20 (2 wk of age)	Individual laboratories must establish normal values; normal value varies inversely with hematocrit.
Fibronectin (g/mL)	<120–145	Sensitivity 30%–70%
Haptoglobin (mg/dL)	>10 (cord blood) >50 (after delivery)	Unreliable due to poor sensitivity
Granulocyte colony-stimulating factor (pg/mL)	>200	Good sensitivity but low specificity

Abbreviation: PMN, polymorphonuclear cell.

From Long SS, Pickering LK, Prober CG. *Principles and Practice of Pediatric Infectious Diseases.* 3rd ed. Philadelphia, PA: WB Saunders; 2009. Copyright 2009, with permission from Elsevier.

tests are not available; however, it is important to decrease development of resistant organisms, limit unnecessary drug toxicity, and contain costs.[182,186,189]

Meningitis should always be considered in a newborn with possible sepsis. Clinical examination alone cannot differentiate a neonate with bacteremia from one with bacteremia with meningitis. Up to 15% of all

neonates with bacterial sepsis will have meningitis. A lumbar puncture is indicated in newborns with possible sepsis unless there is a contraindication. Blood cultures may be negative in newborns with meningitis. Wiswell and colleagues found that up to 28% of newborns with meningitis had sterile blood cultures.[20,203] In a neonate, a normal cerebrospinal fluid (CSF) white blood cell count may be up to 32, normal protein may be up to 170 mg/dL, and glucose is one-half to two-thirds of serum glucose.[20] Bacterial microorganisms are detected on a Gram stain of CSF in approximately 80% of newborns with group B streptococcal and gram-negative meningitis.[204] In contexts in which CSF cultures are not easily obtained, there is value in obtaining CSF for evaluation of cell count and Gram stain examination.

Urine cultures are not needed if a newborn is younger than 48 hours.[182] However, a sepsis workup after the first 48 hours should include a urine culture obtained by suprapubic tap or bladder catheterization whenever possible.[182,205] A urinary tract infection should always be considered in suspected late-onset sepsis.

Treatment Considerations and Options

Antibiotic doses and timing are based on gestational and postnatal age (Table 20-15).

The combination of ampicillin and gentamicin is still inexpensive and considered the appropriate first-line treatment for suspected neonatal sepsis. However, gentamicin does not penetrate well into the CSF and should not be used if meningitis is suspected. In addition, many recent studies, including studies from Tanzania, Nigeria, and India, show an alarming rate of resistance of gram-negative organisms to gentamicin (23%–68%) as well as high resistance rates to other commonly used antibiotics, including cephalosporins.[206]

If staphylococcal infection is common in the nursery, cloxacillin can be substituted for ampicillin, sacrificing coverage for *Listeria,* which is rare.

If the newborn has suspected meningitis, cefotaxime has much better CNS penetration and is more appropriate than gentamicin. If the newborn is not responding to ampicillin and gentamicin or if sensitivities indicate resistance, substitute cefotaxime or other antibiotics to which the organism is sensitive.

Ceftriaxone should be avoided whenever possible in jaundiced neonates because the drug reduces the protein-binding sites available for bilirubin and may increase the risk of bilirubin toxicity. The level of jaundice at which protein binding is significantly affected is unknown. If ceftriaxone cannot be avoided, parental calcium must not be used, as the

Table 20-15. Antibiotic Dosage for Neonates (mg/kg/day)

ANTIBIOTICS	ROUTE	≤2,000 g (0–7 d)	≤2,000 g (8–28 d)	>2,000 g (0–7 d)	>2,000 g (8–28 d)	>28 d
Ampicillin	IV, IM	100 + every 12 h	150 + every 8 h	150 + every 8 h	200 + every 6 h	200 + every 6 h
Cefotaxime	IV, IM	100 + every 12 h	150 + every 8 h	100 + every 12 h	150 + every 8 h	200 + every 6 h
Ceftazidime	IV, IM	100 + every 12 h	150 + every 8 h	100 + every 12 h	150 + every 8 h	150 + every 8 h
Ceftriaxone	IV, IM			50 every day	50 every day	50 every day
Erythromycin	PO	20 + every 12 h	30 + every 8 h	20 + every 12 h	30 + every 8 h	40 + every 6 h
Metronidazole	IV, PO	Load 15 mg/kg, then 15 + every 12 h	Load 15 mg/kg, then 15 + every 12 h	Load 15 mg/kg, then 22.5 + every 8 h	Load 15 mg/kg, then 30 + every 6 h	Load 15 mg/kg, then 30 + every 6 h
Penicillin G	IV	200,000 U + every 12 h	300,000 U + every 8 h	300,000 U + every 8 h	400,000 U + every 6 h	400,000 U + every 6 h
Cloxacillin[a]	IV	50 + every 12 h	75 + every 8 h	75 + every 8 h	150 + every 6 h	150 + every 6 h
Gentamicin	IV, IM	0–14 d	>14–28 d	0–7 d	>7 d	
		<32 wk 5 mg/kg every 48 h	<32 wk 5 mg/kg every 36 h	≥32–36 wk 4 mg/kg every 36 h	≥32–36 wk 4 mg/kg every 24 h	
				≥37 wk 4 mg/kg every 24 h	≥37 wk 4 mg/kg every 24 h	

Abbreviations: IM, intramuscular; IV, intravenous; PO, per os (by mouth; orally).

[a] Recommendations for cloxacillin based on nafcillin/oxacillin dosing, as recommended doses found in the literature vary around these doses. Cloxacillin IV is no longer available in the United States; therefore, doses are not in US drug books.

Modified from Bradley JS, Nelson JD. *2015 Nelson's Pocket Book of Pediatric Antimicrobial Therapy.* 21st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

combination has been associated with death in neonates.[207]

Syphilis should be treated with IV penicillin. Remember to treat the mother and her partner as well.

Gonorrheal conjunctivitis should be treated with single-dose ceftriaxone. It is also helpful to irrigate the eyes frequently. Neonates with gonococcal ophthalmia should be evaluated for disseminated infection and hospitalized if sepsis, meningitis, or arthritis is present.

All IM injections, including antibiotics, should be given in the upper outer thigh, not the buttock, to avoid sciatic nerve damage.

Please note: Gentamicin is stated *per dose based on gestational age* in Table 20-15, while the dosage of other antibiotics is stated *per day based on weight* and needs to be divided to arrive at the individual dose.

Ideally, all neonates with suspected sepsis should be referred to proper health care facilities for evaluation and admitted for parental antibiotics if treatment is indicated. However, in some settings, this is not possible and would result in a significant delay in treatment and increased morbidity and mortality. In those circumstances, it is appropriate to consider home- or community-based treatment of neonatal sepsis. Bang et al in India found home-based diagnosis and treatment of neonatal sepsis to be feasible and effective, with an almost 60% reduction in the case fatality from sepsis.[208] Mothers were asked to see the village health worker if danger signs, such as reduced sucking, drowsiness or unconsciousness, cold to the touch, and fast breathing or chest in-drawing, occurred. Village health workers were then asked to evaluate the newborn for the 7 signs noted in Box 20-6.[208] If 2 or more signs were present on any given

Box 20-6. Home-Based Diagnosis of Neonatal Sepsis

SIGNS/QUESTIONS
1. Previously normal cry became weak or stopped.
2. Previously normal baby became drowsy or unconscious.
3. Previously normal sucking became weak or stopped.
4. Mother feels baby is cold to touch or has a fever.
5. Skin or umbilical infection (pus or abscess).
6. Abdominal distention or 3 consecutive feeds led to vomiting.
7. Grunting or chest in-drawing.

Adapted from Bang AT, Bang RA, Stoll BJ, Baitule SB, Reddy HM, Deshmukh MD. Is home-based diagnosis and treatment of neonatal sepsis feasible and effective? Seven years of intervention in the Gadchiroli field trial (1996 to 2003). *J Perinatol.* 2005;25(Suppl 1):S62–S71, with permission from Macmillan Publishers Ltd.

day, they were to treat for sepsis. Various regimes have been suggested and are in use in different communities. Bang et al[208] used 10 mg per day of gentamicin for preterm neonates with birth weight less than 2,500 g and 15 mg per day for full-term neonates with a birth weight 2,500 g or greater once or twice a day (dose divided into 2) for 7 days, and syrup co-trimoxazole (sulfamethoxazole 200 mg + trimethoprim 40 mg/5 mL) 1.25 mL twice a day for 7 days. In a study by Zaidi et al,[209] the most effective regimen was found to be procaine penicillin (50,000 U/kg/day every day) and gentamicin (5 mg/kg/day every day) given for a total of 7 days.

A recent study looking at the treatment of fast breathing in neonates and young infants actually found fast breathing could be treated effectively as an outpatient, with oral amoxicillin, if hospitalization was not possible.[210]

Acyclovir therapy should be added if available whenever herpes is suspected, especially if physical findings of herpes simplex are noted or the mother has active herpes simplex lesions. For specific recommendations on empiric treatment of herpes simplex, including workup, consult a frequently updated reference book such as the AAP *Red Book*.[58]

Tetanus

Neonatal tetanus is still one of the leading causes of neonatal mortality worldwide, accounting for about 5% to 7% of neonatal deaths.[211] Tetanus is caused by the toxin produced by *Clostridium tetani*. The bacteria itself is noninvasive and nontoxic.

The portal of entry is usually the umbilical stump, although circumcision may also be a portal of entry. Susceptible babies are those whose cords were cut or dressed with an instrument or substance contaminated with *C tetani* and whose mothers were not adequately immunized before birth. Administering 2 to 3 tetanus immunizations to the mother before giving birth and clean cord care is effective in preventing neonatal tetanus.[212]

The incubation period is generally 3 to 31 days, with most cases occurring between 3 and 14 days after birth.[211] The shorter the incubation period, the worse the prognosis.[182]

Symptoms and Treatment

Tetanus symptoms are initially nonspecific, such as difficulty feeding, fever, and irritability, but rapidly progress to provoked and unprovoked tetanic spasms with trismus or sardonic smile and generalized stiffness.[182,211] The goals of treating tetanus include controlling spasms, supporting respirations, providing nutrition, neutralizing toxin,

eradicating *C tetani,* and educating the mother, family, and community or village on tetanus prevention.

Tetanus must be treated until presynaptic nerve endings are regenerated, which usually takes about 2 to 3 weeks. This prolonged hospitalization can be challenging to family resources that are already stretched.

Controlling spasms is usually done with a combination of drugs, including diazepam, phenobarbital, and chlorpromazine. In one study in Turkey, this drug combination led to the lowest mortality of babies.[213] Diazepam is usually started at 2.5 mg every 4 hours per nasogastric tube and escalated to a much as 7.5 to 10 mg every 4 hours. Breakthrough spasms are treated with diazepam at doses of 2.5 mg IV as needed. Chlorpromazine is usually given in a dose of 6.25 mg (quarter of 25-mg tablet) every 4 hours and is alternated with diazepam. Phenobarbital is given at a dose of 5 mg/kg/day divided twice a day. Consider adding magnesium to this regimen, as it may decrease the need for massive doses of diazepam. Although not yet reported in neonates, case studies have found magnesium to be safe and useful in older children.[214,215] If magnesium is used, it can be given as a bolus dose of 25 to 50 mg/kg every 6 hours slowly over 30 minutes or, ideally, as a drip of 25 mg/kg/hour titrated to have an effect as long as reflexes (ie, knee jerks) remain present, but these reflexes can be hard to access in a neonate. Magnesium levels are not toxic if knee jerks remain present and, therefore, can be followed to assess for magnesium toxicity even in facilities where magnesium levels cannot be checked.

Supporting respirations is often necessary for survival. In hospitals where conventional ventilation is not an option, place the neonate on a continuous pulse oximeter with appropriate set pulse oximeter limits. Instruct nursing staff to check on the patient and provide positive-pressure ventilation when the patient is apneic. With close monitoring and quick response, mortality rates for neonatal tetanus can be lowered to below the current mortality rate of 70% to 95%.[216]

Providing nutrition is essential for a good outcome secondary to the prolonged nature of this illness. In neonates, this is usually achieved by nasogastric tube feeding with expressed human milk.

Recommended doses of tetanus immunoglobulin (TIG) and tetanus antitoxin (TAT) vary dramatically from study to study and center to center. In a meta-analysis by Kabura et al,[217] the range of dosing for TIG was 250 to 40,000 units IM and for TAT was 250 to 10,000 units IM. Per that same meta-analysis, intrathecal administration of TIG or TAT was felt to be more beneficial than dosing intramuscularly. The dosing range in this meta-analysis for intrathecal administration ranged from 50 to 1,500 units.[217]

Eradication of *C tetani* is done by thoroughly cleaning the umbilical stump and giving the newborn metronidazole or penicillin G (Table 20-16). Metronidazole is now considered by some to be the drug of choice,[182] but extensive studies comparing the 2 antibiotics have not been done. At least 1 study in patients older than 12 years compared benzathine penicillin, metronidazole, and benzyl penicillin and found equal efficacy among the drugs.[218]

Prevention

Take this opportunity to educate the parent(s), extended family, and community about tetanus prevention. Immunize as many patients as possible while they are in the hospital. Stress the need to complete the series of immunizations. Five immunizations are considered a completed series for an adult. See Table 20-17 for the current WHO-recommended

Table 20-16. Antibiotics for Treatment of Neonatal Tetanus

DRUG	WEIGHT AND AGE	DOSE (mg/kg/d)
Metronidazole Oral or IV doses	<2,000 g 0–7 d	Loading dose of 15 mg/kg then 15 mg/kg/d divided every 12 h for a total course of 10–14 d (adjust dose when baby reaches 8 days of life)
	<2,000 g >7 d	Loading dose of 15 mg/kg then 15 mg/kg/d divided every 12 h for <34 wk and 22.5 mg/kg/d divided every 8 h for >34 wk for 10–14 d
	>2,000 g 0–7 d	Loading dose of 15 mg/kg then 22.5 mg/kg/d divided every 8 h for 7 days for a total course of 10–14 d (adjust dose when baby reaches 8 days of life)
	>2,000 g >7 d	Loading dose of 15 mg/kg then 30 mg/kg/d divided every 6 h for 10–14 d
Penicillin G IV	<2,000 g 0–7 d	100,000 units/kg/d divided every 12 h for a total of 10–14 d (adjust dose when baby reaches 8 days of life)
	<2,000 g >7 d	150,000 units/kg/d divided every 8 h for 10–14 d
	>2,000 g 0–7 d	100,000 units/kg/d divided every 12 h for 7 days for a total course of 10–4 d (adjust dose when baby reaches 8 days of life)
	>2,000 g >7 d	150,000 units/kg/d every 8 h for 10–14 d

Abbreviation: IV, intravenous.

Modified from Bradley JS, Nelson JD. *2015 Nelson's Pocket Book of Pediatric Antimicrobial Therapy.* 21st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

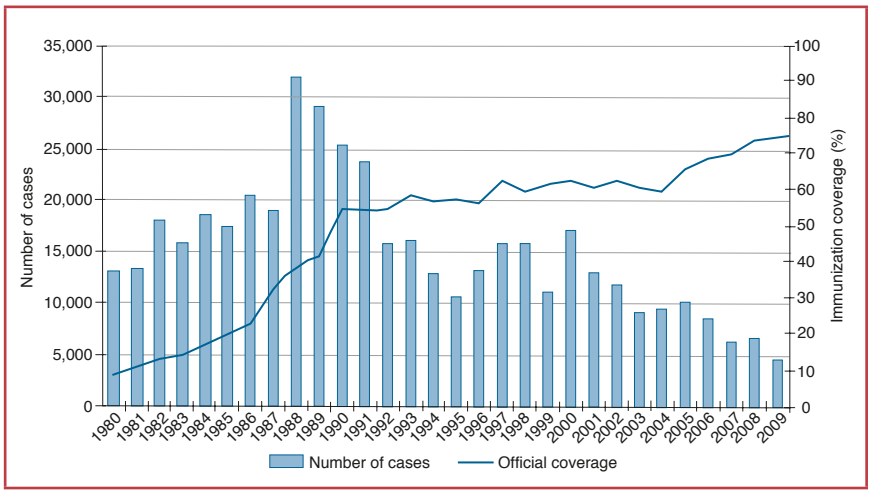
tetanus immunization, which provides immunity at least through the childbearing years. Although maternal immunization rates have been steadily increasing with concomitant decreases in neonatal tetanus, unfortunately, the disease has not been eradicated (Figure 20-23). Most immunization programs in the developing world do not have booster programs beyond childbearing years, and most do not include men and boys. Suggest that men and boys also get immunized. Patients need to

Table 20-17. Tetanus Toxoid Schedule and Period of Protection for Women of Childbearing Age

DOSE	WHEN GIVEN	PERIOD OF PROTECTION
TT1	At first contact with woman of childbearing age, or as early as possible in pregnancy	No protection
TT2	At least 4 weeks after TT1	3 years
TT3	At least 6 months after TT2	5 years
TT4	At least 1 year after TT3	10 years
TT5	At least 1 year after TT4	All childbearing years

Adapted from World Health Organization. Core information for the development of immunization policy. Geneva, Switzerland: World Health Organization; 2002.

Figure 20-23. Neonatal Tetanus Global Annual Reported Incidence and 2-Dose Tetanus Toxoid Coverage, 1980–2009



From World Health Organization. WHO vaccine-preventable diseases: monitoring system. 2010 global summary. http://whqlibdoc.who.int/hq/2010/WHO_IVB_2010_eng.pdf. Accessed June 12, 2015.

be immunized because tetanus does not provide lasting immunity and patients can have repeated tetanus if reexposed without immunizations.

EDUCATION

Educating others in newborn care is essential and effective in improving the health of mother and newborn.[219] Most women in the developing world go through pregnancy, delivery, and early neonatal care without seeing a physician or other trained health care practitioner; this alone contributes to a staggering number of deaths.[220] Structured training for advanced health care practitioners needs to begin in training institutions.[6] Teaching the basics of maternal and newborn care can potentially have a significant effect on the health of mother and newborn. Teaching simple things such as clean delivery, including hand washing and clean instruments, and supplies to clean and cut the cord; basic neonatal resuscitation; thoroughly wiping the baby's eyes after delivery; preventive measures, such as vitamin A for the mother; keeping the newborn warm; exclusive breastfeeding, using colostrum; recognizing danger signs in the newborn; and referring appropriately is possible even in resource-poor settings.[221,222]

Trained health care practitioners must first be aware of the need for training all health care practitioners, including those at the community level. Recognizing the need to train community health workers, traditional birth attendants, and other health care practitioners at the village level is the second step to realizing this goal. Although having advanced health care professionals at every delivery is a worthy goal, it is simply not realistic for most women and babies in lower-income countries. Traditional birth attendants must be included in the training to maximally decrease birth asphyxia,[220] decrease infection, detect significant jaundice, and treat early or provide lifesaving care to the premature newborn.

It is important to ensure that basic supplies are available and use locally available materials whenever possible.[7] When appropriate, items such as positive-pressure resuscitation bags will need to be purchased. Providing a culturally appropriate approach to training with reinforcement and ongoing instruction during the learning period is essential and possible.[202] Finally, yearly retraining is necessary if results are to be sustainable.

KEY POINTS

Neonatal Resuscitation

- Neonatal resuscitation is one of the most important tools in preventing neonatal death and asphyxia.
- Equipment and supplies needed for neonatal resuscitation in low-resource settings include 2 clean cloths, suction, and positive-pressure bag and mask.
- Initial steps of newborn resuscitation are warm, dry, position, suction (if needed), and stimulate.
- Positive-pressure ventilation should begin by 1 minute for any newborn who is not breathing or not breathing well.
- Oxygen is not essential in most newborn resuscitations and, in fact, may actually be harmful when not indicated.
- Epinephrine and volume (ie, normal saline or blood) are the only medications needed in the delivery room.
- Epinephrine should be diluted to 1:10,000 and given in a dose of 0.01 to 0.03 mg/kg (0.1–0.3 mL) IV if heart rate persists at less than 60 BPM after effective positive-pressure ventilation.
- Intubation may be indicated to provide more effective positive-pressure ventilation and suction the trachea in depressed newborns with meconium.
- Resuscitation may be discontinued when the newborn's heart rate is above 100 BPM and the newborn is breathing well.
- Resuscitation may also generally be discontinued after 10 to 20 minutes without signs of life. Judgment must be used to determine when to stop resuscitation in other scenarios.

Fluids and Nutrition

- Fluid and electrolyte requirements change based on gestational age and weight of a neonate.
- When possible, IV fluids should be given with an IV pump or microdrip set.
- Weight should be monitored, followed, and plotted regularly in all sick and premature newborns.
- Ideal nutrition is provided by human milk.
- Calories per kg to gain weight vary with each individual neonate, as well as gestational and chronologic age.
- Premature newborn feedings should be systematically increased as tolerated to full feeds.
- Lacto-engineering with creamatocrit and hind milk often allows the use of high-calorie human milk without the risks of artificial feeds.

- Counseling, encouragement, breast pumps, and medications can all be used to increase milk production in a mother whose newborn is not gaining weight or not gaining weight well.
- Breastfeeding rarely needs to be discontinued for medications or other reasons.
- Iron and vitamin supplements are needed in premature newborns.
- The newest recommendations addressing the use of human milk in babies of mothers who are HIV positive include the fact that unless human milk substitutes are AFASS, human milk is best, but decisions about the type of feeding should always be made in accordance with the mother's desires.
- Three options (A, B, B+) to drastically decrease maternal-to-child transmission of HIV include daily nevirapine to the baby for the entire duration of breastfeeding or antiretroviral therapy to the mother for the entire time the baby is breastfeeding.
- Blood transfusions should only be given when needed, following HCT routinely.

Thermal Regulation

- Keeping premature neonates warm is essential to life.
- A warm, dry environment, coupled with a hat, helps prevent hypothermia.
- Skin-to-skin care helps prevent hypothermia and provides other benefits to the neonate.
- Low-cost incubators can be built if functioning commercial incubators are unavailable.
- If available, overhead warmers may be used if the newborn is monitored closely.

Preventive Care

- The umbilical cord should be cut with a clean instrument.
- Other cord care depends on circumstances, but dangerous practices, such as applying cow dung, should be avoided and a more benign substitute found.
- Delayed cord clamping raises HCT.
- Several options exist for eye prophylaxis, including tetracycline, erythromycin, sliver nitrate, and povidone iodine, which can be made locally and inexpensively.
- Vitamin K_1 can prevent hemorrhagic disease of the newborn.
- Hepatitis B vaccine should be incorporated into all newborn immunization programs.

- HIV prophylaxis is important, and locally available protocols should be implemented.

Neonatal Dermatology

- Skin care is important and often overlooked.
- Delayed bathing is recommended for temperature control and because vernix is antibacterial and an excellent skin cleanser.
- Harmful practices such as applying mustard oil and mentholated compounds need to be avoided.
- Some oils or emollients may be beneficial.
- Several benign rashes are common in the neonate, including erythema toxicum, transient pustular melanosis, milia, sebaceous gland hyperplasia, Epstein pearls, neonatal acne, miliaria, and seborrheic dermatitis.
- Other rashes that are not benign and may require treatment include petechiae, staphylococcal pustules, lesions associated with herpes simplex, and syphilis.

Birth Asphyxia

- Birth asphyxia is a leading cause of neonatal morbidity and mortality worldwide.
- A simple definition of birth asphyxia is failure to breathe at birth.
- Preventing and recognizing intrapartum hypoxia is key to reducing the incidence of birth asphyxia.
- Having at least 1 person trained in positive-pressure ventilation present at delivery is also necessary to reduce the incidence of birth asphyxia.
- Hypoxic-ischemic encephalopathy is the neurologic sequelae of birth asphyxia and a frequent cause of death and disability.
- Severity of HIE can be graded and is predictive of outcome.
- Neonatal hyperthermia after birth asphyxia increases the risk of adverse neurodevelopmental outcome.
- Asphyxia is the most common cause of neonatal seizures.
- Spastic cerebral palsy, mental retardation, ongoing seizures, microcephaly, and hearing deficits are some of the neurodevelopmental sequelae of HIE.
- Anticonvulsants such as phenobarbital are required for treating seizures related to HIE.

Hypoglycemia

- Hypoglycemia is common in the neonatal period, especially in developing countries.
- Newborns who are premature, SGA, and an infant of a diabetic mother are more likely to develop hypoglycemia.
- Screening asymptomatic term newborns for hypoglycemia is not recommended.
- Newborns with symptomatic hypoglycemia should be treated immediately with breastfeeding or formula-feeding. If breastfeeding or formula-feeding is not available, glucose water can be used orally.
- Very low glucose levels in symptomatic newborns or persistent hypoglycemia in asymptomatic newborns should be treated with IV glucose infusion of D10W.
- Concentrated glucose solutions, such as D25W or D50W, should not be used in neonates.

Jaundice

- Neonatal jaundice is common, affecting most newborns.
- Although most neonatal jaundice is benign, severe neonatal jaundice is a significant cause of morbidity and mortality.
- Bilirubin encephalopathy occurs acutely and chronically (kernicterus) and can lead to tone abnormalities, abnormal cry, and abnormal facies acutely and choreoathetoid cerebral palsy, deafness, and dental enamel dysplasia chronically.
- Screening programs using TcB measurements or micro-method serum bilirubin levels should be instituted whenever possible.
- An etiologic diagnosis should be established whenever possible.
- Common causes, such as hemolysis (G6PD deficiency, Rh incompatibility, ABO incompatibility) and infection, should be identified.
- Phototherapy should begin at or below the guidelines suggested by the AAP for newborns at least 35 weeks' gestational age.
- Other guidelines are recommended for premature and sick newborns.
- Phototherapy is generally the first line of treatment.
- Effective phototherapy should be optimized whenever possible, which includes changing bulbs often, measuring irradiance level, and using special blue bulbs.
- Support, including eye protection and adequate hydration, should be provided.
- Exchange blood transfusions should be performed when a newborn meets exchange criteria based on risk, gestational age, or age or at any time the newborn demonstrates evidence of acute bilirubin encephalopathy.

- Exchange blood transfusions are generally performed through a UVC; sterile feeding tubes are appropriate substitutes for commercial catheters when these are not available.
- Guidelines for performing exchange blood transfusions using fresh whole blood are straightforward and can be adapted to low-resource settings.
- Other treatments, such as IVIG or phenobarbital, given prophylactically to the mother or her newborn can be considered in high-risk situations.

Respiratory Diseases

- Respiratory illness is a common cause of neonatal morbidity and mortality worldwide.
- Differential diagnosis of respiratory distress or cyanosis is large and includes etiologies such as prematurity, surfactant deficiency, infection, congenital heart and lung disease, meconium aspiration, transient tachypnea, TEF, and persistent pulmonary hypertension.
- Transient tachypnea of the newborn is common and generally benign and requires only minimal oxygen support.
- Apnea of prematurity can be treated with theophylline, aminophylline, or caffeine, prophylactically or symptomatically.
- Respiratory distress syndrome or hyaline membrane disease is common in the premature neonate and can be treated with surfactant.
- Continuous positive airway pressure is used to treat mild to moderate respiratory distress and apnea. A CPAP device can be made from locally available supplies and used in settings with minimal monitoring available.
- Persistent pulmonary hypertension occurs primarily in late preterm and term newborns and the only treatment available in low-resource settings is usually oxygen. High fraction of inspired oxygen is usually required.
- Meconium aspiration often causes severe respiratory distress. Treatment is generally limited to oxygen therapy. Endotracheal intubation and suctioning at birth is indicated if health care practitioners capable of intubating are available.
- Pneumothoraxes can cause respiratory distress and can often be treated with simple aspiration of the air without the need for a chest tube.
- Infection should always be considered in respiratory distress, and newborns with respiratory distress should be treated promptly for infection until this is ruled out.
- Congenital heart disease should be considered in cyanosis not responding to oxygen therapy.

- Patent ductus arteriosus is common, especially in preterm newborns. Patent ductus arteriosus can usually be closed using an oral agent such as ibuprofen.
- Oxygen should be considered a drug and used conservatively when indicated.
- Blended oxygen is preferable.
- Low-flow nasal cannulas are one mechanism of providing lower fraction of inspired oxygen to newborns.
- Continuous positive airway pressure is indicated for mild to moderate respiratory distress and can be provided using several devices in low-resource settings, including homemade CPAP devices.
- Continuous positive airway pressure is generally safe when used in the 5- to 10-cm range; however, it can be associated with pneumothorax, overdistension of the lungs, and gastric distention.

Seizures

- Seizures in the neonate occur from treatable and untreatable causes.
- Easily treatable causes may include metabolic and electrolyte abnormalities. Treating these abnormalities, such as hypoglycemia, may obviate the need for anticonvulsants in these newborns.
- Other illnesses, such as meningitis and polycythemia, require treatment of the underlying cause and anticonvulsants as well.
- Diagnosis is generally made by observing the newborn's movements carefully, excluding jitteriness, startles, and nonspecific movements.
- Treat the underlying cause of the seizure when possible.
- Anticonvulsants are indicated for seizures that are not caused by specific treatable etiology or when seizures persist despite treatment of cause and correction of metabolic or electrolyte abnormalities.
- Phenobarbital is the anticonvulsant of choice in neonates.

Infections

- Neonatal sepsis remains a leading cause of neonatal morbidity and mortality.
- Untreated neonatal sepsis is rapidly fatal.
- Diagnosis of sepsis in the absence of reliable cultures is challenging, but adjuncts like CRP, CBC with differential, and platelet count can be helpful, especially when followed over time.
- Ampicillin and gentamicin remain the recommended initial, inexpensive choices for most neonatal sepsis in low-resource settings.

- Cefotaxime is the cephalosporin of choice for sepsis that is not responding to ampicillin and gentamicin and for meningitis. If staphylococcal sepsis is suspected, an antistaphylococcal agent such as cloxacillin should be added. Increasing resistance to these common antibiotics will necessitate changes in these recommendations over time.
- Antibiotics are dosed according to weight and postnatal age.
- Despite immunizations, tetanus is still a significant cause of neonatal death.
- Immunizing the mother prior to delivery (minimum of 2) or cutting and caring for the cord in a clean manner will prevent neonatal tetanus.
- Controlling spasms, supporting respirations, providing nutrition, and educating and immunizing family members are the most important elements in caring for a neonate with tetanus.
- Controlling spasms is usually done with a combination of high-dose diazepam, chlorpromazine, and possibly magnesium.
- Tetanus immunoglobulin or tetanus antitoxin or immune antiserum, along with antibiotics (penicillin or metronidazole), are also given.

Education

- Educating others, including the mother herself, extended family, traditional birth attendants, and other health care practitioners, is essential to the ultimate health of the newborn.
- Teaching the basics, such as clean delivery, hand washing, preventive measures, breastfeeding, danger signs, and when to refer, is important, especially in resource-limited settings.
- Positive-pressure resuscitation bags and training in their use should be promoted for all birth attendants, including at the community level.

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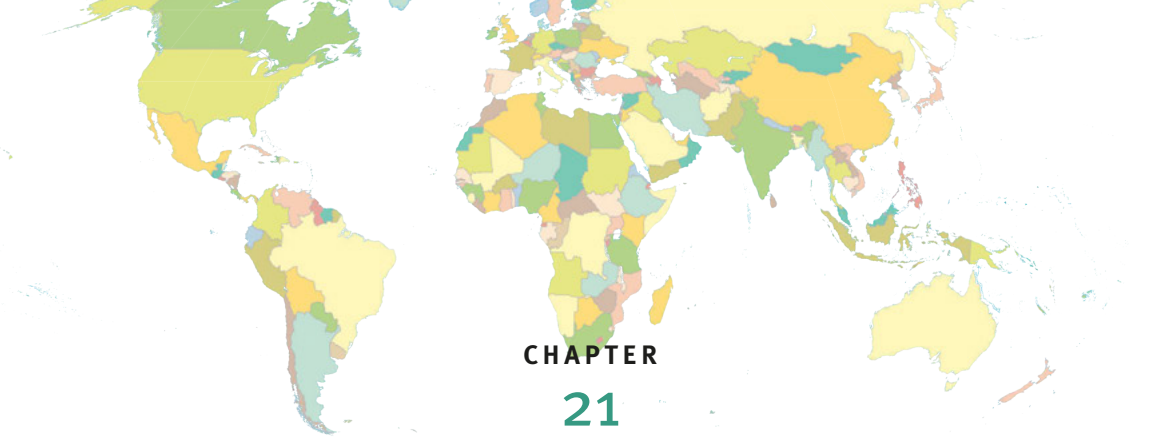

CHAPTER

21

Promoting Early Child Development

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INTRODUCTION

Early child development (ECD) strategies are now widely regarded as key components for improving child health and nutrition programs in developing countries. It is estimated that globally at least 219 million children younger than 5 years do not meet their cognitive potential.[1] Most of these children live in south Asia and sub-Saharan Africa. This substantial loss of human capital affects subsequent educational achievement and future economic productivity. The global challenge to avoid the loss of development potential in the early years must be addressed by the international child health community.

GLOBAL CONTEXT OF CHILD SURVIVAL

It is estimated that around 6.6 million children younger than 5 years died in 2012, with 44% of these deaths occurring in the neonatal period.[2] The leading causes of death among children younger than 5 years include pneumonia, preterm birth complications, intrapartum-related complications, diarrhea, and malaria.[2] Globally, about 45% of younger-than-5 deaths are attributable to undernutrition.[2] Most of these deaths are preventable with the scaling up of proven effective interventions.[3–5] While improvements in child survival rates have been

observed since 1990 with an estimated 47% decline in younger-than-5 mortality from 1990 to 2012,[2] there remains significant disparities across and within populations. Developing more effective strategies to reach the most vulnerable children to achieve Millennium Development Goal (MDG) 4 resulted in strengthened understanding about the circumstances in which children survive. Exposure to risk factors such as intrauterine growth restriction, malnutrition, HIV/AIDS, malaria, lead exposure, lack of access to safe water and adequate sanitation, maternal depression, institutionalization, conflict, and exposure to societal violence not only increase the likelihood of childhood morbidity and mortality but also have long-term detrimental implications on cognitive, language, motor, social, and emotional development.[6] Global data on child health are discussed more extensively in Chapter 1, The Reality of Child Mortality.

The number of young children surviving and not fulfilling their development potential far exceeds 200 million worldwide—a figure reached by looking at worldwide prevalence of people living in absolute poverty and early childhood stunting.[1] Stunting and poverty are indicators closely associated with poor cognitive outcome and educational performance. Understanding the common pathways that lead to poor development, health, and nutrition status can facilitate the identification of a host of interventions that will enhance early childhood outcomes. Integrated early child survival and development strategies will therefore not only help achieve MDG 4 but also contribute to the achievement of MDG 2 (universal primary education).

RATIONALE FOR INTEGRATING EARLY CHILD DEVELOPMENT INTERVENTIONS IN EXISTING CHILD HEALTH SERVICES

Understanding the Early Child Development Period

Understanding the factors influencing early development can help identify interventions that can complement existing child survival, health, and nutrition programs. Child development is shaped by continuous interactions among biology, experience, and the environment. There are several interdependent domains of development, including cognitive, language, motor, social, and emotional development. The ECD period generally includes children from birth to 8 years of age; however, the critical period of early development is usually defined as the first 3 years of life (with growing attention toward interventions in the preconception period). During this early period, there is rapid development of pathways in the brain that influence health, learning, and behavior throughout the life cycle.[7]

Brain development is an interaction among genetics, experience, and the quality of the environment. Evidence from animal experiments demonstrates that deprivation of nutrition, exposure to environmental toxins, maltreatment, and poor quality of social interaction affect brain structure and function, thereby influencing learning ability and behavioral responses throughout the life cycle.[7,8] In humans, exposure to violence, maltreatment, institutionalization, and inadequate caregiving practices in early life are shown to have long-lasting negative implications on subsequent behavior patterns observed in longitudinal studies and studies of brain structure and function.[6]

The basic premise that early development is shaped by nature (biology) and nurture (quality of the environment and maternal care) has helped to elucidate the pathways that operate through poor cognitive and social development, leading to educational failure and subsequent low economic productivity. This loss of developmental potential is, in part, caused by poor health and undernutrition, but it is also the result of non-stimulating environments and inadequate care practices. While many of the risk factors associated with poor health and undernutrition are well recognized and often addressed in child survival, health, and nutrition programs (eg, iodine deficiency, iron deficiency, stunting), stimulation and care is less well understood.

There are many theories about how children learn. Developmental psychologists generally agree that children learn through a process of observation, exploration, imitation, and practice of any given task at developmentally appropriate stages. Social interaction is an important aspect of development; skills are acquired with the guidance of an adult, where the child is encouraged to observe, imitate, explore, and practice a particular task (a *scaffolding* process). Parenting interventions and center-based programs, including psychosocial stimulation support (ie, learning and language development opportunities through interaction with caregivers), can improve their cognitive functioning; thus, young children acquire the skills needed for future school readiness.[9]

The term *care* within the household can extend the provision of appropriate health, hygiene, and feeding practices to also include psychosocial stimulation. Maternal emotional availability is an important factor that can determine the quality of care provided by the mother (or other significant caregiver). The mother's level of sensitivity and responsiveness to her child's needs influences the child's cognitive, social, and emotional development. *Sensitivity* is the mother's capacity to be aware of the infant and his acts and vocalizations that communicate his needs and wants. *Responsiveness* is the caregiver's capacity to

contingently and appropriately respond to the infant's signals. The way a child expresses these needs will change as he develops and the mother must be able understand the changing signals. Therefore, the caregiver must be sensitive to be responsive.

Parenting programs are interventions designed to enhance caregiving capacity. In addition to providing health, nutrition, and development information, support to enhance caregiving capacity (in particular, sensitivity and responsiveness) must be an integral component of a parenting program. These caregiving behaviors will also support the child's physical well-being through timely observation and judgment of a child's health and nutritional needs.[10]

Emotional availability is a determinant of the quality of early attachment and bonding with the child. Studies on children growing up in low-quality institutional care, where they may lack supportive and stable caregiving relationships, show increased risks for failure to thrive, as well as compromised social and emotional development. While the association of maternal physical health and nutritional status with early child outcomes on growth, health, and development are well known, there is now growing recognition to address factors that can impede the mother's ability to provide appropriate emotional care for her child (eg, maternal depression).[6] Helping mothers, particularly those who are vulnerable, to be more responsive caregivers through guidance and provision of adequate support, including health, nutrition, and economic resources as well as social-emotional support, is essential for their children's survival, well-being, and development.[11]

Development is shaped by risk and protective factors throughout the life cycle. The timing of early experience is important and the course of development can be most effectively modified in the early childhood period by strategically timed interventions that strengthen resilience and reduce vulnerability. For the health sector, this window of opportunity is in the first 3 years of a child's life when vital stages of brain development are occurring. This period is also a time when a child and family may see health care professionals more regularly for newborn care, immunizations, and other early childhood services.

Existing health services provide a range of interventions that will benefit child development outcome; however, stimulation, caregiving support, and maternal mental health remain as gaps that, if filled, could strengthen overall outcomes for development, growth, and health (Table 21-1).

Table 21-1. Framework for Early Child Development Programming Across the Early Years

GOAL	PROMOTE OPTIMAL DEVELOPMENT, ENABLING CHILDREN TO THRIVE AND ACQUIRE CONTEXTUALLY RELEVANT SKILLS AND BEHAVIORS.								
ECD PERIOD (AGE, y)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
POSSIBLE INDICATORS			**STUNTING IMPAIRMENT**			**SCHOOL READINESS**	**ACADEMIC ACHIEVEMENT, ENROLLMENT/DROP OUT**		
Interventions[a]									
Antenatal Care Services									
Key Newborn and Young Child Health and Nutrition Services									
Parenting Programs: Education for Health, Nutrition, Development, and Enhancement of Caregiving Capacity									
Early Stimulation									
Maternal Support: Mental Health Services									
Growth and Development Monitoring and Intervention									
Early Child Education: Preschool Programs									
Primary Early Child Education: Primary School									
School Health and Life Skills Programs									

Table 21-1. Framework for Early Child Development Programming Across the Early Years, continued

GOAL	**PROMOTE OPTIMAL DEVELOPMENT, ENABLING CHILDREN TO THRIVE AND ACQUIRE CONTEXTUALLY RELEVANT SKILLS AND BEHAVIORS.**								
ECD PERIOD (AGE, y)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
POSSIBLE INDICATORS			**STUNTING IMPAIRMENT**			**SCHOOL READINESS**	**ACADEMIC ACHIEVEMENT, ENROLLMENT/DROP OUT**		
Main Sector Involvement	Health Services Educational Services ←——→ ←——→ Social Protection and Welfare ←——→								
Policy Considerations	National plan of action, leadership, coordination, and financing								

Abbreviation: ECD, early child development.

[a] Interventions represent areas where ECD can be strengthened by the health sector.

Critical Links to Support Vulnerable Groups

The case for integrated child health services is strengthened further when one considers that many children growing up in developing countries face multiple and co-occurring risks leading to poor development, health, and nutrition status. In a systematic review of risk factors for adverse child development outcomes, Walker and colleagues identified inadequate cognitive stimulation, stunting, iodine deficiency, and iron deficiency anemia as key risk factors, while intrauterine growth restriction, malaria, lead exposure, HIV infection, maternal depression, institutionalization, and exposure to societal violence are other emerging risk factors that prevent young children from attaining their developmental potential.[6] It is noteworthy to observe that nutrition-related factors, including maternal micronutrient deficiencies, intrauterine growth restriction, postnatal growth, and stunting, accounted for most of the identified risk factors for poor development.[12] The delivery of effective evidence-based nutrition services for pregnant women, infants, and young children will have benefits for the development of the child[4]; however, the benefits will be greater if these interventions are combined with psychosocial stimulation and improved caregiving strategies.

There is substantial evidence linking stunting with poor cognitive development and academic achievement.[12] Prevention of early stunting through improved early feeding strategies is a priority intervention; however, the delivery of such strategies can be combined with the delivery of psychosocial stimulation and responsive care for the development of greater benefits. This was demonstrated in studies of Jamaican infants with and without stunting who received nutritional supplementation, psychosocial stimulation, or combined interventions. It was identified that supplementation and stimulation had independent effects and that the effects were additive. Follow-up of these children into adolescence showed that over time, only the benefits from the stimulation intervention were sustained.[13–15]

Psychosocial stimulation can be used to universally promote healthy child development. This intervention can also be used as part of the management or rehabilitation strategy for children especially at risk, such as those with moderate-severe malnutrition.[16,17] Benefits of psychosocial stimulation as a component of the overall management strategy were also observed for other at-risk children and families, such as those affected by HIV/AIDS, although more research is required to support program development.[17] A few studies show that engaging mothers in psychosocial care for their child may reduce symptoms associated with maternal depression; again, the evidence base can be strengthened

through research by ensuring a range of outcome measures affecting child and family are assessed in ongoing and future studies.[18]

Children growing up in poor and disadvantaged communities are often exposed to more than one risk factor that will affect development, health, and nutrition status. Disentangling specific risk factors from the complexity of poverty and determining which combination of interventions should be provided in any given approach to yield optimal benefits for young children and their families are important decisions that are likely to be context and program specific. Such decisions must be guided by evidence for effectiveness.

OPPORTUNITIES FOR INTERVENTION IN EXISTING HEALTH SERVICES

In Western contexts, ECD services are delivered through health sectors. Over the last 20 years, evidence from developing countries has been emerging and a number of ECD intervention studies conducted in developing countries, including Jamaica, Turkey, Bangladesh, Vietnam, Pakistan, and India, have been reported in peer-reviewed literature. The interventions range from parenting education programs to early childhood education preschool programs, psychosocial stimulation, and nutrition supplementation. These interventions can improve ECD with effects greater for programs of higher quality and for the most vulnerable children.[9] Other promising interventions include children's educational media, interventions with children at high risk, and combining the promotion of ECD with conditional cash transfer programs.[9] Program delivery ranges from home visits to center-based sessions with individual counseling or group sessions and center-based activities for children. These interventions are not only effective, but the returns on investment in ECD are also substantial. The *Lancet* series on child development highlights that increasing preschool enrollment rates to 25% could yield an estimated US $10.6 billion through higher educational achievement, while a 50% increase could generate $33.7 billion.[9] The characteristics of successful ECD programs are shown in Table 21-2.

Despite the knowledge gained from a number of efficacy studies on what interventions work, the coverage of ECD programs remains low. The opportunity to improve coverage of ECD programs through integrating services in existing health systems is another benefit to the integrated approach. Integration into existing health services requires review of the local health care scenario and identification of points of integration for action to promote ECD, prevent developmental loss, and implement rehabilitation strategies (Table 21-3). Community health workers and paraprofessionals have been widely used as an essential delivery platform to ensure coverage and equitable delivery of ECD

Table 21-2. Characteristics of Successful Early Child Development Programs

CHARACTERISTIC	
Targeted toward disadvantaged children (eg, poverty, malnourished)	**Core features of services**
Initiate services for younger children (<3 years) with strategies to continue throughout early childhood.	
High quality, defined by structure (child-staff ratio, staff training, intensity) and processes (responsive interactions, variety of activities)	
Provide direct services to children and parents (provide families with skills for providing quality psychosocial support to their children) and, whether individually or in groups, ensure parents can practice with their child.	
Enable children to initiate their own learning through opportunity for exploration of their environment through developmentally appropriate activities. Encourage use of low-cost/no-cost items for exploration.	
Support caregivers (especially mothers).	
Integrated into existing health, nutrition, or education systems	**Important issues for sustainability of services**
Value traditional beliefs and practices combined with evidence-based strategies.	
Developed with and for communities	
Adopt rights-based approaches that value all children.	
Cost-effectiveness and sustainability	

interventions.[19] However, few studies evaluate the feasibility and effect of integrating ECD interventions in existing health systems. A recent series of reviews on integrating nutrition and ECD interventions highlights that there is relatively little evidence on how to align integrated interventions and how to undertake benefit–cost analyses for integrated interventions.[20–23]

Powell and colleagues demonstrated that it was feasible to integrate a psychosocial stimulation program into the primary health care system in an urban setting in Jamaica.[24] While the authors report significant improvements in the development quotient for the intervention group, several issues were raised for consideration when incorporating such interventions within a government system. Health workers were unable to make the recommended weekly visits as a result of the workload, and the cost of integrating ECD in the health care system was not studied.[24]

Table 21-3. Opportunities for Early Child Development Interventions

COVERAGE	EXISTING SERVICES	NEW INTERVENTION TO INTEGRATE
Universal to promote health development and prevent developmental loss Community-based and primary health care	Family Planning Services Antenatal Care EPI Program IMCI Program Growth Monitoring Program	Parenting Program and Key Messages for Newborn Development Care Psychosocial Stimulation Key Developmental Milestones
Selected to support those children at high risk for developmental loss Community-based and primary health care	Nutritional Supplementation HIV/AIDS Programs Community-Based/Outreach Programs for Vulnerable Communities: Slums, Remote Rural/Tribal Areas Cash Transfers	Psychosocial Stimulation and Parenting Programs Maternal/Family Support: Mental Health Services Conditions Linked to ECD Services
Indicated to support those with disability for prevention of secondary conditions Community-based and primary health care	Existing Services for Children With Disabilities	Inclusion in ECD Programs and Outreach/Community-Based Rehabilitation, Including the Training of Multiskilled Development Therapists

Abbreviations: ECD, early child development; EPI, expanded program on immunization; IMCI, integrated management of childhood illness.

A cluster randomized trial on children from birth to 24 months on the cost and effectiveness of responsive stimulation or enhanced nutrition interventions integrated in the Lady Health Worker program in Pakistan suggests it is more cost effective than a nutrition intervention alone in promoting children's early development, with the cost of an integrated responsive stimulation intervention in an existing community-based

service to be approximately US $4 per month per child.[25] A recent program evaluation of a community-level integrated ECD intervention in Nicaragua suggests that delivering micronutrient powders (sprinkles) via an ECD platform could be a cost-effective strategy for promoting human capital accumulation and boosting labor market productivity in resource-constrained and geographically disperse countries.[26]

Opportunities for integrating new interventions to strengthen ECD outcome in existing health services must first review what is feasible in terms of delivery approach, frequency of intervention delivery, existing personnel, training requirements, resource input requirements, and monitoring processes. The evidence base for the effectiveness of integrating ECD interventions into existing health services in developing countries requires further strengthening. With the growing support for integrated delivery of ECD interventions with the existing programs, challenges like staff workload, communication and coordination among different ministries and among staff in different sectors, and common language and measurements must also be acknowledged at the national and community levels.[27,28] Furthermore, there is a need for capacity building for development of practical skills, effective partnerships between health workers and families, and knowledge mobilization across multiple institutional levels to support frontline health workers delivering integrated ECD interventions.[29]

CHALLENGES IN SCALING UP EARLY CHILD DEVELOPMENT STRATEGIES

In a review of strategies to avoid the loss of developmental potential, Engle and colleagues noted that awareness of child development is increasing in many countries.[9] Governments, multilateral and bilateral agencies, and civil society have invested in a range of ECD programs. For example, more than 40 countries are developing or have developed and received parliamentary approval for ECD policies, while the World Health Organization Commission on Social Determinants of Health made child development one of its key focus areas. Progress has also been made on the 2007 recommendation to develop a core set of globally accepted measurements and indicators for child development that could be adapted across countries for monitoring, planning, and assessment.[9] The United Nations Children's Fund (UNICEF) supported 53 countries to prepare their own standards for what preschool children should know and be able to do. Available evaluations of these programs are few but necessary to help meet the challenge of ensuring that ECD strategies will reach the most vulnerable populations. In this review, maximizing the quality of ECD programs, promoting multi-sectoral integration, prioritizing monitoring and assessment, and emphasizing

policy actions were highlighted as crucial future directions.[9] While many opportunities can be identified for points of integrating ECD interventions in existing health systems, more information is needed to ensure that coverage, quality, and effectiveness are achieved. A recent cross-national analysis of ECD governance structures in low- and middle-income countries highlighted involvement of ministries of finance, partnerships with nongovernmental organizations and civil society, innovative measures for improving and expanding local governance, and control in budgeting and decision-making as critical factors to ECD prominence in national policy.[30]

Program Sustainability

Program sustainability necessitates investigating feasibility within existing health services. Additional costs may limit the service to selected populations (those identified most at risk) rather than universal coverage. The constraints on going to scale in health-related interventions are well described, and particular attention needs to be paid to such constraints that may occur at many levels of the system. Focus must be paid to the quality of the program as well as constraints that may prevent scaling up, eg, the level of family and community acceptance, competing priorities within the health program, cost and cost benefit of scaling up, and general environmental and contextual issues that exist. Attention to these issues is required if effective ECD scale-up is to be demonstrated.

Compliance

Compliance at the program or community level within ECD studies has not been extensively reported. It is essential to capture information relating to facilitators and barriers for participation in the program and compliance with activities to understand processes of information flow and behavioral change across the population.[31] For example, families are often highly motivated by seeing their child's improved development, which may encourage them to more regularly visit health services. At the health service level, the extent to which health personnel comply with the delivery of the additional interventions may need to be identified. This will help identify factors that can be strengthened in a new integrated program design.

Monitoring and Evaluation

Currently, there is no internationally agreed-on set of indicators to monitor child development, with the UNICEF and Multiple Indicator Cluster Survey ECD module being the only population-level indicator on ECD. Existing programs may have a set of indicators already

collected (eg, prevalence of stunting) that might be helpful for evaluating child development status in the population. There may also be value in reviewing whether the addition of ECD interventions benefits other parameters of child health and nutrition status in a given population (eg, reduced morbidity because of improved responsive care strategies). In addition to reanalyzing existing indicators, a simple to collect but effective set of population-level indicators needs to be agreed on to directly assess child development outcomes.

Policy

The UN Convention on the Rights of the Child values the child's right to survival and development. A coordinated ECD policy is important to ensure that children's holistic needs are met by all sectors. A common policy situation is when the education sector has a policy or action plan to improve ECD through effective preschool programming and early childhood education strategies, while the health sector has no specific action plan. Health policy makers need to be convinced of the importance of ECD and the benefits to integrated survival and development services.

Inclusion of Children With Disabilities

While this chapter primarily focuses on ECD promotion for healthy development and reduction of risk for loss of developmental potential, it can be argued that the rationale for integrated services can be expanded to include children with disabilities. International estimates suggest 4.5% prevalence of moderate to severe impairment leading to disability in a developing country. However, it is acknowledged that the accurate estimate of people living with a physical, visual, hearing, communication, or intellectual impairment poses many challenges, not the least of which are the difficulties in identifying impairment in settings where there are limited screening and rehabilitation services.[32]

In a study on neurodevelopmental outcomes of preterm infants in Bangladesh, the authors comment that while the overall prevalence of disability remained constant over the last decade, there was a shift from more severe disabilities to milder problems related to cognitive impairment, behavioral problems, hearing impairments, and communication impairments. It may be argued that these children will also benefit from the types of interventions suggested.[33] An expanded rationale to include treating physical conditions, reducing the effect of impairments and preventing secondary conditions, and supporting families with additional caregiving demands brings another dimension to existing services that

have yet to be discussed extensively in the ECD literature with respect to developing countries.[34]

Therefore, when integrating new interventions to strengthen overall ECD in health care services, program planners need to review local health scenarios to identify gaps and opportunities and evaluate the most effective combination of interventions, feasible delivery mode, additional time and cost taken for delivery, and training and materials, as well as monitor the benefits to the development, health, and nutrition status of the target population.

FUTURE ACTION

Several important actions must be prioritized to address the challenges mentioned herein, improve coverage of ECD strategies, and ensure quality and effectiveness if new interventions are integrated into existing systems.

- Rigorous research is required to look at the effectiveness of integrating what is known to work from ECD intervention studies in existing health programs.
- Research is needed to explore the effectiveness of integrated ECD interventions delivered by community health workers in resource-constrained settings.
- International experts must agree to a minimal set of standard indicators that countries can collect at the national level for ECD across the early year age range. For the health sector, particular focus should be on a set of standards for the first 3 years of life.
- There must be capacity development of personnel that can plan, educate, and train in ECD in the health services.
- Health policy makers must be convinced of the case for integrating survival and development services. They must also be persuaded that they have a critical role in improving the development status of children so they will act on it.

KEY POINTS

- The loss of developmental potential in more than 200 million young children worldwide and its implications for future human development cannot be ignored.
- The goal of ECD programs is to promote optimal development by enabling children to thrive and acquire contextually relevant skills and behaviors.
- The health sector has a critical role in helping to avoid early developmental loss in the first 3 years of life when children are in regular contact with health services.

- Prenatal and postnatal periods are the most critical time in a child's development, laying the foundation for physical, emotional, and intellectual well-being.
- Evidence suggests that children with higher risk factors for developmental loss, such as malnourishment or living in poverty, will benefit most from participating in ECD programs.
- Integrated interventions (ie, survival, health, nutrition, stimulation, and maternal support) together with responsive care practices are likely to result in successful child development, health, and nutrition outcomes.
- Research is needed to understand the nature and composition of integration according to local context and feasibility and to support quality and effectiveness in integrated models for advocacy and capacity development.

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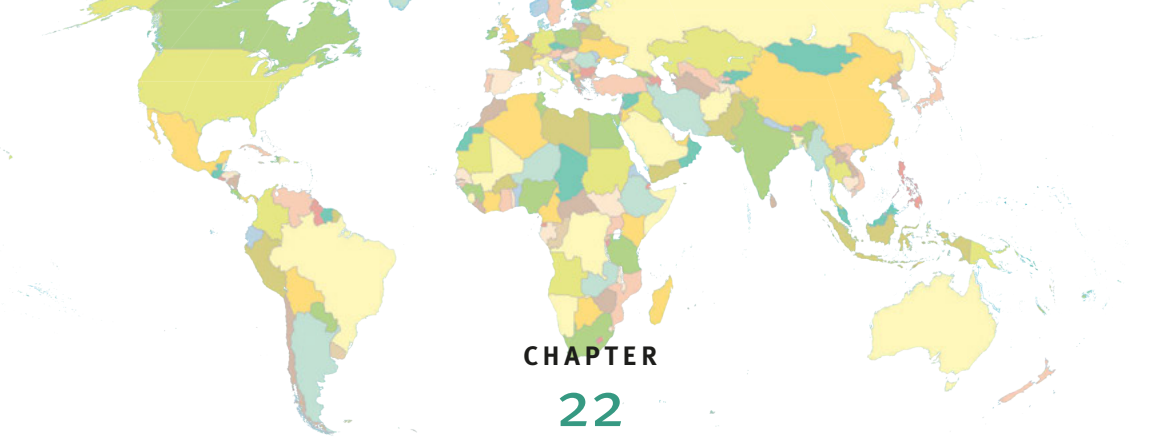

CHAPTER

22

Malnutrition

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INTRODUCTION

Even in our current affluent high-technology era, more than 1 billion people, one-sixth of the world's population, do not have enough to eat.[1] In spite of huge advances in health, in 2013 an estimated 6.3 million children younger than 5 years died, and malnutrition was a major contributor.[2] Malnutrition in children younger than 5 years is extremely prevalent in developing countries. Globally, in 2011 stunting was estimated to affect 165 million children younger than 5 years, or 26%.[3] For those with the most severe forms of malnutrition, the risk of death is 10 times greater than well-nourished children.[4] One out of 4 children in developing countries are underweight.[5] Specific micronutrient deficiencies (eg, vitamin A, iron, iodine, zinc) affect more than half of the children in developing countries and contribute heavily to additional morbidity and mortality.[6] While nearly two-thirds of the world's hungry individuals are in just 7 African and Asian countries,[7] malnutrition is indeed a global problem—global in its distribution as well as the effect it has on the lives of children, families, communities, and entire countries. Overweight and obesity are major problems in developed countries and are increasingly problematic in resource-limited countries. In developed countries, malnutrition often presents as a complication of another condition such as anorexia nervosa, prematurity, renal dysfunction, and inflammatory bowel disease. However, this chapter will focus

on undernutrition. Indeed, the first of the United Nations Millennium Development Goals is to "end extreme poverty and hunger."[8,9]

PEDIATRIC MALNUTRITION

To identify malnutrition, it is necessary to know what is meant by being well nourished and where one crosses the line from being nourished to being malnourished.[10] Simply stated, with pediatric malnutrition, there is a discrepancy between a child's dietary needs (ie, protein, energy/calories, and micronutrients) and what is actually consumed.[11] Conditions such as wasting, stunting, kwashiorkor, and marasmus are all types of generalized malnutrition and unfortunately are common in many of the world's lower-income countries.[11,12]

Wasting refers to a weight for height more than 2 SD below a reference population mean. *Stunting* is the state of having a height for age more than 2 SD below a reference population mean. *Underweight* is defined as a weight for age more than 2 SD below the mean of a reference population.

Severe malnutrition can present as kwashiorkor (with edema) or marasmus (wasting without edema). In addition to generalized malnutrition resulting from macronutrient deficiencies, specific micronutrient deficiencies also plague many children in the developing world. In whatever form, insufficient nutrient intake at a young age affects the child's physical stature and neurodevelopmental progress with adverse effects on subsequent mental and cognitive abilities.[13,14] To effectively combat the problem of pediatric malnutrition, it is important to define measurable features of malnutrition so as to accurately identify those who truly are at risk and need nutritional aid while excluding those who do not. The criteria by which the condition is screened will determine who is identified to be at nutritional risk and who receives treatment.[10]

GLOBAL SIGNIFICANCE AND CONSEQUENCES

Pediatric malnutrition occurs worldwide, making a global perspective necessary for strategic interventions to reduce mortality and morbidity rates. Understanding the various etiologies of malnutrition is crucial for successfully combating the problem on a global level. Solutions should be specific for each targeted population, identifying needs, parameters, and goals tailored for that population. Practical, strategic nutrition interventions are necessary to understand and meet specific nutritional needs and deficits in high-risk areas.[14,15]

Collaboration of skills to reduce pediatric malnutrition and the consequent risks of mortality is of great importance. By joining academic, health, economic, and political knowledge and putting policies into

place, one might actively combat malnutrition, adequately train staff, and provide the necessary resources.[10] Due to their practical experience and knowledge, health professionals have the opportunity to play a valuable role in initiating action to combat the problem of malnutrition.[15] To help ensure that programs are sustainable and adequate for culturally specific needs, whole communities should be involved, engaging them in the education process. Fighting malnutrition can then be done on a larger scale when knowledge is passed on by those who possess the skills and knowledge needed to help those who are in need.[10,15] Encouraging education and awareness of available resources and examining proven methodology and current research are important components in empowering health professionals, communities, families, and individuals.[15]

In addition to malnutrition's direct adverse effects, there are also secondary health, societal, and economic effects. These economic challenges represent a large burden, particularly affecting areas in Asia, Africa, and South America.[10] Adverse effects of widespread malnutrition include

- *Increased mortality.* Ending avoidable deaths is not merely a financial issue but an ethical challenge in which access to necessary resources predicts survival.[15]
- *Additive decreases in health.* Individuals with inadequate nutrient stores become more susceptible to illness and have greater difficulty fighting illness. The cycle of illness begins with poor nutrition during pregnancy and continues through childhood.[15]
- *Loss of educational potential.* Inadequate nutrient intake is shown to affect a child's cognition, ability to learn, and degree of education achieved, thus affecting the child's ability to succeed in school and potential opportunities that may follow.[14] Severe malnutrition tends to delay the age at which schooling is initiated. Furthermore, children affected by malnutrition are often sick more frequently than other children, causing them to be absent from school more often.[16] Impairment in cognitive development has long-term economic consequences for individuals, families, and nations.
- *Loss of labor earnings.* Commonly, if malnutrition does not resolve but continues through childhood, an individual's poor health may affect labor force earnings throughout that person's lifetime.[15,16] A malnourished person's lifetime earnings are estimated to be 10% lower than those of a well-nourished person, and a country's loss of gross domestic product could be as much as 2% to 3% when malnutrition is prevalent.[17]

The issue of malnutrition is one that needs to be taken seriously because it affects life on individual as well as global levels. The intertwining relationships of nutrition with life, health, education, and productivity are complex. We must strive to understand them and push to eliminate malnutrition.

EPIDEMIOLOGY

Incidence, Distribution, and Control of Malnutrition

Current and Historical Trends

Malnutrition continues to be a worldwide problem.[18] In the developing world, it is estimated that there are more than 800 million individuals who suffer from various degrees of malnutrition. This currently represents approximately 20% of the developing world's population.[18,19] Pediatric malnutrition is particularly a problem in Asia (ie, Bangladesh, Pakistan, India, China, and Indonesia) and Africa (ie, Democratic Republic of Congo, Ethiopia, and Somalia).[7] Deficiencies of macronutrients (ie, protein, carbohydrates, and fat) often lead to protein-energy malnutrition (PEM). This is currently the most common type of malnutrition among children in India.[14,19] Current trends in hunger and malnourishment around the world are often associated with the increase of migration to urban settings, as families settle in slums where there is a high prevalence of poverty and hunger.[14] In contrast with the very poorest countries, many others are now seeing trends of children consuming a high intake of fat, which is contributing to a different type of malnutrition, often referred to as *overnutrition.* Despite the high caloric consumption, a balance of sufficient nutrients is often not achieved, which causes other problems, such as diet-related chronic diseases.[15]

Africa

Some African countries (ie, Nigeria, Niger, Angola, Malawi, Madagascar, Ghana, Tanzania, and some northern Africa nations) are seeing a decline in malnutrition. In contrast, Africa's eastern countries now have the most rapidly increasing rates of underweight children.[15] Despite progress, malnutrition continues to increase in sub-Saharan Africa. A high incidence of preschool malnutrition is associated with the devastating effect of the HIV/AIDS epidemic.[15] Predictions suggest that between 2000 and 2020, the overall prevalence of malnutrition in Africa will drop from 34% to 31%. However, because of an increasing population, the number of malnourished children will actually increase from 44 million to 48 million in that same period.[20] The prevalence of malnutrition in

sub-Saharan Africa is increasing rapidly, such that it will soon surpass the prevalence of malnutrition in Asia. Projections show that there will soon be an increase in wasted (low weight for height) preschoolers in every region in Africa.

Asia

The majority (70%) of malnourished children live in Asia. South-central Asia has the world's highest prevalence of wasted children. With substantial increases in dietary fat and sugar intake, the Chinese population reported a significant reduction in the number of undernourished children. Unfortunately, this is contributing to other unhealthy trends in mortality related to chronic diseases, such as coronary vascular disease and type 2 diabetes, in areas that already have high mortality rates.[15,20]

The current and predicted trend toward urban migration of children in rural India is of great concern because of the high prevalence of malnutrition in urban slums. Strategic plans should be initiated to reverse malnutrition among children living in urban slums; these children are a reasonable target population for pro-nutrition activities.[14]

South America, Latin America, and the Caribbean

In South America, malnutrition commonly manifests as stunting and micronutrient deficiency, which are significant public health concerns. A large hurdle in the fight against malnutrition in Latin American countries is the lack of malnutrition-related curricula in health professional training programs.[10] It is predicted that the number of stunted children in Latin America and the Caribbean will decrease between 2000 and 2020.[20] There has been significant progress in the fight against malnutrition in South America, in contrast with Central America, where there has been little progress and acute malnutrition has a high fatality rate. Ending avoidable deaths due to malnutrition remains a major health challenge and represents an ethical imperative.[10]

Developed Countries

To a certain degree, malnutrition even affects developed countries; underweight can be seen. But developed countries especially see the other extreme of malnutrition, caused by overnutrition, in which nutrients are eaten in excess, causing an increase in obesity among children. Reasons for this trend have been associated with the increased availability and convenience of calorically dense foods high in sugar and fat, as well as reduced physical activity in children.[20,21]

Pediatric Mortality Related to Malnutrition

Young children bear the greatest brunt of malnutrition.[18] Currently, malnutrition contributes directly or indirectly to 45% of all child deaths.[22] More than 6 million preschool-aged children die each year; most of these deaths occur in developing countries where malnutrition is a strong factor. Table 22-1 outlines (by region) the prevalence of the various types of PEM in children younger than 5 years. Adequate nutrition would likely prevent many of these tragic deaths.[15]

In Asia and Africa, 20% of children younger than 5 years are underweight, 30% to 35% have stunted growth, and up to 11% show signs of wasting.[22] Figure 22-1 shows the acute causes of death in malnourished children are often diarrhea, pneumonia, malaria, measles, AIDS, and perinatal conditions. Micronutrient deficiencies, such as inadequate zinc or vitamin A, further contribute by increasing the severity and length of infectious illnesses. With nutrition affecting immunity, malnutrition frequently contributes to infection-related deaths. Continuing a vicious cycle, malnutrition leads to prolonged infectious illnesses, which then lead to increased caloric needs during a time of anorexia, thus further worsening nutritional status. Similarly, gastrointestinal diseases and malnutrition combine to further decrease intestinal absorption of nutrients, leaving the child even more vulnerable to subsequent illnesses.[15]

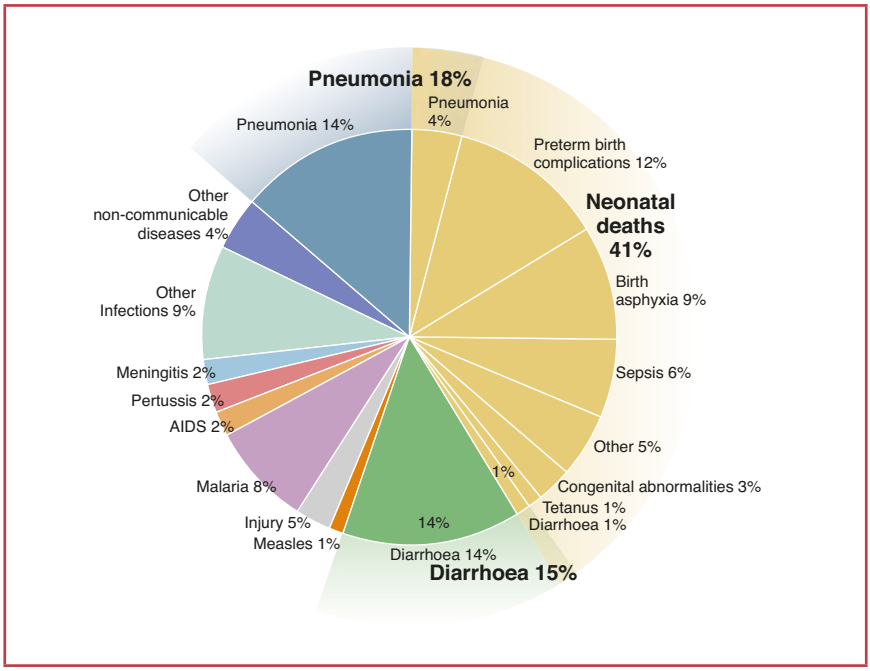
Low birth weight is often linked to poor maternal nutrition and can, in part, be prevented by improved prenatal nutrition. Intrauterine growth retardation leads to low birth weight (<2,500 g) in neonates. Children who are born with low birth weight are at high risk for stunting, continued underweight, increased infant mortality, and more chronic diseases during childhood.[15]

Table 22-1. Prevalence of Protein-Energy Malnutrition Among Children Younger Than 5 Years in Developing Countries

REGION	STUNTING %	UNDERWEIGHT %	WASTING %
Africa	35.6	17.7	8.5
Asia	26.8	19.3	10.1
Latin America and Caribbean	13.4	3.4	1.4
Oceania	35.5	14	4.3

Derived from Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet.* 2013;382(9890):427–451.

Figure 22-1. Causes of Death Among Children Younger Than 5 Years
Note: Malnutrition contributes to 45% of these deaths.



From Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet.* 2010;375(9730):1969–1987. Copyright 2010, with permission from Elsevier.

ETIOLOGY

Environmental Factors

The etiology of malnutrition is multifaceted and best described by examining the many factors contributing to its cause.[14] On a population level, the problem goes deeper than a simple lack of food availability in the home. Despite etiologic complexity and regional variance, factors contributing to global pediatric malnutrition in developing countries include

- Food production, availability, and intake[19]
- Political and economic situation and overall poverty[13,19]
- Prevalence of sickness, infectious diseases, and access to and quality of health services[19]
- Seasonal natural disasters and climate conditions[19]
- Maternal nutritional status and breastfeeding habits[19]

- Education level, sanitation practices, and access to uncontaminated water[19]
- Availability and effectiveness of nutrition programs for the population[19]
- Cultural and religious food customs and practices[19]
- Most immediate and detrimental causes—inadequate dietary intake with severe and repeated infectious diseases[19]

Poverty

Poverty is often seen as an underlying theme in malnutrition and food insecurity. However, reducing the prevalence of malnutrition has the potential of simultaneously contributing to reducing poverty. Good nutritional status not only contributes to lessening the risk of diet-related disease; slowing the progression of some diseases, such as AIDS; and increasing the survival rate of malaria, but it is also a significant factor in improving learning and educational capabilities. Better educational outcomes can be expected if good nutrition is provided in childhood. Improved nutrition directly reduces poverty by contributing to increased productivity, thus creating a healthier workforce. Another way in which nutrition directly affects poverty is by its relationship to health care costs. Individuals who have a good nutritional base need fewer days to recover from sickness, are less likely to suffer from diet-related chronic diseases, have an increased likelihood of surviving malaria, and have a slower onset of AIDS, thus reducing costs otherwise needed for health care. There is also a positive correlation between improved nutritional status and the empowerment of women.[15,23]

Inadequate Food Intake, Availability, and Security

Food security is often seen in the context of a nation's ability to produce adequate food for the entire population. However, food security for an individual depends not only on the national situation but also on personal availability of and access to that food.[24,25] Food insecurity "exists whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain."[26] Viewed from the positive side, "Food security exists when all people, at all times, have physical and economic access to sufficient, safe nutritious food to meet their dietary needs and food preference for an active and healthy life."[25]

Discrepancies in food security occur within family units in which adequate food may be available but not distributed in accordance to varying needs of family members. This, in turn, may cause malnutrition in some family members while sparing others.[24] For example, some African

cultures will give meat preferentially to the men of the household with women and children only receiving what is left over. According to the Food and Agriculture Organization of the United Nations, 18% of the population in the developing world was undernourished in the mid-1990s, presumably related to insecure food sources. The situation improved to 15% between 2010 and 2012.[27]

There are varying degrees of food insecurity. Some people experience insecurity but do not necessarily have hunger or malnourishment. Others have diseases caused by micronutrient deficiency or are food deprived and severely malnourished. Identifying at-risk populations is a helpful step in developing effective preventive interventions to obviate detrimental physical and economic outcomes.[25] Table 22-2 shows different levels of food insecurity and examples of what they may look like.

Although there are instances in which children are malnourished because of a community-wide lack of adequate intake due to limited food access, there are some areas where children are not meeting adequate food requirements even though there is not an absolute food shortage.[24] One reason (of many) is lack of knowledge of sufficient intake of the various food groups needed for health during different stages of life. In fact, nutritional education and adequate provision of nutritional intake have the potential to prevent low birth weight deliveries and malnutrition in poor urban households for women of childbearing age. Malnutrition becomes especially high risk in situations in which there is not a responsible caregiver to look after and care for a child. A child

Table 22-2. Levels of Household Food Insecurity Experienced Across Cultures

LEVEL	DESCRIPTION	ILLUSTRATION
Core domains	The deepest structure, the universal food insecurity experience	Inadequate quality of food
Sub-domains	Elements of core domains that are likely to be of concern in many but possibly not all cultures	Lack of dietary diversity
Items	Expression of sub-domains using culturally relevant examples and language	Limited food variety offered to child; eg, just rice and vegetable curry

From Coates J, Frongillo EA, Rogers BL, Webb P, Wilde PE, Houser R. Commonalities in the experiences of household food insecurity across cultures: what are measures missing? *J Nutr.* 2006;136(5):1438S–1448S, with permission from American Society for Nutrition.

is at particular risk for malnutrition between the ages of 6 months and 2 years because she cannot provide her own food but depends on others to feed her.[24]

One approach to improving food security is through targeted nutritional education of women. Women can be taught specific nutritional needs and interventions for themselves and their infants to avoid deficits and prevent nutrition-related complications.[15] There are various approaches that may be used to reach this population; even the use of mass media, such as television and radio, may have the potential to educate through relevant nutrition messages.[15]

Sickness and Disease

Most pediatric morbidity and mortality in the developing world is the consequence of

- Acute respiratory infection
- Diarrhea
- Malaria
- Measles
- HIV/AIDS
- Anemia
- Maternal factors

Malnutrition not only potentiates the negative effects of each of these but, in cyclic nature, is also exacerbated by each of them.

Acute Respiratory Infection

Pneumonia is the leading cause of pediatric mortality and morbidity, causing approximately 20% (3 million people per year) of all deaths occurring in children younger than 5 years; most take place in developing countries and are amenable to health and nutritional interventions.[28] There are many nutrition-related factors that positively correlate with the risk of contracting pneumonia, including low birth weight, anemia, acute malnutrition, rickets, and lack of breastfeeding.[28]

Children in developing countries are commonly deficient in zinc, which is an important micronutrient specifically involved in cell growth and differentiation. Severe deficiency can lead to stunting of growth, an impaired immune system, anorexia, and impaired cognitive ability.[29] In addition, a child with zinc deficiency is at increased risk of contracting pneumonia, having a more severe illness, and higher mortality and morbidity.[15]

Zinc supplementation prevents and reduces the severity of respiratory illness primarily in children who have severely depleted zinc stores. Healthy children who preventively receive zinc supplementation have

fewer incidences of lower respiratory illness. Carefully monitored zinc supplementation programs in areas where zinc deficiency is common would likely improve child health. Children with marginal or very poor nutritional status are especially likely to benefit from supplementation.[28]

Vitamin D deficiency and rickets are associated with increased risks of acute respiratory infection and death from pneumonia,[30,31] which is likely related to hypovitaminosis D causing reductions in B cells and natural killer cell numbers.[32]

Breastfeeding enhances a child's immune system and gives the child the advantage of protection against contracting pneumonia at an early age. While the protective mechanisms of breastfeeding are not completely understood, current research indicates that exclusive breastfeeding in the first 6 months of life protects the infant's immune system by maturational, anti-inflammatory, immunomodulatory, and antimicrobial actions. On average, children who are not breastfed spend longer periods in the hospital with acute respiratory infection, are more likely to contract pneumonia, and often need multiple antibiotic regimens for successful treatment, all of which contribute to an overall increased mortality rate. By initiating and implementing effective community programs and targeting specific risk factors, the incidence of pneumonia may be reduced and its complications prevented.[28]

Diarrhea

There has been great progress in reducing diarrhea-related mortality over the past 20 years, which is largely related to an increased use of oral rehydration solution (ORS). Approximately 4.6 million children died each year from diarrhea in the early 1980s. Globally, it is now estimated that 700,000 children younger than 5 years die annually from diarrhea[33]; this is an improvement from past years[34] but still excessive. Notwithstanding this improvement, diarrhea remains a leading reason for morbidity and mortality in much of the developing world. Up to 30% of hospital admissions and up to one-fourth of pediatric deaths in developing countries are associated with diarrheal infections.[35,36] In many cases, diarrhea can lead to undernutrition in children, contributing to compromised immune function, increased incidence of hospitalization, and even increased mortality rates.[37] Box 22-1 outlines the most common reasons for hospitalization in children with diarrhea in lower-income countries.[36] In the case of acute diarrhea, overall survival rates have improved; however, incidence remains relatively unchanged.[35] Clearly, diarrhea and malnutrition interact in devastating ways, with each aggravating the other.

Box 22-1. Contributing Factors Increasing Risk of Hospitalization Due to Diarrhea

- Malnutrition
- Diarrheal episode lasting longer than 7 days
- Low socioeconomic status
- Poor sanitation at home
- Presence of *Escherichia coli* in stool
- Parents with poor education and high multiparity
- Unawareness of benefits of using oral rehydrating solutions in dehydrated children

Derived from Khalili B, et al. Risk factors for hospitalization of children with diarrhea in Shahrekord, Iran. *Iran J Clin Infect Dis.* 2006;1:131–136.

Intervention and Prevention

Much success in the decrease in mortality rate associated with acute diarrhea is because of successful implementation of oral rehydration therapy. Breastfeeding education is another factor that has minimized incidence and severity in the pediatric population.[34] Vaccinations for rotavirus, a primary source of viral diarrhea, are commonly used and shown to be effective in Latin America, the United States, and Europe. Basic nutritionally sound interventions to prevent and manage diarrhea and thus prevent subsequent fatality include

- Breastfeeding promotion
- Appropriate complementary feeding (eg, use of nutritional weaning foods when transitioning beyond exclusive breastfeeding)
- Hygiene and sanitation
- Zinc and vitamin A supplementation
- Oral rehydration therapy
- Education of these practices

Breastfeeding

Breastfeeding has a protective effect against the incidence of diarrhea. Breastfed infants tend to have lower incidence and duration of general illnesses compared with non-breastfed infants. Lactoferrin and lysozyme, which are present in human milk, may play a protective role. Lactoferrin has bacteriostatic and bactericidal activity, protecting against a large range of harmful pathogens even when the infant's iron stores are low. Lysozyme kills gram-positive bacteria.

Encouraging mothers to exclusively breastfeed for the initial 6 months not only reduces the risk of diarrhea related to unsanitary formula-feeding practices but also provides biological protection against diarrhea and other illnesses by enhancing the infant's immune system.[37]

Sanitation

The etiology of some diarrhea is of bacterial and viral origin associated with a lack of sanitation, hygiene, and clean water. It is estimated that approximately 30% of diarrheal illness could be eradicated by simply following sanitary hand-washing guidelines.[34] Improving the quality of drinking water by securing a safe water source or implementing point-of-use disinfection is also important for reducing diarrheal episodes.

Zinc Supplementation

The use of zinc in treating diarrhea in children older than 6 months is shown to be safe and beneficial. Studies indicate that giving ORS together with zinc reduces the risk of morbidity caused by diarrhea, as well as hospitalization. Zinc supplements given for 10 to 14 days following an episode of acute diarrhea can prevent subsequent episodes over ensuing months. Providing this supplement may also be financially beneficial because it reduces the overall cost of antidiarrheal drugs and can prevent or reduce hospital stay duration.[34,38]

Hydration and Electrolytes

Optimal care is vital to prevent possible adverse outcomes from high fluid losses and electrolyte imbalances present in diarrheal episodes. A standardized ORS was first created in 1978 by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) to prevent and treat diarrhea. Since then, millions of childhood deaths have been avoided secondary to the successful treatment of diarrhea with ORS. Initially, the formula replaced needed nutrients and fluid but did not reduce the volume of stool or duration of the diarrheal episode. When used to treat children and infants, the formula tended to be somewhat hyperosmolar compared with their bodies' plasma, which caused hypernatremia and created an osmotic-related diarrhea. In response to this problem, modified solutions were made with a lower sodium content, creating a more favorable, lower osmolarity that proved to be effective. Table 22-3 outlines the composition of the original ORS formula and the modified glucose ORS formula.[37,39]

Oral, instead of intravenous (IV), rehydration is safer and more effective in treating malnourished children with diarrhea even when they are moderately dehydrated. In fact, IV fluids given to severely malnourished children can precipitate or exacerbate existing heart failure, which may be fatal. The only indication for IV fluids in severely malnourished children is shock.

Table 22-3. Composition of Oral Rehydration Solution

CONTENT	G-ORS	ORS
Sodium	75 mmol/L	90 mEq/L
Potassium	20 mmol/L	20 mEq/L
Chloride	80 mmol/L	98 mEq/L
Citrate	10 mmol/L	290 mg/dL
Glucose	20 g/L	20 g/L (111 mmol/L)
Osmolarity	224 mOsm/L	311 mOsm/L

Abbreviations: G-ORS, glucose oral rehydration solution; ORS, oral rehydration solution.

Adapted from Zavaleta N, Figueroa D, Rivera J, Sánchez J, Alfaro S, Lönnerdal B. Efficacy of rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme in Peruvian children with acute diarrhea. *J Pediatr Gastroenterol Nutr.* 2007;44(2):258–264; and Alam NH, Yunus M, Faruque AS, et al. Symptomatic hyponatremia during treatment of dehydrating diarrheal disease with reduced osmolarity oral rehydration solution. *JAMA.* 2006;296(5):567–573.

Malaria

It is estimated that malaria causes 1 million childhood deaths each year, mostly in Africa. Most of the casualties (90%) are children younger than 5 years.[34] Despite substantial progress in the prevention and management of malaria, it is still considered to be "out of control" in sub-Saharan Africa and has a devastating effect on the child mortality rate.[12] Countries with a high prevalence of malaria often have high incidences of malnutrition. Factors contributing to an increased risk of contracting malaria include poor nutritional status, underweight, and the rainy season.[12] The severity and duration of malarial episodes, as well as malaria-related mortality, are affected by micronutrient deficiencies, such as vitamin A and zinc, as well as general malnutrition and being underweight. Socioeconomic factors also contribute to malarial morbidity in situations in which poverty is the major contributor to poor nutritional status.[12,15]

Signs and Symptoms

Malaria is sometimes defined as "any parasitemia plus fever." Anemia almost always accompanies severe malaria and is considered one of the main features. Contrary to the previous belief that chronic malnutrition is a protective factor against malaria morbidity, current research reveals that children who are malnourished are more susceptible to malaria and have a harder time fighting it because of a compromised immune response to the pathogens involved.[12]

Interventions

Interventions for malaria include insecticide-treated bed nets, complementary feeding, and prompt antimalarial use.[34] Because nutritional status strongly correlates with susceptibility to and recovery from malaria, providing appropriate dietary needs has the potential to positively affect morbidity and mortality. Currently, early diagnosis and treatment are the primary methods by which malaria control is attempted in sub-Saharan Africa; bed nets and residual insecticides are used in communities and intermittent preventive treatment is being explored. Because anemia is considered an independent risk factor for contracting malaria, it is reasonable to assume that by identifying and preventing factors contributing to the prevalence of anemia, a decrease in the susceptibility to and severity of malaria may occur as well. Studies suggest that by including nutritional counseling and education for the malnourished population as part of malaria-control programs, one might directly target one of the main contributing factors of malaria.

Health professionals of various disciplines should be able to identify children with poor nutritional status that would benefit from such education. Education should be provided for mothers, families, and the susceptible population. These programs should include recommendations for feeding programs that focus on improving nutritional health to decrease overall morbidity caused by malaria.[12]

Measles

Between 2000 and 2012, there was a 78% reduction in the number of deaths resulting from measles. This reduction is attributed to better measles vaccination coverage; however, measles remains one of the leading causes of death among children.[40] Globally, in 2010 there were 122,000 deaths attributed to measles.[40] The incidence of death associated with measles is significantly higher in lower-income countries when compared with higher-income countries.[40,41] The severity of existing malnutrition contributes proportionally to the risk of death from infections such as measles, and prolonged measles illness often leads to subsequent malnutrition. Approximately 45% of all measles-related pediatric deaths are directly attributable to malnutrition.[10,12,16] Preschool-aged children are at particular risk of serious morbidity and mortality from measles.[41] There is also some correlation between childhood mortality from measles and maternal education level, presumably because maternal education leads to improved nutritional activities and health-seeking behaviors.[42] Other reasons for increased mortality rates associated with measles in developing countries include young age at which

the infection occurs, lack of previous vaccination, malnutrition, vitamin A deficiency, and compromised immune system due to other underlying conditions. Environmental factors, such as crowding, lack of access to medical care, poor hygiene, and the presence of famine and warfare, also contribute to its prevalence, complications, and severity.[24,41] Infants are often initially protected by antibodies received maternally and during breastfeeding. However, in cases in which children are born to mothers with compromised immune systems (eg, HIV infected), susceptibility and severity to measles tend to be heightened.[41]

Signs and Symptoms

There are many complications commonly seen during and after contracting measles that affect practically every organ system in the body. Pneumonia tends to be the most common severe complication and contributes to the risk of mortality. Nutrition-related complications seen with measles include

- Hypocalcemia
- Renal failure
- Malnutrition
- Diarrhea
- Croup
- Stomatitis
- Death

Common complications occurring after measles include

- Mouth sores, including cancrum oris
- Decreased food intake
- Protracted diarrhea
- Weight loss
- Severe protein calorie malnutrition
- Disruption of epithelial surfaces

Having an underlying vitamin A deficiency increases the risk of fatality in children with measles in developing countries. Vitamin A deficiency also makes the child more susceptible to severe keratitis, corneal scarring, and blindness. This is one of the most common causes of acquired childhood blindness in developing countries. The risk of death associated with pneumonia caused by measles also increases when adequate stores of vitamin A are lacking.

Children who are already suffering from malnutrition and are infected with measles tend to have more severe complications and a higher risk of death due to a weak immune system and prolonged post-infectious immunosuppression. On the other hand, having measles also makes the child more susceptible to malnutrition because of decreased intake while

having higher metabolic needs, often causing significant protein loss. Anthropometric measures, such as weight for age, also tend to be significantly reduced in cases in which measles were developed early in life.[41]

Interventions

Provision of adequate nutrition, including vitamin A micronutrient supplementation, has proven to be effective and necessary in treating measles. Along with antibiotics for bacterial superinfections, these interventions reduce the risk of mortality.

Because measles often leads to a deficiency in vitamin A and vitamin A treatment of children with measles is known to reduce morbidity and mortality, WHO recommends including vitamin A as part of the treatment plan for all children who have measles. This treatment has shown to reduce the rate of mortality by approximately 50% in countries where the incidence of mortality tends to be high. The suggested regimen for hospitalized patients is vitamin A treatments once daily for 2 days.

- 12 months and older: 200,000 IU[43,44]
- 6 to 12 months: 100,000 IU[41]
- Younger than 6 months: 50,000 IU

According to the WHO recommendation, to reduce the risk of further infections and improve general health, it is beneficial to regularly continue vitamin A supplementation every 4 to 6 months in children between 6 and 59 months of age.[45]

Prevention

Vaccination is the most effective way to reduce the incidence of measles, as it protects more than 90% of those inoculated. Before vaccine use, between 95% and 98% of children were infected by the measles virus by the age of 18 years. Undoubtedly one of the most economically beneficial health interventions, the measles vaccine reduced the estimated number of annual deaths from measles from 2.6 million in 1980, before widespread vaccinations, to approximately 122,000 in 2012.[40]

HIV/AIDS

Despite progress in the fight against malnutrition, the rapid spread of HIV/AIDS presents a significant hurdle to eradicating malnutrition and risks reversing previous progress.[15] HIV currently affects approximately 2.5 million children younger than 15 years worldwide, causes premature death, and devastates the family structure, leaving many children orphaned with limited resources and access to food.[34] Most new cases involving children younger than 10 years are caused by the transmission occurring between mother and child.[15] Infant mortality rates are directly

associated with the prevalence of malnutrition and its complications in those who have contracted HIV/AIDS.[35] Thus, nutritional intervention to prevent and halt the progress of malnutrition in children with HIV/AIDS plays an important role in reducing overall mortality rates. Dietary education plays a vital role in the solution, equipping mothers and other care providers with adequate and accurate knowledge of safe feeding practices for their infants to minimize risk and complications.[15]

Nutrition Intervention

The body's nutritional demands increase prior to the symptomatic phase of HIV. Weight loss and malnutrition are strongly associated with increased risks of mortality. Providing adequate nutrition has shown to slow the progression of HIV to AIDS. The primary nutritional concern is to optimize daily dietary intake to meet increased estimated needs and maintain a good nutritional status. By doing so, good nutritional health can contribute to quality of life by providing nutrients necessary to function in daily activities. Medical treatment also tends to be more effective and symptoms reduced when an adequate diet is maintained. Dietary needs increase and malnutrition becomes more prevalent as infection progresses.

Strategies for nutritional intervention include multiple components. Because HIV/AIDS often devastates the family structure, communities play a central role in nutrition care. Awareness of adequate nutritional intake, meal planning, and nutritional counseling are needed to provide for nutritional needs. It is important to be aware that certain antiviral drugs often used to slow the progression of HIV/AIDS alter the metabolism of energy, fat, and bone. These drugs may also alter the way various nutrients are used in the body, the amount eaten, and overall nutritional status.[15] It is common to use replacement feeding as part of the intervention.[34]

Prevention

Replacement Feeding

It is imperative that mothers are correctly informed about the risks and benefits of available feeding options for their newborns to minimize the spread of HIV and reduce infant mortality risks associated with malnutrition. The following recommendations are based on those proposed by the United Nations Population Fund/UNICEF/WHO/Joint United Nations Programme on HIV/AIDS Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children and the updated 2010 WHO guidelines.[46] To

reduce transmission of HIV, replacement feeding is recommended over breastfeeding only when it is "acceptable, feasible, affordable, sustainable and safe."[46] Possible clinical risks associated with unsafe replacement feeding practices include infections, diarrhea, and malnutrition.[35] Therefore, optimal feeding practices must be evaluated to determine the risks associated with the woman's situation; the evaluation should also include the social environment and circumstances where the feeding will take place.[46] Following national guidelines, the feeding plan that best maximizes chances for infant survival may be followed; when breastfeeding is advised, especially if antiretroviral medication is not available, breastfeeding should be exclusive for the first 6 months of life.

Multiple studies confirm the likely relationship between nutritional status and HIV transmission. Implementing vitamin supplementation decreases mother-to-child infection transmission when nutritionally compromised mothers receive a multivitamin supplement while breastfeeding.[46]

Anemia

Anemia is commonly seen in infants and children in developing countries and is often prevalent in more than 50% of the pediatric population. Iron deficiency affects more than 1 billion people worldwide; thus, it is the most common nutrient deficiency. However, many additional factors contribute to the etiology of widely prevalent anemia, which contributes to the difficulty of reducing its prevalence. If hemoglobin levels are the sole test available, etiologic diagnosis of anemia will often be missed.[47–49]

Many illnesses and diseases are more difficult to treat if simultaneously battling anemia due to poor treatment response, resulting in an increased risk of morbidity. Pediatric anemia is also known to have a negative effect on learning, language, and development, often resulting in poor scholastic results. It can cause poor coordination, motor, and behavioral skills.[50,51]

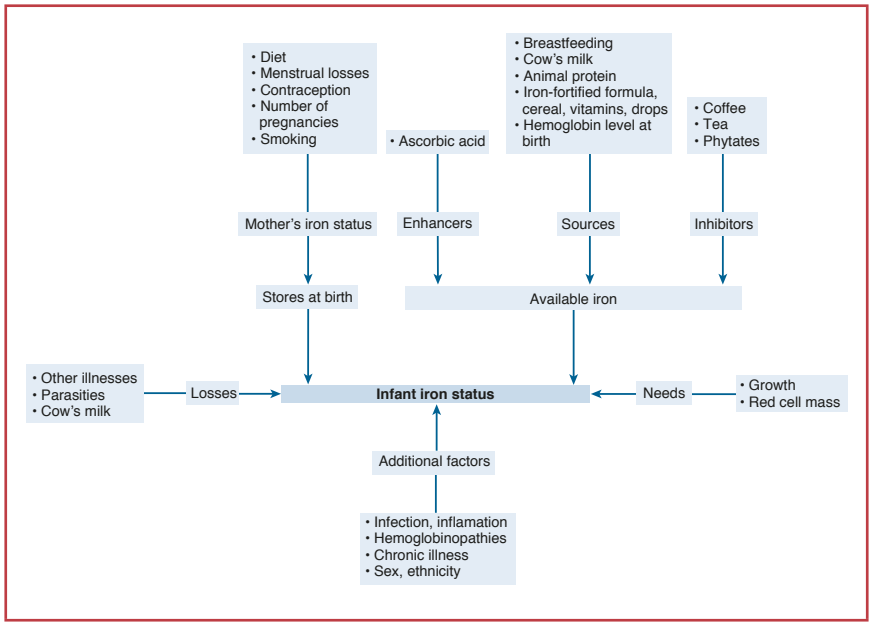
Pathophysiology

The etiology of anemia is multifactorial. Figure 22-2 outlines the major factors influencing an infant's total iron stores.[52]

Factors leading to anemia include

- Poor dietary intake and choices
  - — Inadequate intake of food containing heme iron
  - — Presence of nutritional deficiencies
  - — Poor intake and practices when weaning infant from human milk

Figure 22-2. Factors Contributing to Infant Iron Status



Adapted from Lozoff B, Kaciroti N, Walter T. Iron deficiency in infancy: applying a physiologic framework for prediction. *Am J Clin Nutr.* 2006;84(6):1412–1421, with permission from American Society for Nutrition.

- Inappropriate intake of cow's milk
  - — High intake of calcium, inhibiting iron absorption
  - — Milk protein intolerance, provoking intestinal blood loss
- Lack of breastfeeding in the first 4 months of infancy
- Excessive blood loss
- Parasitic infections
  - — Presence of malaria or hookworm, contributing to blood and iron loss
- Cellular micronutrient deficiencies
  - — Iron
  - — Retinol (vitamin A)
  - — Folate (vitamin B_9)
    - Associated with macrocytic anemia (elevated mean corpuscular volume)
  - — Cobalamin (vitamin B_{12})
    - Associated with macrocytic anemia (elevated mean corpuscular volume)

- Presence of infections and diseases
  - —Presence of malaria, HIV/AIDS, and chronic or repeated infections
- Premature birth
  - —Smaller amounts of absolute iron in the body, predisposing the infant to postnatal iron deficiency
- Genetic blood disorders
  - —Genetic variations
  - —Common within particular ethnic groups
  - —Affected hemoglobin production[24,47–49,52,53]

Malarial episodes are often associated with anemia; sometimes anemia precedes acute malarial infection. There is a complex relationship among malnutrition, anemia, and malaria, with each affecting the other. Typically, severe anemia is a symptom of severe malaria in areas where malaria is common. It is important to ensure that treatment and prevention strategies include antimalarial agents as well as address the nutritional issues present to provide optimal treatment and ultimately reduce incidence of childhood deaths.[12] Helminth infection should be investigated or presumptively treated in anemic, malnourished children in areas where helminthiasis is common.

Anemia is often present in hospitalized HIV-infected children. Studies show that the presence of HIV infection tends to increase the risk of anemia up to 6 times that of a child who does not have HIV. In many cases, a poor hemoglobin value is indicative of the progression of HIV to AIDS. Specific factors making HIV-infected infants more prone to anemia include

- Repeated illness
- Increased metabolic demand
- Early age of HIV infection
- Low maternal $CD4^+$ lymphocyte count[47]

Because vitamin A plays a role in the creation of new blood cells, a retinol deficiency also contributes to anemia. Infants are born with very poor stores of this vitamin and rely heavily on dietary intake to supply needs. In most cases, the mother's breast milk contains an easily absorbed and adequate source. However, if the mother is deficient in retinol (as are 20% of women in developing countries), breast milk will not supply an adequate amount and the infant is likely to become anemic.[47]

Intervention

Because the presence of anemia in an infant is strongly related to the mother's nutrient intake, a key intervention is to encourage expecting mothers to consume adequate amounts of iron, as well as other prenatal vitamins, to optimize their nutritional status. In some cases, providing

iron supplementation to infants may be necessary to treat anemia. Options for such supplementation include formulas fortified with bioavailable iron or, in some cases, medical supplementation. However, it is important to verify the etiology to ensure that the right treatment is provided because lack of iron may not be the root cause of anemia. Providing additional iron may, in fact, worsen the problem instead of curing the anemia, especially in cases of infection and certain other micronutrient deficiencies. The safety of iron supplementation in the case of HIV-related anemia is unknown. While the exact risks and benefits of iron supplementation are not completely understood, potential benefits support iron supplementation in anemic children.[45,47]

Prevention

To prevent and treat anemia, great care should be given to provide infant and mother with optimal nutrition and health. Exclusive breastfeeding in infancy has shown a positive effect in preventing anemia, and exclusive breastfeeding for 6 months typically provides adequate iron for the infant.[47] According to the WHO guidelines, recommendations for additional preventive measures during pregnancy include daily iron-folate supplementation of 60 mg of iron and 400 mg of folate during the final 6 months of pregnancy. Twice this daily dose should be used if the mother is severely anemic. It is also beneficial to use a multivitamin supplement that includes vitamin B complex, vitamin C, and vitamin E to reduce the risk of adverse pregnancy outcomes and encourage healthy birth weight. It is recommended that mothers continue taking a multivitamin while breastfeeding to reduce infant mortality and morbidity as well as increase the infant's $CD4^+$ cell counts. Multivitamins are also recommended for HIV-positive women during pregnancy and lactation.[45] In remote locations where there are insufficient resources to determine underlying causes of anemia, once malaria and serious infection are ruled out, many physicians treat empirically with iron, folate, and anti-helminths (in areas where helminthiasis is common).

Potential for Intrauterine Advantage

The nutritional status of the mother giving birth has a large effect on the future nutritional well-being of the infant and later on as the child develops. Malnutrition may be replicated from generation to generation. When a malnourished pregnant woman gives birth, the baby is often malnourished as well; this cycle of malnutrition is likely to continue if there is no intervention.[15]

Reducing malnutrition, especially in women, may be a key to reducing many cases of infant malnutrition and thus preventing the

continuation of intergenerational malnutrition and poverty. Children who are already malnourished in the womb are unable to fully catch up to the nutritional status of infants who were not malnourished in the womb. Children born with a low birth weight are at a greater risk of

- Increased morbidity and mortality
- Poor neurodevelopment outcomes
- Reduced strength and work capacity
- Chronic disease in adulthood
- Having shorter and lighter than normal birth weight infants on average[15]

The first 2 years of life are deemed critical to the effect of nutrition on health, as these years represent a child's most rapid growth and most critical period of brain development. Sadly, the devastating consequences of poor nutrition are only partially reversible at best, which underscores the need for preventive measures, as well as early recognition and treatment of nutrition-related disorders. Appropriately, there is increasing attention focused on the "first thousand days," including the prenatal months.[54]

DIAGNOSIS AND MANAGEMENT OF MALNUTRITION

Severely and moderately malnourished children are at increased risk for short- and long-term mortality and morbidity, including cognitive deficiencies that may feed the cycle of poverty. Clearly, diagnostic screening tools are needed that will accurately identify those children at risk for mortality and morbidities associated with undernutrition early in the course of their disease. It is important that these tools identify not only those at immediate risk of mortality from malnutrition (ie, those with severe malnutrition) but also those who display warning signs of impending severe malnutrition and its sequelae (ie, those with signs of moderate malnutrition or growth faltering).

Many approaches have been developed over the years in an attempt to identify and categorize undernutrition disorders. In 1956, Gomez introduced the concept of measuring anthropometric data to identify malnutrition by using weight for age as a clinical indication for PEM.[10,55] To determine the parameters of normal nutritional status, Gomez used a comparative reference population with the mean reference value serving as the standard against which subjects were compared (using *percent* of the mean, not percentiles, as on routine American growth curves).[10] Table 22-4 outlines the criteria for mild to severe weight-for-age loss according to Gomez's criteria.

In 1970, Wellcome proposed a method of distinguishing among different clinical forms of malnutrition by using weight for age as well as

Table 22-4. Gomez Criteria of Malnutrition (Weight-for-Age Loss)	
Mild	10% to 25% deficit of the reference
Moderate	26% to 40% deficit of the reference
Severe	More than 40% deficit of the reference

Based on Gómez F. Desnutrición. *Bol Med Hosp Infant Mex.* 1946;3(4):543–551.

the absence or presence of edema. Through his definition, a differentiation was made among various types of PEM, such as kwashiorkor and marasmus, as outlined in Table 22-5.

Despite promising progress, both definitions are limited in their clinical utility. One of the problems in using these diagnostic tools is that exact age is not always available or known, making comparison to a certain standard difficult. Furthermore, when evaluating a child's nutritional status, weight for age does not always tell the whole story. Factors such as stunting and wasting should also be considered.[55] For example, a stunted child who is chronically malnourished may have only modestly reduced weight for age. In this instance, the child's degree of malnutrition may be underestimated if only weight for age or weight for length is used. The true extent of his nutritional deficiency would best be exhibited with height-for-age comparison. This demonstrates an important point in the diagnosis of malnutrition disorders: the best way to diagnose malnutrition is not through the evaluation of a single anthropometric measurement. Rather, malnutrition is best diagnosed and defined by evaluating numerous anthropometric measurements (as defined in the following section) in combination with a developmental screening and clinical evaluation for evidence of macronutrient and micronutrient deficiencies.

ANTHROPOMETRY

Numerous anthropometric measurements may be used in evaluating a child's nutritional status. As already mentioned, weight for age may be used to determine if the child is underweight or overweight. Height for age may be used to determine if the child is stunted. Weight for height is used to determine if the child is wasted or obese; this particular measurement is useful when the exact age of the child is unknown. When combined with the presence or absence of edema, weight for height may be the most useful measurement in assessing those who are severely malnourished. For this reason, among others, this measurement is the preferred method of diagnosing severe malnutrition based on a

Table 22-5. Wellcome Classification of Protein-Energy Malnutrition		
WEIGHT FOR AGE	**EDEMA PRESENT**	**EDEMA ABSENT**
80% to 60%	Kwashiorkor	Underweight
Less than 60%	Marasmic kwashiorkor	Marasmus

From Gernaat HB, Voorhoeve HW. A new classification of acute protein-energy malnutrition. *J Trop Pediatr.* 2000;46(2):97–106, with permission from Oxford University Press.

one-time measurement only. Furthermore, other measurements, such as mid-upper arm circumference (MUAC) and tri-fold skin thickness, can be used to determine the degree of wasting of lean body mass or loss of subcutaneous fat, respectively. Mid-upper arm circumference measurement can be particularly useful in settings where scales are not readily available, such as in rural or community-based screening programs. Many anthropometric measurements are most useful when measured in series over time. In this way, loss of growth velocity can be identified early, with subsequent intervention also initiated early. Unfortunately, this most desirable strategy is often not possible in the developing world. Many children are seen only once and often in an emergency situation. As a result, WHO and UNICEF developed a strategy for identifying those children most at risk for mortality and morbidity from undernutrition. Box 22-2 provides a summary of the elements included in the WHO child growth standards. These criteria have been clinically shown to identify those children most likely to benefit from nutritional intervention, making this diagnostic tool perhaps the most clinically useful.[56]

The aims of these references, published in 2006, are to represent normal early childhood growth and be applicable for the pediatric population across ethnic, socioeconomic status, and feeding types. Therefore, these guidelines were developed through evaluating children from numerous countries around the world. These children were born to mothers who practiced healthy breastfeeding habits and did not smoke during or after pregnancy. The guidelines show that despite different environmental factors, children throughout the world grow and develop similarly when their nutritional and health care needs are met.[57] Because these new reference anthropometric values were based on a global pediatric population, they can be used universally irrespective of a country's wealth or development status.

The WHO criteria are based on *z* scores, which represent individuals in relation to SD from the population mean. A *z* score of 0 would

Box 22-2. New Elements Included in the World Health Organization Child Growth Standards

- Prescriptive approach; focusing on a standard for growth and development in contrast to a growth reference.
- Population reference is based on a global pediatric population and can therefore be used worldwide.
- Links between physical growth and motor development.

Adapted from World Health Organization. *WHO Child Growth Standards: Methods and Development.* Geneva, Switzerland: World Health Organization; 2006. http://www.who.int/childgrowth/standards/technical_report/en. Accessed June 8, 2015.

represent a child whose measurement is the same as the mean of her comparison group. A *z* score of +1 represents a measurement equal to 1 SD *above* the mean in the comparison group, while a *z* score of -2 represents a measurement equal to 2 SD *below* the mean in the comparison group. As seen in Figure 22-3, only about 2% of a population will have a *z* score below -2 and only 0.1% of a population will have a *z* score below -3.

Table 22-6 demonstrates appropriate diagnoses, including severity for various anthropometric measurements relative to their *z* score.[58]

For clinical utility in the developing world, it is useful to consider children with weight-for-height *z* scores between -2 and -3 as having moderate malnutrition and those with weight-for-height *z* scores less than -3 as having severe malnutrition. Height for age below -2 is also likely to have at least moderate malnutrition. These definitions of moderate versus severe malnutrition can be useful in therapeutic decision-making. Children with severe malnutrition may need to be hospitalized and require intensive treatment. Outpatient or community-based treatment, however, is appropriate in children with severe malnutrition who maintain a healthy appetite and have no medical complications. On the other hand, children who fall into the moderate malnutrition category often do not need hospitalization and can be managed at home with appropriate dietary and other counseling with regular follow-up. Fortified milks and ready-to-use therapeutic food (RUTF) are not usually needed for these children but rather an appropriate diet based on locally available foods.

The WHO changed the cutoff for diagnosing severe acute malnutrition (SAM) based on MUAC for children between the ages of 6 and 60 months. Previously, the cutoff was placed at 110 mm. However, the same study used to develop *z* score criteria also revealed that lowering the MUAC criteria to 115 mm increased sensitivity to nearly 99%

Figure 22-3. Prevalence of Normal Population *z* Scores

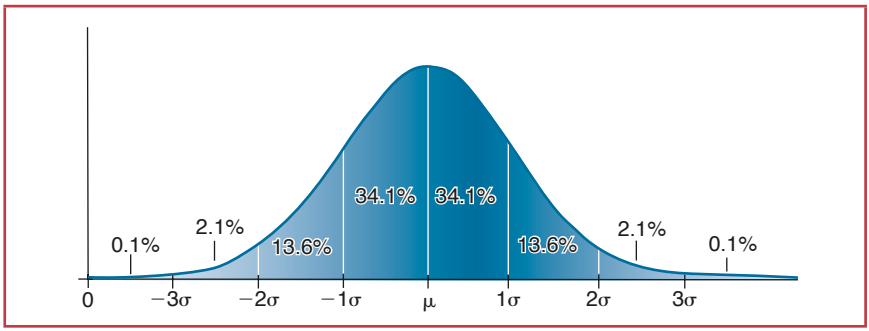


Table 22-6. Classification of Nutritional Status by *z* Scores

z SCORE	WEIGHT FOR AGE	HEIGHT FOR AGE	WEIGHT FOR HEIGHT
+3	Possibly overweight[a]	Very tall	Obese
+2	Possibly overweight[a]	Normal	Overweight
+1	Possibly overweight[a]	Normal	Possible risk of overweight
0	Median	Median	Median
-1	Normal	Normal	Normal
-2	Underweight	Stunted	Wasted
-3	Severely underweight	Severely stunted	Severely wasted

[a] A child whose weight for age falls in this range may have a growth problem, but this is better assessed from weight for length/height or body mass index for age.

Adapted from World Health Organization. Training course on child growth assessment. Geneva, Switzerland: World Health Organization; 2010. http://www.who.int/childgrowth/training/en. Accessed June 12, 2015.

while still maintaining high specificity for SAM.[59] The MUAC is easily measured in children with a standard tape measure; however, many prefer color-coded tapes made specifically for identifying these cutoffs. This makes MUAC measurements a useful tool in community screening programs in which height and weight measuring tools may be unavailable or burdensome. The main MUAC disadvantage for diagnosing SAM is the often-observed inconsistency in technique. For this reason, many malnutrition programs use weight for height as the primary measurement. Table 22-7 describes the diagnostic criteria used for diagnosing SAM in children between the ages of 6 and 60 months.

Table 22-7. Diagnostic Criteria for Diagnosing Severe Acute Malnutrition in Children Aged 6 to 60 Months

INDICATOR	MEASURE	CUTOFF
Severe wasting[a]	Weight for height[b]	<3 SD
Severe wasting[a]	MUAC	<115 mm
Bilateral pedal edema[a]	Clinical sign	Any present

Abbreviation: MUAC, mid-upper arm circumference.

[a] Independent indicators of severe acute malnutrition that require urgent action.

[b] Based on World Health Organization standards (www.who.int/childgrowth/standards).

Adapted from World Health Organization, United Nation Children's Fund. *WHO Child Growth Standards and the Identification of Severe Acute Malnutrition in Infants and Children: A Joint Statement by the World Health Organization and the United Nations Children's Fund.* Geneva, Switzerland; World Health Organization; 2009. http://www.who.int/nutrition/publications/severemalnutrition/9789241598163_eng.pdf. Accessed June 8, 2015.

DEVELOPMENTAL MILESTONES

As mentioned previously, the diagnosis of malnutrition is best made with a holistic approach to the child rather than on the basis of anthropometric measurements alone. The child's developmental status is often useful when making the diagnosis of malnutrition, as many children with true SAM will demonstrate developmental delay or regression. There are numerous developmental screening tools available; however, many are time consuming and may present difficulties in training others in their proper use. The WHO recommends a simplified approach to developmental screening that focuses on 6 major developmental milestones from ages 3 to 24 months. These milestones are easy to remember and train staff to recognize.[60]

- Sitting without support
- Standing with assistance
- Hands-and-knees crawling
- Walking with assistance
- Standing alone
- Walking alone

Charts demonstrating appropriate age ranges for these milestones are available for download from the WHO Web site (www.who.int/childgrowth/standards/motor_milestones/en) and are useful in gathering further information for those children at risk for malnutrition.

CLINICAL MANIFESTATIONS OF MACRONUTRIENT DEFICIENCY

A full history and physical examination are indispensable in determining evidence of macronutrient or micronutrient deficiencies leading to the diagnosis of malnutrition. Micronutrient deficiencies are covered starting on page 611, limiting the focus of this discussion to clinical manifestations of macronutrient deficiency, namely PEM. Protein-energy malnutrition develops from deficiencies of caloric intake and protein quantity and quality. The child who is not receiving appropriate calories (energy) is likely to have a diet deficient in protein as well. Furthermore, if the diet contains insufficient calories, even what little protein is consumed will be used as an energy source instead of building lean body mass. Protein-energy malnutrition is most prevalent in children 6 months to 2 years of age.[19] Because of children's complete dependency on their caregiver for intake, children in this age range are at a particularly high risk for multiple nutritional problems associated with inappropriate feeding practices. Educational gaps, certain cultural traditions, and taboos are a few reasons leading to this deficit. This particular population is at high risk due to potential errors in the many feeding transitions during this time of life, such as

- Early weaning
- Introduction of nutrient-poor foods
- Late introduction of complementary foods
- Inadequate protein intake
- Frequent or severe infections and illness

Deficiency of energy and protein largely manifests as 2 different clinical pictures: marasmus and kwashiorkor. Traditionally, the differences between these 2 clinical manifestations of PEM have been explained with reference to the amount of protein deficiency relative to energy deficiency. However, both conditions result from deficiencies in protein and caloric intake and cannot be explained simply on the basis of protein content in diets. Furthermore, some children will have manifestations of both clinical pictures, so-called marasmic kwashiorkor (see Wellcome criteria in Table 22-5), and a change from marasmus to kwashiorkor is often a poor prognostic indicator. Although some controversy remains as to the mechanisms leading to the differences seen in these 2 clinical pictures, one of the best explanations comes from the *adaptation hypothesis*.[61] According to this hypothesis, children with predominantly marasmic clinical features are well adapted. In response to energy and protein deficiency, these children break down fat and lean muscle stores to produce the needed energy to survive. In a way, their bodies act appropriately in response to the deprivation.

On the other hand, children who manifest kwashiorkor seem to have a maladaptive response to deprivation—they retain some subcutaneous fat while continuing to break down lean muscle in addition to developing edema, which further complicates their ability to adapt. This maladaptive process is likely a combination of genetic as well as environmental factors, such as infections and aflatoxin exposure. Marasmus tends to be easier to treat and has fewer clinical complications. This may be because the marasmic reaction to malnutrition is the "correct" response to nutrient deprivation, whereas the maladaptation displayed in kwashiorkor places the child at a metabolic disadvantage. Thus, recovery rates for marasmus tend to be higher than those for kwashiorkor.[62]

Several factors influence clinical manifestations of PEM, including magnitude and duration of deprivation, relative deficiency of different nutrients, accompanying infections or chronic disease, and exposure to environmental toxins (ie, aflatoxins). It is useful to think of PEM as a metabolic disorder resulting from a "reductive adaptation."[53] To preserve energy, reductions occur in physical activity, growth, and basal metabolic rate—much like in hibernation. These metabolic derangements form the basis of many of the treatments initiated in the WHO-recommended 10 steps for successfully treating severe malnutrition (detailed on page 597).

Water, Electrolytes, and Minerals

Total body water is increased in marasmus and kwashiorkor, with more severely malnourished children having higher total body water. Thirst is paradoxically increased because of a defective thirst mechanism despite the increase in total body water. In addition, total body potassium is reduced while total body sodium is increased.[53] For this reason, fluid resuscitation in severely malnourished children should be accomplished using a solution that is low in sodium and high in potassium, such as ReSoMal. Electrolyte disturbances also contribute to the edema of kwashiorkor. Numerous other minerals are also deficient in many children with severe malnutrition, including calcium, iron, magnesium, zinc, copper, phosphorus, and chromium.

Protein

As expected, total serum protein is reduced as evidenced by hypoalbuminemia, leading to pitting edema, which is a hallmark of kwashiorkor.

Lipids

Chronic malnutrition often leads to atrophy of the gastric as well as intestinal mucosa. This, in turn, leads to reduction of fat absorption

from the gut. As a result, there is often increased fecal fat that may present as chronic diarrhea. There is also abnormal lipid metabolism, which results in fatty infiltration of the liver in kwashiorkor. Fatty liver may be observed as an increase in liver transaminases or as hepatomegaly, which contributes to the characteristic abdominal distension seen in kwashiorkor.

Carbohydrates and Metabolism

Multiple abnormalities may exist in carbohydrate metabolism and endocrine function in the malnourished child. Among these abnormalities are impaired glucose absorption, transient disaccharide intolerance, and a low basal metabolic rate. These changes, in turn, may lead to bradycardia, hypothermia, and hypoglycemia, which can be fatal. Circulating thyroglobulins are often reduced in PEM, although the thyroid-stimulating hormone may remain normal.[63]

Immunity

Severely malnourished children are relatively immunocompromised and are therefore subject to numerous infectious diseases. Often, lymphocytopenia with reduced T-helper cells is present along with impaired cell-mediated immunity. There may also be a reduced response to antigens with reduction in cytokine production and antibodies.[64] These changes place the child at increased risk for common, as well as uncommon, childhood infections, which forms the basis for the WHO recommendation to give broad-spectrum antibiotics to all children treated for severe malnutrition. These children will also often benefit from antiparasitic and anti-helminth treatment.

Cardiac

The effects of malnutrition on cardiac size and function must not be overlooked, as heart failure often leads to death in these children, especially if unrecognized. The size and weight of the heart, and thereby cardiac function, are often reduced in proportion with the severity of wasting elsewhere in the body.[65] Bradycardia and reduced blood flow are common findings that further contribute to the common finding of hypothermia, which can be fatal. High vigilance must be kept when rehydrating the malnourished child to prevent the onset or exacerbation of heart failure. Intravenous fluids should never be used for rehydration unless the child shows clear signs of shock. Furthermore, as previously mentioned, a low-sodium (high-potassium) oral solution is preferred.

Renal

As elsewhere in the body, malnutrition affects the renal system. The glomerular filtration rate is reduced and there is inefficient acid excretion due to tubular damage.[66] However, despite this inefficiency, urine remains acidic secondary to excretion of hydrogen ions in the body's attempt to preserve potassium through the hydrogen/potassium pump.

Gastrointestinal

Lastly, diarrhea is commonly associated with malnutrition, although it is often difficult to determine if it is a contributor to the malnutrition or part of the sequelae; often it is both. In fact, the prevalence and duration of diarrhea are increased in malnourished children.[67] Diarrhea may result from a combination of bacterial, parasitic, or candidal causes in addition to common viral causes. Furthermore, there is often intestinal and gastric mucosal damage from prolonged malnutrition, which leads to malabsorption, particularly in marasmic patients; this, in turn, may cause further diarrhea. Of course, chronic or recurrent diarrhea itself is also a risk factor for developing malnutrition.

These metabolic and functional changes resulting from PEM are the basis for many of the treatments for malnutrition discussed as follows.

CLINICAL FEATURES OF PROTEIN-ENERGY MALNUTRITION

Marasmus

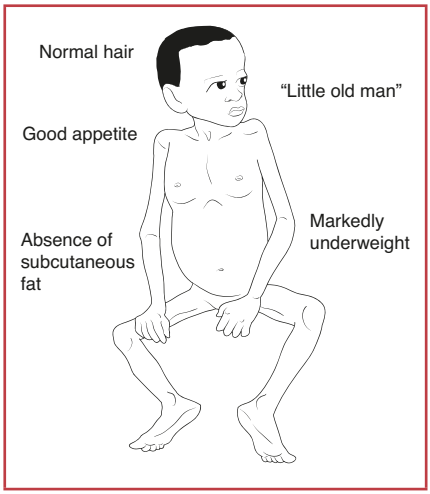
There may be numerous clinical findings in a child with marasmus, but the principle signs include severe wasting manifested by weight for age less than 60% of expected and the absence of edema (see Table 22-5). The child will often have a wizened appearance or the so-called "old man facies." There will also be visible wasting with loss of subcutaneous fat and lean muscle mass, resulting in a wrinkled skin appearance (Figure 22-4). These losses could also be measured with MUAC and tri-fold thickness, but the wasting in marasmus should be apparent on simple inspection of the child, who is often withdrawn and apathetic (figures 22-5 and 22-6). Table 22-8 classifies the degree of wasting based on anatomic location of subcutaneous fat loss.

Kwashiorkor

Kwashiorkor may also present with numerous clinical manifestations. However, the following 4 major signs are most agreed on:

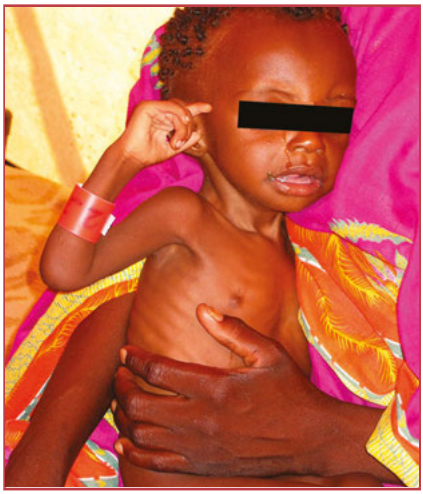
- Body weight that is 60% to 80% of predicted for age.
- There is retention of at least some subcutaneous fat even though muscle wasting may be present.

Figure 22-4. Clinical Features of Marasmus



From Fischer PR. Tropical pediatrics. *Pediatr Rev.* 1993;14(3):95–99.

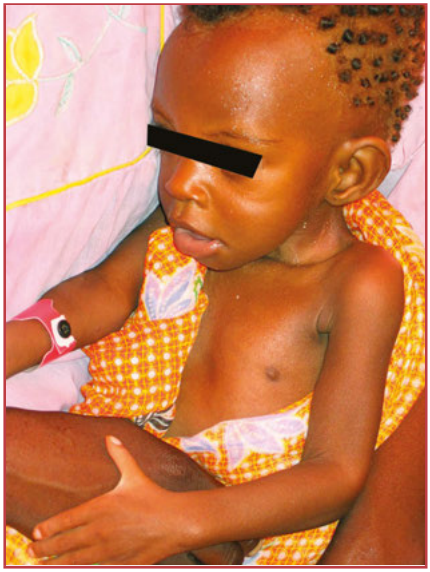
Figure 22-5. Marasmus



Marasmus in a young child whose family had been displaced as a result of civil conflict in Angola.

From American Academy of Pediatrics. *Atlas of Pediatrics in the Tropics and Resource-Limited Settings.* Spector JM, Gibson TE, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Figure 22-6. Improvement in Marasmus



Substantial improvement was observed following only 2 weeks of treatment at an inpatient therapeutic feeding center.

From American Academy of Pediatrics. *Atlas of Pediatrics in the Tropics and Resource-Limited Settings.* Spector JM, Gibson TE, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

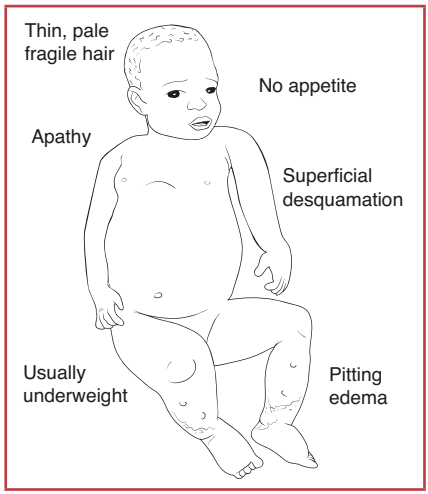
Table 22-8. Grading of Nutritional Marasmus

1	Loss of fat from axilla/groin
2	Loss of fat from abdominal wall and gluteal region
3	Loss of fat from chest and back
4	Loss of buccal fat (composed of fatty acid and the last area to be affected)

- Psychomotor changes (apathy).
- Pitting edema (Figure 22-7).
  - —Often seen in the feet bilaterally
  - —May be present only in the periorbital region

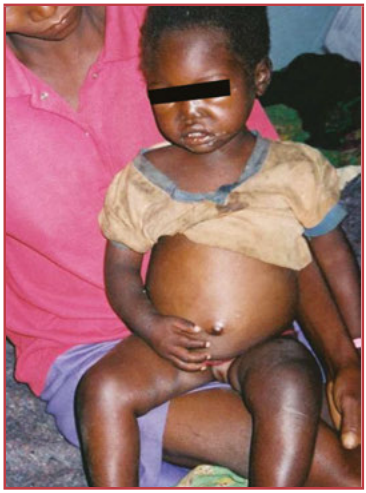
However, some diagnostic tools, such as the Wellcome criteria, focus only on the percentage of the mean weight for age and presence of pitting edema. In fact, the presence of edema alone in a young child is cause for concern for severe malnutrition in many malnutrition programs, including those advocated by WHO.[53] In addition to these major findings, evidences of macronutrient and micronutrient deficiency may be seen in various systems throughout the body in a child with kwashiorkor. There are frequently skin and hair changes, including hypopigmented or hyperpigmented areas of skin, areas of desquamation (especially in the groin and axilla), peeling skin (so-called "flaky paint" rash [figures 22-8 through 22-10]), sparse or patchy hair, and darkening or whitening of the hair.[18] These children will also often have striking abdominal distention. At first glance, when combined with edema, these children may be incorrectly diagnosed as overnourished. The abdominal distension is not the result of ascites, as some may presume, but is often the result of hepatomegaly from fatty infiltration of the liver and weakened abdominal muscles from loss of muscle mass.

Figure 22-7. Clinical Features of Kwashiorkor



From Fischer PR. Tropical pediatrics. *Pediatr Rev.* 1993;14(3):95–99.

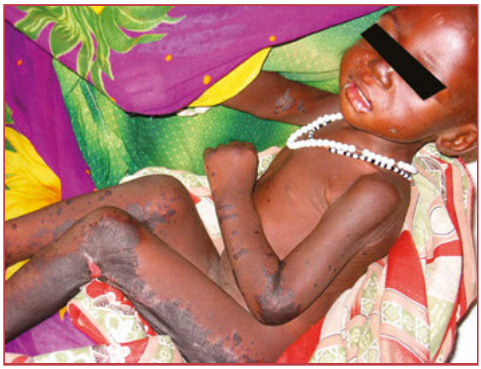
Figure 22-8. Kwashiorkor Showing Edema



From American Academy of Pediatrics. *Atlas of Pediatrics in the Tropics and Resource-Limited Settings.* Spector JM, Gibson TE, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

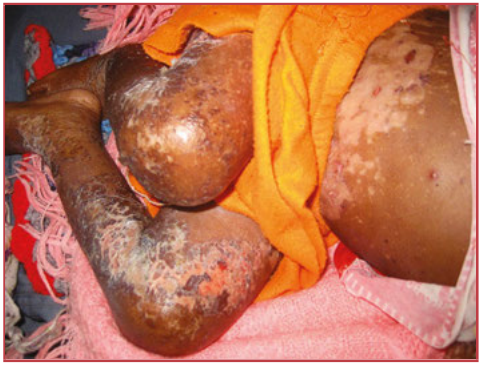
Table 22-9 provides a summary of critical laboratory values to consider in assessing severe malnutrition. Although the general guidelines for treating marasmus and kwashiorkor are the same, it is clinically important to distinguish between marasmus and kwashiorkor, as some aspects of the treatment, prognosis, and follow-up may differ. The easiest way to identify the presence of kwashiorkor is with the observation of lower extremity pitting edema or periorbital edema in an underweight child.

Figure 22-9. Kwashiorkor Showing Peeling Skin ("Flaky Paint")



From American Academy of Pediatrics. *Atlas of Pediatrics in the Tropics and Resource-Limited Settings.* Spector JM, Gibson TE, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Figure 22-10. Kwashiorkor Showing Abdominal Distention and Peeling Skin ("Flaky Paint")



Courtesy of David Fox II, MD.

Prevention

Prevention of PEM should be an integral part of any comprehensive plan to manage malnutrition. Preventive measures to reduce the incidence of kwashiorkor and marasmus include increasing nutritional education to people of various incomes, ages, and education levels. Mothers, children, and communities at particularly high risk may also benefit from supplemental food programs, subsidiaries, and maternal-infant support programs. Encouraging immunization use, early treatment of infectious diseases, and good sanitary practices are vital in preventing illnesses that are likely to put a child at high risk of PEM and prevent growth and development.[19]

Table 22-9. Laboratory Features of Severe Malnutrition

BLOOD OR PLASMA VARIABLES	INFORMATION DERIVED
Hemoglobin, hematocrit, erythrocyte count, mean corpuscular volume	• Degree of dehydration and anemia; type of anemia (iron/folate and vitamin B_{12} deficiency, hemolysis, malaria)
Glucose	• Hypoglycemia
Electrolytes and alkalinity	
Sodium	• Hyponatremia, type of dehydration (despite increased total body sodium content)
Potassium	• Hypokalemia
Chloride, pH bicarbonate	• Metabolic alkalosis or acidosis
Total protein, transferrin, (pre-)albumin	• Degree of protein deficiency
Creatinine	• Renal function
C-reactive protein, lymphocyte count, serology, thick and thin blood films	• Presence of bacterial or viral infection or malaria
Stool examination	• Presence of parasites

From Müller O, Krawinkel M. Malnutrition and health in developing countries. *CMAJ.* 2005;173(3):279–286, with permission.

TREATMENT OF MALNUTRITION

Moderate Malnutrition

Moderate malnutrition includes all children with *moderate wasting,* which is defined as weight for height between -3 and -2 *z* scores, and all those with *moderate stunting,* which is defined by height for age between -3 and -2 *z* scores, both from the WHO child growth standards. Most of these children will be *moderately underweight* (weight for age between -3 and -2)[68]; research concerning morbidity and mortality in moderate malnutrition clearly reveals that both are increased. Death from diarrhea, pneumonia, malaria, and measles are all significantly increased in moderately malnourished children. Furthermore, many of these children will progress to severe malnutrition before dying.[68] Unfortunately, moderate malnutrition has not received the same intensity of research or intervention as severe malnutrition, and nearly two-thirds of undernourished children are in the moderately malnourished category. It is clear that moderate malnutrition requires the most serious attention.

Unfortunately, the optimum strategy for treating moderate malnutrition has yet to be definitively described. What is clear is that more

specific strategies and counseling are needed for treatment to be effective. Previous attempts at generic nutritional advice have proven ineffective. In many resource-poor areas, it is likely that treating moderate malnutrition with the same supplements as severe malnutrition, while likely to be effective, is cost or resource prohibitive.[69] While recognizing that further research is needed, recent research and consensus panels reached some conclusions concerning the most appropriate diet for moderately malnourished children. These dietary recommendations include the following components[70]:

High Energy Density

Malnourished children should receive a diet with a high energy density. This can be accomplished by reducing the meal's bulk by reducing water content. Foods that contain large amounts of water may cause the child early satiety before she consumes enough calories. The child should be offered clean water between meals to ensure adequate hydration. Additionally, adding oil or sugar to meals, when appropriate (ie, porridge), can increase the food's energy content.

Adequate Protein Quantity, Quality, and Bioavailability

Clearly, children with PEM need to consume adequate amounts of protein if they are to recover. However, there is also concern that too much protein may adversely affect appetite as well as provide undue financial burden on caregivers. Therefore, it has been suggested that protein should account for 12% of daily energy consumption in moderately malnourished children. In addition, protein quality and bioavailability are important. Protein consumed from animal sources (ie, meat and eggs) is of higher quality and greater bioavailability than protein consumed from vegetable sources. These advantages must be balanced with the higher cost of meat-based proteins. Often a cost-effective balance is needed, combining at least some higher quality animal-based proteins with cheaper plant-based proteins.

Fat Quantity and Quality

Fat has more than twice the energy of protein or carbohydrates. Therefore, it is a key component to the diet of malnourished children as a source of high energy density. It is recommended that 35% to 50% of daily calories come from fat. Furthermore, fat quality is also important; in fact, it is likely that deficiency of essential fatty acids is responsible for many of the cutaneous manifestations of malnutrition. Therefore, malnourished children should receive appropriate amounts of polyunsaturated fatty acids with an appropriate n-3/n-6 ratio.

Animal-Sourced Foods

As previously mentioned, meat is an excellent source of high-quality and highly bioavailable proteins. Meat products are also high in micronutrients and low in anti-nutrients. In addition, the so-called "meat factor" allows for greater absorption of iron from nonheme (plant-based) sources. Animal products, especially milk protein, are shown to increase linear growth as well as lean muscle mass. Although meat products are often the most expensive ingredients in meals, they are indispensable in the diets of malnourished children. Every effort should be made to introduce at least some meat product into the diet of these children.

Micronutrients

Typically, diets for malnourished children focus on energy and protein content. However, it is now clear that foods high in micronutrients should be added to meals. Nutrient deficiencies can be divided into 2 types based on the presence or absence of a specific physical finding. Deficiency of type 1 nutrients will lead to depletion of body stores, followed by signs or symptoms of deficiency (eg, iron, folate). Deficient consumption of type 2 nutrients, however, will lead to reduction of growth to preserve plasma and tissue stores of these micronutrients. There is often no specific physical finding of deficiency of type 2 nutrients (eg, zinc). Micronutrients are often only needed in small quantities and can be obtained from a variety of animal, fruit, and vegetable sources.

Anti-nutrients

The term *anti-nutrients* refers to compounds largely found in plant-based foods that bind nutrients found in other foods that are consumed simultaneously. Phytates and tannins are important anti-nutrients that bind to numerous positively charged minerals, such as calcium, magnesium, and iron, preventing their absorption. Phytates are found in several legumes and vegetables, while tannins are found in black tea and dark sorghum. Although it is impossible to avoid these foods altogether in feeding a malnourished child, methods such as roasting, malting, and fermenting can reduce the content of phytates before consumption. Black tea should be avoided in all malnourished children.

In addition to these recommendations, any dietary advice should include meals containing a low risk of contamination. For example, if lack of clean water is a concern, powdered milk is not the best option because it is likely to be contaminated while being mixed with water. Also, foods must have an appropriate taste and texture and be culturally

appropriate, easy to prepare, made with locally available products, and affordable. Tension is constant between choosing the best foods (usually animal products), which are typically the most expensive, and choosing the cheapest foods (usually roots or cereals). Research is making it clear that not merely the cheapest foods should be recommended but rather the proper balance of those foods that provide the best nutrients and are the most affordable.[70]

In addition to specific dietary advice, it may be reasonable to test for or empirically treat helminths or parasites in areas with high prevalence. Consideration may also be given to supplementation of micronutrients such as vitamin A, zinc, and a multivitamin with folate. Immunizations should be brought up-to-date, with particular attention given to the measles vaccine.

Severe Malnutrition

Guidelines for treating severe malnutrition are much more clearly defined subsequent to more extensive research and testing. Although some children with severe malnutrition will need intensive inpatient treatment, many will do well with outpatient, community-based treatment. In fact, recent meta-analysis confirms that community-based treatment for appropriately selected children is effective and affordable.[4] Treatment in hospitals mainly occurs when PEM is severe, appetite is poor, and infections complicate the case.[8] When considering the most appropriate location for SAM treatment, factors that should be considered include coexisting medical complications, access to a treatment center, availability of a supportive caregiver, sanitary conditions, prevalence of severe malnutrition in the area, and availability of a complementary feeding program.[10]

The WHO growth standards are designed as indicators to identify the need for nutritional intervention. Treatment methods are largely based on the presence of medical complications (Table 22-10). According to the WHO child growth standards (see Table 22-6), a child between the ages of 6 and 60 months with signs of bilateral edema or severe wasting, with a weight for height of less than -3 SD or MUAC less than 115 mm, is considered to have SAM and should be treated. Table 22-10 outlines factors that should be considered when discerning approaches to treatment. A medical facility is recommended when symptoms are severe, appetite is lacking, and there are medical complications. On the other hand, an outpatient, community-based management approach may be more appropriate if no medical complications are evident and the child has an appetite.[56]

Table 22-10. General Management of Severe Acute Malnutrition

TREATMENT LOCATION	FACILITY BASED	OUTPATIENT COMMUNITY BASED
Symptoms	• Lack of appetite • Medical complications — +++ Edema — IMCI "danger signs"	• Appetite preserved • No medical complications
Interventions	• F-75 (starter formula)[a] • Progress to F-100 (catch-up formula)[b] or RUTF • 24-hour medical care	• RUTF • Basic medical care
Discharge criteria	• Reduced edema • Good appetite • Clinically well and alert • Discharged to community-based care	• *z* score >-2 • MUAC >125 mm • Monitor periodically to prevent relapse.

Abbreviations: IMCI, Integrated Management of Childhood Illness; MUAC, mid-upper arm circumference; RUTF, ready-to-use therapeutic food.

[a] World Health Organization– and United Nation Children's Fund–provided starter milk-based formula, commonly available in developing countries.

[b] World Health Organization– and United Nation Children's Fund–provided catch-up milk-based formula, commonly available in developing countries.

Adapted from World Health Organization, United Nation Children's Fund. *Updates on the Management of Severe Acute Malnutrition in Infants and Children.* Geneva, Switzerland; World Health Organization; 2013.

The importance of community and family involvement leading to empowerment in successful malnutrition prevention and treatment is well known. Treatment options in which cultural settings are taken into consideration have been implemented with good results. For example, the National Health Services System in Chile provides an alternative to hospital treatment with psychomotor stimulation in addition to nutritional care. Additionally, the child's caregiver participates in the recovery process. Because this approach was used among some of the poorest in Chile, there was also an emphasis on improving the socioeconomic situation of the families involved. Not only did these centers show results in treating malnutrition, but they also demonstrated reductions in mortality rates related to malnutrition through simultaneous education. The main problems with this approach are the financial costs of the program as well as the potential disruption to a family's daily dynamics. Today, alternative programs are implemented, including treatments based in child care centers as well as staff monitoring children in their home.

These programs appear to be more cost-effective while providing care that does not disrupt the family's normal life.[10]

Strategies to Reduce Mortality in Treating Severe Acute Malnutrition: 10-Step Approach

Despite advances in the understanding and treatment of SAM, fatality rates remained about the same in children who were hospitalized with malnutrition from 1950 through 1990. However, mortality rates in treatment centers range from 50% to less than 5%. Accordingly, it is clear that mortality rates can be dramatically reduced if tested strategies are implemented. Severely malnourished children who die in the hospital typically die from 4 main causes: hypoglycemia, hypothermia, heart failure, and infection.[53] In response, WHO developed a strategic treatment plan to address the common elements present in severe malnutrition[71] as outlined and detailed in the following charts and tables. Currently, the widespread availability of special feedings designed for malnourished children (ReSoMal, F-75, F-100, Plumpy'Nut) in developing countries has been very beneficial in improving clinical management.

When considering inpatient management for SAM, the format outlined in the WHO guidelines[71] provides a tested method to treat signs and symptoms associated with severe protein-energy deficiency. This proven 10-step approach[72,73] can be divided into 2 phases, initial stabilization and rehabilitation.

- Stabilization phase
  - —Provide cautious low-lactose, low-protein feeding and hydrate with a low-sodium solution to reduce the risk of hypoglycemia, hypothermia, and dehydration.
  - —Closely monitor volume loads (oral, enteral, and parenteral intake) to avoid heart failure.
  - —Modify a standard ORS (eg, by using ReSoMal) to reduce sodium concentrations and increase potassium, magnesium, copper, selenium, and zinc concentrations.
  - —Treat concomitant infections with broad-spectrum antibiotics (bacteremia, especially with gram-negative bacteria, is not uncommon).
- Rehabilitation phase
  - —Limit protein intake to less than 1 g/kg to avoid ammonia buildup due to
    - Impaired liver function with breakdown of the urea cycle
    - Reduced urine excretion with dehydration

The key treatment elements of the 10 steps are further described in the following sections.[16] Table 22-11 describes the approximate timeline

Table 22-11. Elements in the Management of Severe Protein-Energy Malnutrition (According to the World Health Organization)

STEP	MANAGEMENT	PHASE		
		STABILIZATION		REHABILITATION
		DAYS 1–2	DAYS 3–7	WEEKS 2–6
1. Prevent and treat hypoglycemia.	Monitor blood glucose; provide oral (or intravenous) glucose as indicated; initiate early cautious feeding every 2 hours.	→		
2. Prevent and treat hypothermia.	Warm patient and keep dry; maintain and monitor body temperature; initiate early cautious feeding every 2 hours; administer broad-spectrum antibiotics.	→		
3. Dehydration	Rehydrate carefully with oral solution containing less sodium and more potassium than standard mix (ReSoMal).	→		
4. Electrolytes	Supply plenty of potassium and magnesium.	→	→	→
5. Infections	Administer broad-spectrum antibiotics; consider anti-helminth, antiparasitic, and antimalarial therapy (if indicated); begin/continue immunizations (especially measles).	→	→	
6. Micronutrients	Provide copper, zinc, iron, folate, and multivitamins. Sufficient amounts are often available in milk-based formulas for SAM or in RUTF.	→ No iron	→	→ With iron
7. Starter nutrition	Keep protein and volume load low (F-75 if available).	→	→	
8. Tissue-building nutrition, catch-up growth	Furnish a rich diet dense in energy, protein, and all essential nutrients that are easy to swallow and digest (F-100 if available or RUTF such as Plumpy'nut).			→

Table 22-11. Elements in the Management of Severe Protein-Energy Malnutrition (According to the World Health Organization), continued

STEP	MANAGEMENT	PHASE		
		STABILIZATION		REHABILITATION
		DAYS 1–2	DAYS 3–7	WEEKS 2–6
9. Sensory stimulation and emotional support	Prevent permanent psychosocial effects of starvation with psychomotor stimulation and tender, loving care.	→	→	→
10. Prevention of relapse; prepare for follow-up.	Start early to identify causes of protein-energy malnutrition in each case; involve family and community in prevention.			→

Abbreviations: RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition.

Modified from Müller O, Krawinkel M. Malnutrition and health in developing countries. *CMAJ.* 2005;173:279–286; and Ashworth A, Jackson A, Khanum S, Schofield C. Ten steps to recovery. *Child Health Dialogue.* 1996;(3-4):10–12.

for when various interventions take place in the treatment process,[71] and Table 22-12 includes a perspective for children with concurrent diarrhea.

Steps 1 and 2: Prevent and Treat Hypoglycemia and Hypothermia

1. Hypoglycemia often occurs in combination with hypothermia, indicating infection.
2. Monitor temperature regularly and check for hypoglycemia whenever the child is hypothermic.
3. Provide small, frequent feedings (eg, F-75 every 2 hours) to control hypoglycemia and hypothermia.
4. Severely malnourished children should be treated as though they are hypoglycemic if it is not possible to measure blood glucose levels.
5. Refer to tables 22-13 and 22-14 for detailed treatment plans.

Step 3: Treating and Preventing Dehydration

1. The degree of dehydration in severely malnourished children is often difficult to assess when only using clinical signs. Signs, such as sunken eyes, reduced skin turgor, and lethargy, may be caused by malnutrition or dehydration. Even children with edema may be dehydrated.

Table 22-12. Phases of Management of Diarrhea in Malnourished Children

PHASE	FOCUS	MANAGEMENT
Acute	• Dehydration • Infection • Hypoglycemia • Hypothermia • Water/electrolyte imbalance	• Correction of micronutrient imbalances with supplementation • Broad-spectrum antibiotics • Initiate feeding immediately after admission or 2 h after rehydration started. • Scheduled frequent, small feedings • Rehydration
Nutritional rehabilitation	• Regaining weight lost • Maintaining weight	• Intensive feeding • Involvement/instruction of caregiver • Child given emotional and physical stimuli
Follow-up	• Minimize relapse. • Ensure optimal physical and mental growth and development.	• Follow-up instruction and education to meet needs and prevent recurrence of diarrhea

2. All children with watery stools should be assumed to have dehydration and should be treated.
3. Oral rehydration is preferred and should be used whenever possible.
4. Dehydration in malnourished children is rarely more than 5% of total body weight (in the absence of severe watery diarrhea). This 5% goal can therefore be used to guide the amount of total fluids that should be given.
5. ReSoMal, a solution formulated especially for severely malnourished children, contains reduced sodium and increased potassium. Standard solutions are often too high in sodium and too low in potassium for severely malnourished children.
6. Refer to Table 22-15 for detailed treatment plans and tables 22-16 and 22-17 for ReSoMal and electrolyte solution recipes.
7. Intravenous rehydration should only be used in cases of shock or severe dehydration that is not responsive to oral therapy. Although high-quality evidence is lacking, careful, slow infusion of 15 mL/kg over 1 hour to avoid excess fluid flooding the circulation and overloading the heart is prudent. Use of lactated Ringer solution with 5% dextrose, half-strength Darrow solution, or D5 ½ NS (in that order of preference) is suggested.

Table 22-13. Treatment and Prevention of Hypoglycemia

	SYMPTOMS: CONSCIOUS WITH BLOOD GLUCOSE BELOW 54 mg/dL	SYMPTOMS: UNCONSCIOUS, LETHARGIC, OR CONVULSING
Treatment	1. 50-mL bolus of 10% glucose or 10% sucrose solution (1 rounded teaspoon of sugar in 3.5 tablespoons water), orally or by nasogastric tube	1. IV sterile 10% glucose (5 mL/kg), followed by 50 mL of 10% glucose or sucrose by nasogastric tube
	2. Feed starter F-75 every 30 minutes for 2 hours (giving one-quarter of the 2 hourly feedings each time).	
	3. Provide antibiotics.	
	4. Provide 2 hourly feeds, day and night.	
Monitor	• Glucose level: monitor after 2 hours (most children stabilize within 30 minutes after treatment). • Blood glucose less than 54 mg/dL — Additional 50-mL bolus 10% glucose or sucrose solution. — Feed continuously every 30 minutes until stabilized. • Retest blood sugar if — Rectal temperature is below 35.5°C or axillary temperature below 35°C. — Level of consciousness deteriorates.	
Prevention	• Initiate 2 hourly feedings immediately or after rehydration if needed. • Provide feedings day and night.	

Abbreviation: IV, intravenous.

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

Step 4: Correcting Electrolyte Imbalance

1. Total body sodium in all severely malnourished children will be high even when plasma sodium may be normal or low. Providing high concentrations of sodium is often fatal.
2. Potassium and magnesium are routinely deficient in severely malnourished children. While taking at least 2 weeks for levels to normalize, additional potassium and magnesium can be added to feeds when indicated (recipe is included in Table 22-18). However, most premixed feedings (eg, F-75, F-100, Plumpy'Nut) will contain adequate amounts.
3. Edema may be partly caused by electrolyte imbalances. Do not use diuretics to treat edema in severely malnourished children, as it is counterproductive.

Table 22-14. Treatment and Prevention of Hypothermia	
Treatment	**SYMPTOMS: RECTAL TEMPERATURE BELOW 35.5°C (95.9°F), AXILLARY BELOW 35°C**
	1. Initiate feeding immediately or after rehydration if needed.
	2. Rewarm child.
	3. Provide antibiotics.
Monitor	• Rectal temperature: Monitor every 2 hours until above 36.5°C (every half hour if heater is used). • Cover child at all times. • Feel for warmth. • If hypothermic, check for hypoglycemia.
Prevention	• Initiate 2 hourly feedings. • Provide feedings day and night. • Cover child and keep away from drafts (kangaroo care is best). • Keep child dry (eg, change wet diapers, clothes, bedding). • Avoid exposure (eg, bathing, prolonged medical examinations). • Let child sleep with mother or caregiver at night for warmth.

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

Step 5: Treating and Preventing Infections

1. Normal signs and symptoms of infection (eg, fever) are usually not present in the severely malnourished child due to a weakened immune system.
2. Give a measles vaccine on admission to a child older than 6 months unless the child is in shock.
3. Provide a broad-spectrum antibiotic on admission.[74] Intravenous antibiotic choices include ampicillin or benzylpenicillin, with gentamicin or a third-generation cephalosporin (ie, ceftriaxone) as a second-line choice. The addition of chloramphenicol after 48 hours of treatment can be considered if no improvement is seen. An oral antibiotic should be used first if the child is stable with no obvious complications. Oral choices include amoxicillin with or without gentamicin intramuscularly or cefdinir (may be more effective than amoxicillin if available).[50]
4. If anorexia persists after 5 days of antibiotic treatment, continue a full 10 days of antibiotic treatment. If anorexia persists after 10 days of antibiotic treatment, reassess the child, checking for infection sites and potentially resistant organisms and if micronutrient supplements are being provided correctly.

Table 22-15. Treatment and Prevention of Dehydration

	SYMPTOMS: WATERY STOOLS
Treatment	1. ReSoMal ● 5 mL/kg every 30 minutes for 2 hours. ● Orally or by nasogastric tube. ● 5 to 10 mL/kg/h for the next 4 to 10 hours as clinically indicated. ● Target volume replacement is around 5% body weight. ● Determine the exact amount by taking into consideration —How much the child wants —Stool and vomiting losses
	2. Replace the ReSoMal doses at 4, 6, 8, and 10 hours with F-75 if rehydration is continuing at these times.
	3. Continue feeding starter F-75.
	4. During treatment, rapid respiration and pulse rates should slow down and the child should begin to pass urine.
Monitor	● Monitor every half hour for the first 2 hours. ● Monitor hourly for the next 6 to 12 hours, recording — Pulse rate — Respiratory rate — Urine frequency — Stool/vomit frequency ● Signs of rehydration (will not appear in children who are severely malnourished until fully rehydrated) — Return of tears — Moist mouth — Eyes and fontanels appearing less sunken — Improved skin turgor ● Signs of excess fluid (overhydration) or infection — Increasing respiratory rate (>5 bpm) — Increasing pulse rate (>25 bpm) — Increasing edema — Puffy eyelids ● Stop fluids immediately and reassess needs after an hour if overhydration occurs. Do not routinely give diuretics.
Prevention	When diarrhea is present ● Continue starter F-75 feedings. ● Replace stool volume losses with ReSoMal. ● Provide 50 to 100 mL after each watery stool. ● If the child is breastfed, encourage continuation.

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

Table 22-16. Recipe for ReSoMal Oral Rehydration Solution

INGREDIENTS	AMOUNT
Water (boiled and cooled)	2 L
WHO oral rehydration solution	One 1-L packet (includes 3.5-g sodium chloride, 2.9-g trisodium citrate dihydrate, 1.5-g potassium chloride, 20-g glucose)
Sugar	50 g
Electrolyte/mineral solution	40 mL

Abbreviation: WHO, World Health Organization

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

Table 22-17. Recipe for Electrolyte/Mineral Solution (Used in Preparation of ReSoMal and Milk Feeds)

- Weigh the following ingredients and make up to 2,500 mL.
- Add 20 mL of electrolyte/mineral solution to 1,000 mL of milk feed.

INGREDIENTS	QUANTITY (g)	MOLAR CONTENT OF 20 mL
Potassium chloride	224	24 mmol
Tripotassium citrate	81	2 mmol
Magnesium chloride	76	3 mmol
Zinc acetate	8.2	300 µmol
Copper sulfate	1.4	45 µmol
Water	2,500 mL	

Note: Add selenium if available (sodium selenate 0.028 g) and iodine (potassium iodine 0.012 g) per 2,500 mL.

PREPARATION

- Dissolve the ingredients in cooled boiled water.
- Store the solution in sterilized bottles in the refrigerator to slow deterioration.
- Discard solution if it turns cloudy.
- Make fresh solution each month.

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

5. Consider anti-helminth therapy for all children older than 1 year with SAM. Treatment should be delayed until the rehabilitation phase.
6. Consider metronidazole to help with healing damaged intestinal mucosa as well as for possible concurrent parasitic infections.

Table 22-18. Potassium and Magnesium Solution

- Provide 20 mL of liquid potassium and magnesium solution to 1 L of feeds or ReSoMal.

INGREDIENTS

Additional potassium	3–4 mmol/kg/d
Additional magnesium	0.4–0.6 mmol/kg/d

- When rehydrating, provide a low-sodium rehydration solution (eg, ReSoMal).
- Food prepared should be without salt.

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

7. Consider antimalarial treatment if in an endemic area or if otherwise indicated.
8. Consider HIV testing of severely malnourished children in countries where HIV is common.

Step 6: Correcting Micronutrient Deficiencies

1. Micronutrients should be supplemented to the diets of severely malnourished children if they are not already being provided in a premixed feeding product (Table 22-19).
2. Anemia is common in malnutrition. Iron may be provided once a child regains an appetite and signs of weight gain are evident (often in the second week of treatment). Providing iron too early may suppress appetite and can be fatal.

Step 7: Starting Cautious Feedings

1. The stabilization phase usually lasts up to 7 days. Hospitalization is crucial for patients with complicated SAM because of the critical and complicated condition during this state.[75]
   - In this phase, cautious feedings are initiated as soon as possible after admission to maintain basic physiologic functions and needs and provide adequate energy and protein (Table 22-20). The goal is not to begin weight gain but only to provide enough nutrients for proper physiologic functioning. Diarrhea usually starts to resolve[76] and weight loss is seen in children with edema.[71]
   - The return of an appetite is the primary sign of recovery, signaling the need for transition to catch-up feedings.

Table 22-19. Treating Micronutrient Deficiencies With Daily Supplements

1. Multivitamin supplement
2. Folic acid, 1 mg/d (5 mg on day 1)
3. Zinc, 2 mg/kg/d
4. Copper, 0.3 mg/kg/d
5. Iron, 3 mg/kg/d (but only when gaining weight)
6. Vitamin A 5,000 IU daily orally—often found in WHO-approved premixed feedings

Abbreviation: WHO, World Health Organization.

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015

Step 8: Achieving Catch-up Growth/Rehabilitation Phase

1. The rehabilitation phase typically starts around week 2 after the return of the child's appetite and lasts until week 6 of treatment. This phase aims to replenish lost nutrient stores to attain healthy weight gain.[71] This is accomplished by changing to a milk (ie, F-100) or RUTF (ie, Plumpy'Nut) that contains higher protein and energy content (Table 22-21).
2. During this phase, a child should be weighed at least every 3 days.

Step 9: Providing Sensory Stimulation and Emotional Support

1. Malnutrition can lead to delays in mental and behavioral development.
2. To avoid such delays, it is important to provide emotional care and sensory stimulation as part of the treatment process, involving the child's caregiver as much as possible.

Step 10: Preparing for Follow-up and Recovery

1. Recovery criteria should include weight for height being greater than -2 *z* score. Weight for age tends to be low secondary to stunting in children recovering from severe malnutrition. The percentage of weight gain is no longer acceptable criteria. The child should have a MUAC greater than 125 mm and no edema for more than 2 weeks.
2. Close follow-up as an outpatient or with home visits is crucial for long-term recovery. To reduce relapse, it is very important that the caregiver is aware of diet goals and is instructed on how to continue to provide necessary care.

Table 22-20. Treatment During Stabilization Phase

<table>
<tr><td rowspan="4">Treatment</td><td>Feeding Route</td><td>

Oral or nasogastric feeds (never parenteral preparations).
Feed from a cup; very weak children may be fed by spoon, dropper, or syringe.
Breastfeeding

Encourage mother to continue breastfeeding.
Provide the prescribed amounts of starter formula to make sure the child's needs are met.

Indication for nasogastric feeds

Provide remaining feed by nasogastric tube if, after allowing for any vomiting, intake does not reach 80 kcal/kg/d (105 mL starter formula/kg) despite frequent feedings and encouraging.
Do not exceed 100 kcal/kg/d in this phase.

</td></tr>
<tr><td>Composition</td><td>

Small, frequent feeds of low osmolarity and low lactose.
In most cases, milk-based starter F-75 is adequate for most children.
Starter F-75 provides

75 kcal/100 mL
0.9 g protein/100 mL

</td></tr>
<tr><td>Needs</td><td>

100 kcal/kg/d
1–1.5 g protein/kg/d
130 mL/kg/d of fluid (100 mL/kg/d if the child has severe edema)

</td></tr>
<tr><td>Intake</td><td>
Recommended Feeding Schedule
<table>
<tr><th>DAYS</th><th>FREQUENCY</th><th>vol/kg/FEED</th><th>vol/kg/d</th></tr>
<tr><td>1–2</td><td>2 hourly</td><td>11 mL</td><td>130 mL</td></tr>
<tr><td>3–5</td><td>3 hourly</td><td>16 mL</td><td>130 mL</td></tr>
<tr><td>6–7+</td><td>4 hourly</td><td>22 mL</td><td>130 mL</td></tr>
</table>

With good appetite and no edema, this schedule can be completed in 2 to 3 days (eg, 24 hours at each level).

</td></tr>
<tr><td>Monitor and Record</td><td colspan="2">

Intake amounts offered and left over
Vomiting
Frequency of watery stool
Daily body weight

</td></tr>
</table>

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

Table 22-21. Treatment During the Rehabilitation Phase

TREATMENT DURING TRANSITION		MONITOR DURING TRANSITION
Initiate	• Approximately 1 week after admission. • Signaled by return of appetite. • Gradually transition to avoid risk of heart failure, which can occur if a child suddenly consumes huge amounts.	• Respiratory rate • Pulse rate If respirations increase by 5 or more breaths per minute and pulse by 25 or more beats per minute for 2 successive 4-hourly readings, reduce the volume per feed (give 4 hourly F-100 at 16 mL/kg/feed for 24 hours, then 19 mL/kg/feed for 24 hours, then 22 mL/kg/feed for 48 hours, then increase each feed by 10 mL as above).
Goal	• Vigorous feeding to achieve very high intake and rapid weight gain of more than 10 g gain/kg/d	
Intake	• F-100 — Milk based — Containing 100 kcal and 2.9 g protein/100 mL • RUTFs such as Plumpy'Nut • Modified porridges — If with comparable energy and protein concentrations to F-100 • Modified family foods — If with comparable energy and protein concentrations	
Method	• Transition between starter and catch-up formula — Replace starter F-75 with the same amount of catch-up formula F-100 for 48 hours. — Thereafter, increase each successive feed by 10 mL until some feed remains uneaten. — The point when some remains unconsumed is likely to occur when intake reaches about 30 mL/kg/4-h feed (200 mL/kg/d).	

Table 22-21. Treatment During the Rehabilitation Phase, continued

TREATMENT DURING TRANSITION		MONITOR DURING TRANSITION
Intake	1. Frequent feeds (at least 4 hourly) of unlimited amounts of a catch-up formula. 2. 150 to 220 kcal/kg/d 3. 4 to 6 g protein/kg/d 4. If the child is breastfed, encourage to continue *(Note:* Human milk does not have sufficient energy and protein to support rapid catch-up growth).	• Weigh child each morning before feeding. • Plot weight. • Each week calculate and record weight gain as g/kg/d. **To calculate weight gain** (example for a 7-day period) • Subtract from today's weight (in g) the child's weight 7 days earlier. • Divide by 7 to determine the average daily weight gain (g/d). • Divide by the child's average weight in kg to calculate the weight gain as g/kg/d. • Weight gain — Poor (<5 g/kg/d): Requires full reassessment. — Moderate (5–10 g/kg/d): Check if intake targets are met or for presence of infection. — Good (>10 g/kg/d): Continue to praise staff and mothers.

Abbreviation: RUTF, ready-to-use therapeutic food.

Adapted from Ashworth A, Khanum S, Jackson A, Schofield C. *Guidelines for the Inpatient Treatment of Severely Malnourished Children.* Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/nutrition/publications/guide_inpatient_text.pdf. Accessed June 8, 2015.

3. The child *needs*
   - Macronutrients
     - — At least 150 kcal/kg/d.
     - — At least 4 g protein/kg/d.
     - — Consider discharging the caregiver with RUTFs to cover these demands if available.
   - Micronutrients
     - — Provide 20 mL (4 teaspoon) electrolyte/mineral solution daily in feeds to mask flavor (1 teaspoon/200-mL fluid).
     - — Provide vitamin A every 6 months.
   - Meals
     - — At least 5 meals per day.
     - — High energy and protein content.
       - Approximately 100 kcal and 2 to 3 g protein per 100 g
     - — Encourage child to finish entire meal.
   - Snacks
     - — Provide snacks with high energy content between meals.
     - — Often continuation of RUTF supplements can be helpful during this transition period.
4. Encourage follow-up and booster immunizations to minimize chance of relapse.

Special Circumstances: Malnutrition in Infants Younger Than 6 Months

Traditionally, little has been known about the prevalence of malnutrition in infants younger than 6 months, and the hallmark of prevention is exclusive breastfeeding for the first 6 months of life. However, recent research shows that the prevalence of malnutrition in the younger-than-6-months age group is quite prevalent, reaching levels of greater than 30% in some countries, with a mean prevalence of 15% in many lower-income countries. Furthermore, using the WHO standards nearly doubles the prevalence.[77] The goals of treatment for severe malnutrition are generally the same in this age group, with a couple of differences. First of all, because most of these children have not been exclusively breastfed, the goal is to return the child to exclusive breastfeeding whenever possible. Often there is a transitional period when supplemental formula is used until the mother is able to give adequate breast milk feedings and the child is gaining weight well. The WHO recommends using human milk, infant formula, F-75, or diluted F-100 (1:1.5 ratio of formula to water), in that order, for feeding infants younger than 6 months. If the infant has been adequately and exclusively breastfed from birth, an organic cause should be sought for the malnutrition. Often, these young

infants will require a higher caloric intake than older children to gain appropriate weight (>5–10 g/kg/d).

MICRONUTRIENT DEFICIENCIES

For centuries, generalized malnutrition has plagued many people, especially those who are economically disadvantaged and those who are displaced by political and social problems. During the second half of the 20th century, the Green Revolution involved using new agricultural technologies and procedures to boost overall production. As a result, generalized malnutrition became less common. At the same time, however, dietary intake became less varied in many regions, and micronutrient deficiencies again emerged as causes of specific pathologic clinical conditions in children.

Today, millions of children around the world suffer from specific micronutrient deficiencies. Rather than relegating conditions (eg, scurvy, beriberi, rickets) to history books, clinicians must be prepared to recognize and manage micronutrient deficiencies when caring for children in lower-income countries.

Table 22-22 summarizes key features of important micronutrients. Figure 22-11 identifies common symptoms and signs of micronutrient deficiencies.

SPECIFIC MICRONUTRIENT DEFICIENCIES

Vitamin A[78,79]

Importance

Vitamin A deficiency is the major cause of preventable blindness in the world. Hypovitaminosis A is also linked to increased infection-related morbidity and mortality, especially following diarrhea and measles. Of course, vitamin A deficiency is also seen anywhere in the world where a child has a problem with fat malabsorption, such as celiac disease, cystic fibrosis, and hepatic insufficiency.

Physiology

Vitamin A refers to retinol and related compounds that share a beta-ionone ring (eg, retinal and retinoic acid). Dietary vitamin A consists of retinyl esters from animal sources (ie, liver, dairy, kidney, and eggs) and from plants (ie, carotenoids, such as beta-carotene in green and yellow vegetables). Vitamin A is absorbed through the intestines and stored in the liver. Retinol is important in the growth and integrity of epithelial cells; the retina uses retinal to promote normal vision and retinoic acid to promote glycoprotein synthesis.

Table 22-22. Causes, Manifestations, Management, and Prevention of Major Micronutrient Deficiencies

NUTRIENT	ESSENTIAL FOR THE PRODUCTION OR FUNCTION OF	CAUSES OF DEFICIENCY	MANIFESTATION OF ISOLATED DEFICIENCY	MANAGEMENT AND PREVENTION
Iron	• Hemoglobin • Various enzymes • Myoglobin	• Poor diet • Elevated needs (eg, while pregnant, in early childhood) • Chronic loss from parasite infections (eg, hookworms, schistosomiasis, whipworm)	• Anemia and fatigue • Impaired cognitive development • Reduced growth and physical strength	• Foods richer in iron and with fewer absorption inhibitors • Iron-fortified weaning foods • Low-dose supplements in childhood and pregnancy • Cooking in iron pots
Iodine	• Thyroid hormone	• Except where seafood or salt fortified with iodine is readily available, most diets worldwide are deficient.	• Goiter, hypothyroidism, constipation • Growth retardation • Endemic cretinism	• Iodine supplement • Fortified salt • Seafood
Vitamin A	• Eyes • Immune system	• Diets poor in vegetables and animal products	• Night blindness • Xerophthalmia • Immune deficiency • Increased childhood illness • Early death • Contributes to development of anemia	• More dark-green leafy vegetables, animal products • Fortification of oils and fats • Regular supplementation
Zinc	• Many enzymes • Immune system • Wound healing	• Diets poor in animal products • Diets based on refined cereals (eg, white bread, pasta, polished rice)	• Immune deficiency • Poor wound healing • Acrodermatitis • Increased childhood illness, early death • Complications in pregnancy and childbirth	• Zinc treatment for diarrhea and severe malnutrition • Improved diet

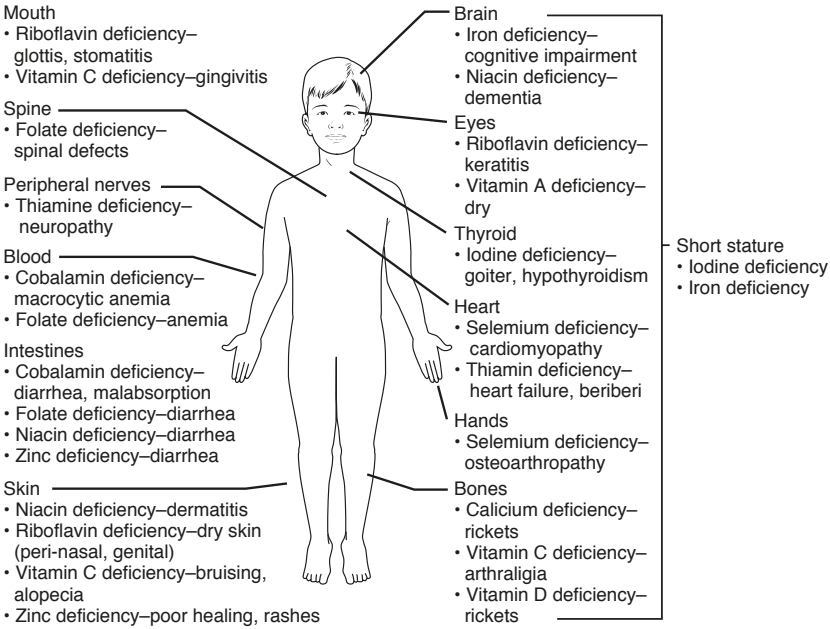
Table 22-22. Causes, Manifestations, Management, and Prevention of Major Micronutrient Deficiencies, continued

NUTRIENT	ESSENTIAL FOR THE PRODUCTION OR FUNCTION OF	CAUSES OF DEFICIENCY	MANIFESTATION OF ISOLATED DEFICIENCY	MANAGEMENT AND PREVENTION
Thiamine (B_1)	• Coenzyme for various metabolic pathways	• Diets poor in meat, eggs, legumes • Poor dietary diversity	• Beriberi (causing heart failure and peripheral neuropathy) • Wernicke encephalopathy (ophthalmoplegia with nystagmus and ataxia)	• Maternal intake during pregnancy and lactations • Supplementation
Riboflavin (B_2)	• Metabolism of protein, fat, and carbohydrate • Metabolism of other B vitamins	• Diets poor in animal protein and green vegetables • Restrictive diets	• Oral and ocular problems • Other vitamin B deficiencies • Stomatitis, glossitis, keratitis, dry skin	• Consuming a broad diet • Multivitamin supplementation • Supplementation
Niacin (B_3)	• Component of enzyme used in glycolysis	• Poor intake of meat, milk, and eggs • High intake of corn without animal protein intake	• Pellagra (with diarrhea, dementia, and dermatitis)	• Consuming a well-balanced diet • Adequate intake of animal protein • Multivitamin supplementation if on a restrictive diet • Supplementation
Folate (B_9)	• Cell growth • DNA synthesis • Red blood cell maturation	• Diets poor in fresh green vegetables and fruit • Malabsorption due to celiac disease • Short gut syndrome with bacterial overgrowth • Chronic diarrhea • Sickle cell disease	• Anemia • Neural tube defects in children born of mothers with deficiencies • Failure to thrive	• Adequate intake of fruits and vegetables • Supplementation

Table 22-22. Causes, Manifestations, Management, and Prevention of Major Micronutrient Deficiencies, continued

NUTRIENT	ESSENTIAL FOR THE PRODUCTION OR FUNCTION OF	CAUSES OF DEFICIENCY	MANIFESTATION OF ISOLATED DEFICIENCY	MANAGEMENT AND PREVENTION
Cobalamin (B_{12})	• Contributes to DNA synthesis	• Diet restricting animal products • Absent or diseased ileum	• Macrocytic anemia	• Adequate intake of animal products • Supplementation
Vitamin C (ascorbic acid)	• Hydroxylation of collagen • Capillary epithelium and osteoid tissue integrity • Antioxidant • Wound healing	• Diets poor in fruit and vegetable intake	• Scurvy (often with symptoms of severe fatigue, joint pain, excessive bruising, and bleeding gums) • Poor wound healing	• Adequate dietary intake of vitamin C • Supplementation
Vitamin D and calcium	• Vitamin D stimulates the absorption of calcium. • Calcium is for bone health.	• Poor dietary intake (fortified milk or liver). • Lack of exposure to ultraviolet sunlight. • Darkly pigmented skinned people are at higher risk for deficiency.	• Rickets • Osteomalacia • Stunting • Infantile heart failure and muscle weakness • Negatively affects risk and severity of other diseases and conditions	• Adequate sun exposure. • Vitamin D supplementation. • Adequate calcium intake. • Breastfed infants should be supplemented with vitamin D daily.
Selenium	• Several enzymes • Metabolism of free radicals	• Soil depletion of selenium causing inadequate amounts in food sources	• Myxedematous cretinism (in combination with iodine deficiency) • Keshan disease (a form of cardiomyopathy) • Kashin-Bek osteoarthropathy • Poor pregnancy outcomes • Poor longitudinal growth	• Selenium supplementation; preventively if in an area of high risk or as treatment if deficiency is identified

Figure 22-11. Effects of Micronutrient Deficiencies



Epidemiology

Approximately 28 million preschool-aged children suffer from clinical vitamin A deficiency (xerophthalmia with serum vitamin A level <0.35 mmol/dL), and 251 million have subclinical deficiency (no xerophthalmia but deficient levels).[80,81] Two-thirds of Asian children are thought to have vitamin A deficiency, while about one-half of African children are affected; deficiency is less common in other areas. Vitamin A deficiency is very common in children with generalized malnutrition, and vitamin A levels fall during the course of infections, such as measles.

Clinical Presentations

Inadequate tissue integrity, poor healing, and complications of infections, such as diarrhea and measles, occur with low levels of vitamin A, even before seeing the pathognomonic feature of hypovitaminosis A: xerophthalmia (dry eyes). Skin over extensor surfaces is dry and scaly, and similar keratinization of the conjunctiva and lacrimal glands leads to dry eyes with follicular conjunctivitis (xerophthalmia). Night blindness results from delays in rhodopsin synthesis and is considered the

earliest eye manifestation of vitamin A deficiency. Bitot spots can be seen as small, silvery, triangle-shaped patches on the conjunctiva where keratinization occurred. Inflammatory changes in the eyes lead to keratomalacia, corneal ulceration, and blindness.[78] Symptoms can be reversed with treatment as long as scarring has not already occurred. Therefore, it is imperative to recognize the symptoms of vitamin A deficiency early before keratomalacia and corneal ulcerations develop.

Prevention

Unless mothers are vitamin A deficient, human milk contains adequate levels of this vitamin to support a growing child. Supplementation (single doses of 200,000–400,000 IU) to postpartum women can increase vitamin A content in human milk.[82] When maternal hypovitaminosis A is common, supplementation is recommended during the first postpartum visit; high-dose supplementation during pregnancy might carry a risk for teratogenesis and is usually avoided. Vitamin A supplementation is suggested in areas where childhood vitamin A deficiency is common. Many countries require vitamin A to be added to frequently ingested foods, such as milk, oils, and margarines, which may be recommended. Direct supplementation with vitamin A may be preventive if such fortified foods are unavailable. Since 1987, WHO has recommended oral supplementation with 100,000 IU vitamin A at 6 to 9 months of age (the time of routine measles vaccination).[83] Additional booster doses of 200,000 IU can be given every 4 to 6 months until 4 years of age. In fact, in many areas in the developing world, the WHO immunization campaigns now include routinely giving vitamin A supplementation. While smaller daily doses could be considered, care providers in developing countries usually find that intermittent large doses are more feasibly delivered.

Treatment

Children with documented low levels of vitamin A (in the rare situations where testing is done in developing countries) or with clinical findings of xerophthalmia or night blindness should be treated for vitamin A deficiency. Daily doses of 200,000 IU (100,000 IU if <1 year) for 2 days are effective. Similarly, children younger than 2 years in lower-income countries should be given 2 days of treatment at the onset of measles.[84]

Thiamine (B_1)[78,79]

Importance

Thiamine deficiency, which causes beriberi, is widespread in Southeast Asia. Affected infants are at risk of death because of heart failure, while older children are at risk of peripheral neuropathy complications.

Physiology

Thiamine is a water-soluble vitamin that serves as a coenzyme in various metabolic pathways, including acetylcholine synthesis. It is readily available in meat, eggs, legumes, and rice but is inactivated during the cooking process. Natural rice is a good source of thiamine; however, the thiamine remains with the husks. Therefore, it is lost during the dehusking or polishing process.

Epidemiology

As previously mentioned, thiamine deficiency is common in Southeast Asia[85,86] and is a significant cause of infantile death. Wet beriberi is associated with populations who discard the washings produced during rice preparation and have low socioeconomic status and minimal dietary diversity. Beriberi is common in some refugee populations.

Clinical Presentations

Infants 1 to 6 months of age manifest thiamine deficiency as wet beriberi with right heart failure.[87] They often are irritable with a hoarse or absent cry. They sleep poorly, often vomit, and can sweat excessively. They appear critically ill (septic) and can die of heart failure within hours to days on development of symptoms.

Older children with dry beriberi have peripheral neuropathy that progresses to increasing muscle weakness, gait abnormalities, ataxia, and dysesthesias; areflexia is noted on examination. Ophthalmoplegia with nystagmus and ataxia (Wernicke encephalopathy) has been reported with thiamine deficiency.

Prevention

Infantile beriberi is prevented by ensuring adequate maternal thiamine intake during pregnancy and lactation. Mothers may be supplemented orally with 50 mg thiamine daily.

Treatment

The diagnosis of infantile beriberi should prompt treatment of mother and child. Infants are treated once with 50 mg of thiamine intramuscularly; a repeat dose can be given if symptoms are not resolving over several hours (while also evaluating and treating for sepsis and other potential confounding conditions). Less acute cases of beriberi in older children and mothers can be treated with 10 mg (young child) to 50 mg (adult) of oral thiamine daily for 1 month (assuming that adequate subsequent thiamine intake is assured).

Riboflavin (B_2)[77,79]

Importance

Riboflavin deficiency is an occasional cause of oral and ocular problems in poorly nourished children.

Physiology

Riboflavin is a precursor of enzyme cofactors important to oxidation-reduction reactions related to protein, carbohydrate, and fat metabolism. It is found in animal protein and green vegetables. Riboflavin plays a role in the metabolism of other B vitamins; other B-vitamin deficiencies are often identified concurrently with riboflavin deficiency.

Epidemiology

Riboflavin deficiency is found in malnourished children with extremely restricted diets.

Clinical Presentations

Angular stomatitis, glossitis, keratitis, and dry skin around the nose and genital area are physical signs suggesting riboflavin deficiency.

Prevention

Riboflavin deficiency is fully preventable by using a broad diet particularly consisting of at least some meat products or multivitamin preparations.

Treatment

Riboflavin deficiency is treated with 1-mg riboflavin orally 3 times daily until signs of deficiency are resolved.

Niacin (B_3)[78,79]

Importance

Niacin deficiency, commonly known as pellagra (Italian for "rough skin"), is still seen in some developing countries where malnutrition is widespread.

Physiology

Niacin is the end product of tryptophan metabolism and a building block for enzymes that are required for protein transport and glycolysis. Niacin is found in milk, meat, and eggs.

Epidemiology

Pellagra is most often seen in individuals who primarily eat maize (corn) without animal protein. Other signs of generalized malnutrition and other micronutrient deficiencies often coexist with pellagra. Individuals on isoniazid can develop isolated niacin deficiency.

Clinical Presentations

Pellagra is characterized by 3 Ds: diarrhea, dermatitis, and dementia. Glossitis and angular stomatitis accompany the diarrhea (perhaps in part because of concurrent riboflavin deficiency). Sun-exposed skin becomes painful and erythematous (or hyperpigmented in dark-skinned individuals); repeat sun exposure can lead to blistering and bullae formation. Eventually, sun-exposed skin becomes rough and scaly; hair, nails, and sun-unexposed areas are spared. Individuals may have insomnia, fatigue, irritability, and mental dullness, which progress to frank dementia.

Prevention

Regular ingestion of animal protein can prevent pellagra, as can multivitamin preparations in individuals with severely restricted diets. Maize contains some niacin but only in a poorly absorbed bound form.

Treatment

Niacin deficiency is treated orally with 50 to 100 mg of nicotinamide 3 times daily. A varied diet should be instituted and other potentially co-occurring vitamin deficiencies should be treated at the same time. Pharmacologic supplementation can be discontinued when signs and symptoms of deficiency resolve.

Folate (B_9)[78,79]

Importance

Folate deficiency contributes to anemia in many parts of the world. However, the greatest effect of this deficiency is associated with neural tube defects in children because of a deficiency in women of childbearing potential.

Physiology

Dietary folate, as contained in fresh green vegetables and some fruit, is absorbed through the small intestines. It affects cell growth by providing purine and thymine and, thus, DNA synthesis. Its effects are most obvious as they relate to red cell maturation and, with deficiency, a risk of anemia.

Epidemiology

Inadequate folate intakes are common around the world, but frank deficiency is most common in children with intestinal malabsorption caused by celiac disease, short gut with bacterial overgrowth, and chronic diarrhea. Deficiency does not seem specific to any particular geographic region or population group.[88] Children with chronic hemolysis caused by sickle cell disease have an increased need for folate and frequently become deficient.

Clinical Presentations

Folate deficiency presents with anemia, irritability, and failure to thrive. Chronic diarrhea is often present, frequently because diarrhea predisposed the child to becoming folate deficient.

Prevention

Eating multiple daily servings of fruits and vegetables is effective in preventing folate deficiency. Folate supplements (1–5 mg per day, given orally) are actually better absorbed than folate in food. Preemptive or preventive folate supplementation should be considered for children with chronic diarrhea, sickle cell disease, and other chronic hemolytic anemias (ie, thalassemia, glucose-6-phosphate dehydrogenase deficiency) and for women of childbearing age.

Treatment

When suspected or diagnosed, folate deficiency may be treated orally (or parenterally, if required) with 1 (young infants) to 5 (adolescents) mg daily. Treatment should be continued until the symptoms resolve and adequate dietary intake is established.

Cobalamin (B_{12})[78,79]

Importance

Vitamin B_{12} (cobalamin) deficiency occurs around the world but usually in individuals with no intake of animal products or with an absent or diseased ileum.

Physiology

Vitamin B_{12} is produced by microorganisms living in animals; however, humans are not capable of producing it. Ingested B_{12} combines with intrinsic factor in the stomach and is eventually absorbed in the ileum. It is stored in the liver and contributes to DNA synthesis.

Epidemiology

Vitamin B_{12} deficiency is seen around the world but is not specifically associated with any particular geographic area or population subgroup.[88] Deficiency is most common in strict vegetarians who do not eat animal products and in patients who had surgical resection involving the stomach or terminal ileum.

Clinical Presentations

Vitamin B_{12} deficiency manifests itself as macrocytic anemia, often with diarrhea and, in young infants, failure to thrive. Hyper-segmented neutrophils are noted on peripheral blood smears of deficient individuals.

Prevention

Vitamin B_{12} deficiency is avoided by eating animal products or taking supplements.

Treatment

Vitamin B_{12} deficiency is readily treated with parenteral (or oral if absorption is adequate) administration of 1 mg of vitamin B_{12}. Hematologic improvement occurs within a few days. Subsequent assurance of adequate B_{12} intake is necessary (monthly doses of 0.1 mg if dietary intake is not possible).

Vitamin C[78,79,89,90]

Importance

Scurvy, the vitamin C deficiency bane of 18th-century sailors, is uncommon. Nonetheless, it is still seen from time to time in children who do not eat fruits and vegetables.

Physiology

Some animals are able to synthesize vitamin C, but humans depend on exogenous sources. Vitamin C, otherwise known as ascorbic acid, is contained in citrus fruits, papaya, tomatoes, potatoes, spinach, and cabbage. About 90% of a human's intake of vitamin C comes from fruit and vegetable sources. Cooking reduces active vitamin C content by about one-third. Vitamin C is active in the hydroxylation of collagen and is therefore important in the formation and integrity of capillary epithelium and osteoid tissue. Ascorbic acid is an antioxidant and, thus, is relevant to several disease states. It reduces dietary iron from the ferric to the ferrous form to facilitate iron absorption.

Epidemiology

Scurvy is uncommon but does present in individuals with restricted diets (because of poverty, presumed food intolerances, or misconceptions about dietary needs). A review of 28 children with scurvy in Thailand[91] identified associations not only with an absence of dietary fruits and vegetables but also with ultrahigh-temperature milk processing; the role of heat-treated milk in altering vitamin C is not well understood. Preschoolers are more affected by scurvy than older children.

Clinical Presentations

Children with scurvy often have severe fatigue and weakness, as well as a limp because of joint pain. They may demonstrate a frog-leg posture (pseudoparalysis) because of severe joint pain. Pseudoparalysis should be distinguished from true paralysis by lifting the child from under her axilla and allowing the legs to hang freely. The child with pseudoparalysis will flex her hips from the pain caused by the sudden extension of her legs, while the child with true paralysis will be unable to flex her hips. Capillary fragility is seen as unusual skin bruising and swollen bleeding gums; splinter hemorrhages of the nail beds and subconjunctival hemorrhage may be seen. Hyperkeratotic papules and corkscrew hairs and alopecia can develop. Subperiosteal hemorrhages lead to severe bone pain and radiographic evidence of separated epiphyses. Arthralgia and myalgia are common, and hemarthrosis is possible. Wound healing is delayed. Normochromic normocytic anemia is common. Some may present with a scorbutic rosary in the costochondral regions, which can be distinguished from the rachitic rosary of vitamin D deficiency by its more angular nature and its exquisite tenderness. A serum vitamin C level below 11 mmol/L confirms vitamin C deficiency as the cause of clinical findings. Symptoms and signs of scurvy resolve rapidly with treatment.

Prevention

A daily intake of 50 mg of ascorbic acid (the amount in one orange) is recommended; however, 10 mg per day should be adequate to prevent childhood scurvy. Children should be encouraged to eat a wide variety of uncooked fruits, including guava (which contains nearly 3 times the vitamin C as oranges) and other citrus fruits.

Treatment

Children with scurvy should receive 25 mg of vitamin C 4 times a day for 1 week. Symptoms resolve within hours to days. Subsequently, adequate vitamin C intake should be ensured.

Vitamin D and Calcium[78,79,92,93]

Importance

Rickets, a consequence of calcium or vitamin D deficiency, affects up to 10% of the population in some parts of the developing world. More subtly, osteomalacia and stunting result from combined or isolated calcium and vitamin D deficiencies. In addition, hypovitaminosis D likely affects the risk and severity of diabetes, cancer, multiple sclerosis, chronic pain, and infections, including tuberculosis, leprosy, and HIV.[94] Rickets increases the risk of mortality with acute respiratory infection.[30]

Physiology

Vitamin D is produced in ultraviolet light–exposed skin or ingested in fortified dairy products or liver. Following hepatic and renal hydroxylation, biologically active 1,25-dihydroxyvitamin D stimulates calcium absorption from the intestines, calcium deposition into bones, and a variety of other metabolic actions through interactions with parathyroid hormones. In addition, there are potential metabolic, infectious, and neoplastic actions that seem to result from the influence of vitamin D receptors scattered throughout the body. Rickets results when a child's isolated calcium or vitamin D deficiency leads to an inadequate delivery of minerals to developing bones. Calcium deficiency also leads to an increased metabolic need for vitamin D, and many children get rickets with a combined insufficiency of calcium and vitamin D. Less commonly, rickets occurs because of renal disease with inadequate bioactivation of 25-hydroxyvitamin D.

Epidemiology

For centuries, rickets has been reported in northern climates of industrialized countries where young children are minimally exposed to sunlight

because of weather and cultural conditions. Rickets has reemerged as a clinical problem in North America, especially in breastfed babies with darkly pigmented skin. In developing countries, rickets occurs in infants, young children, and adolescents who are shielded from the sun (sometimes because of cultural practices, such as the Muslim purdah, or from living in crowded slum dwellings), as well as in older infants and young children with calcium-insufficient diets. Rickets has been reported in most countries of the world in recent decades. Calcium-deficiency rickets seems especially common in Nigeria, South Africa, India, and Bangladesh.

Clinical Presentations

Vitamin D–deficiency rickets traditionally presents late in the first year of life with hypocalcemic tetany or during the toddler years with curving deformities of lower limbs. Calcium-deficiency rickets usually presents with limb deformities during the toddler and childhood years. Bowed legs, knock-knees, and anterior curvature of the tibiae are all possible. Widened wrists and ankles, beaded ribs which are typically non-tender, large fontanels, chest wall deformities, and dental hypoplasia are seen with either form of rickets. Bone pain and increased fractures result from calcium or vitamin D deficiency. Infantile heart failure and muscle weakness are possible with vitamin D deficiency. When available, laboratory testing can show hypovitaminosis D (levels <10 nmol/L associated with rickets, levels 10–25 nmol/L subnormal but unlikely to cause rickets without concurrent calcium deficiency). Serum levels of 1,25-dihydroxyvitamin D are low in vitamin D–deficiency rickets but elevated in children with calcium-deficiency rickets. Alkaline phosphataselevels are elevated due to rapid bone turnover in rachitic children. Radiographs show osteopenia along with cupping, fraying, and epiphyses widening. A radiograph scoring system for the severity of rickets was developed[95] and is useful in following the adequacy of a child's response to treatment.

Prevention

Rickets is avoidable by fostering adequate sun exposure, taking vitamin D supplements, or ensuring adequate calcium intake. Infants should get at least 60 minutes per week of sunshine exposure to the head, and older children should get at least 60 minutes of head and extremity sun exposure. Human milk does not contain adequate vitamin D for children who do not have another source, but fortified formulas and processed milk often do contain adequate vitamin D. As needed, all infants and children can be supplemented with additional vitamin D to ensure at least 400 IU of daily intake.

Nigerian and South African children with calcium-deficiency rickets take in less than 25% of the recommended 800-mg elemental calcium daily allotment. Calcium intake can be encouraged by the use of dairy products, eating small fish with the bones included (ground, as in many parts of Africa, or whole, as in parts of Asia), or taking calcium supplements. Adolescents should take at least 1,200 mg of elemental calcium per day; ultimate adult bone strength likely depends on the peak bone mass achieved during adolescence.

Treatment

Children with tetany require aggressive calcium supplementation and intensive care monitoring. Children with rickets, especially when vitamin D levels are not available, should receive adequate vitamin D; this can be done by giving 2,000 to 5,000 IU vitamin D orally per day for 3 to 6 months or by giving 300,000 to 600,000 IU vitamin D intramuscularly every 3 to 6 months. After acute treatment of rickets over 6 months (and normalization of the serum alkaline phosphatase level and resolution of radiographic abnormalities, if such tests were indeed available), ongoing adequacy of sun exposure or vitamin D intake should be ensured.

Concurrently, in areas where calcium-deficiency rickets is common and in a child who presents with rickets after 12 months of age with a history of seemingly adequate sun exposure, daily oral calcium supplements should be given to provide 1,000 mg of elemental calcium (as found in 2.5 g of calcium carbonate).

Ongoing adequacy of calcium intake should be ensured after 6 months of treatment and resolution of laboratory and radiographic abnormalities. Even striking leg deformities can straighten over time with ongoing growth. Beading of ribs can persist for years. Surgery (whether scraping or stapling growth plates or actual osteotomies) should be considered when deformities limit function years after actual bone mineralization defects are resolved. Children with rickets caused by renal disease need full treatment for the underlying kidney condition.

Iodine[78,79,96,97]

Importance

Iodine deficiency is the world's leading cause of preventable brain damage. Primarily through its effects on thyroid function, iodine deficiency plagues about half of children in Asia and one-third of children in Africa.

Physiology

Iodine is an essential component of thyroid hormone. Deficiency in pregnant women can lead to endemic cretinism (severe irreversible mental retardation along with hypothyroidism). Acquired iodine deficiency in children causes goiter, hypothyroidism, and subclinical learning difficulties. Humans eat iodine when they ingest plants grown in iodine-rich soil or iodine-fortified products (eg, salt in North America). Natural products contain inadequate iodine in most parts of the world, and people must depend on iodine-fortified foods for their intake. Iodine metabolism depends on selenium and iron to some degree, and iodine-deficient children do not respond completely to iodine treatment until their selenium and iron statuses are normal.

Epidemiology

Most people in the world are at risk of iodine deficiency, but the widespread use of iodized salt obviates this risk in industrialized areas. Iodine deficiency remains common in developing countries where salt is not routinely fortified or where there is not a central (fortifiable) source of salt. Nonetheless, 35% of the world's children have inadequate iodine intakes. Approximately 90% of salt is iodized in the Americas and Caribbean and approximately only two-thirds of salt is iodized in Asia and Africa—children in these areas remain at significant risk. Consequences of iodine deficiency are most severe during pregnancy and childhood.

Clinical Presentations

Infants born to severely iodine-deficient mothers may be heavy, sluggish, and mentally retarded. Mental deficits persist even after hypothyroidism is corrected. Cretins vary from myxedematous (large and slow) to spastic (hypertonic with trouble ambulating) with deafness depending on whether selenium deficiency concurrently affected the children. Acquired iodine deficiency usually presents as goiter and is reversible with iodine replacement. Iodine-deficient children have a lower intelligence quotient by 30 points and more fine-motor control problems than do iodine-replete children. Chronically iodine-deficient children have short stature.

Prevention

Preventing iodine deficiency depends on adequate iodine intake and is best approached at community, regional, and national levels. In areas where salt fortification is not yet feasible, supplementing individual children with iodized oil leads to decreased goiter rates and decreased

hypothyroidism. Some studies also reported significant improvement in cognitive function, psychomotor ability, and growth with iodized oil.[96]

Treatment

Successfully treating iodine deficiency depends on adequate selenium and iron status; iodine therapy will be incompletely effective if other deficiencies are not corrected concurrently. Iodine may be given safely as potassium iodide orally (usually 150 mcg per day; 200 mcg per day if pregnant) or, if treatment compliance is uncertain, an intramuscular iodized oil injection (200 mg) is adequate for 1 year of coverage.

Iron[79,98]

Importance

Iron deficiency is the most common form of malnutrition in the world; by current estimates, 42% of young children on this planet are iron deficient. More than one-third of iron-deficient children are anemic, but even without anemia, iron deficiency causes neurodevelopmental compromise and altered activity tolerance.

Physiology

Iron is available in dairy products, vegetables, and meat. However, absorption varies with the iron source. Iron from vegetable sources (nonheme iron) is less well-absorbed than iron from dairy or meat sources (heme iron). Iron from human milk is best absorbed (50%), while only 4% to 10% is absorbed from (bioavailable in) infant formulas and cow's milk. Iron absorption is facilitated by vitamin C and inhibited by antacids, phytic acid (legumes, rice, and grains), polyphenol (eg, tea), and other divalent cations (ie, calcium and zinc). Pathologic iron loss occurs with gastritis, infantile cow's milk protein intolerance, and hookworm infection; excessive blood or iron loss can occur with menstruation. Iron deficiency results when iron absorption is inadequate to balance iron loss and iron needs (which increase during times of growth). Iron is directly required for red cell synthesis. Even without anemia, iron deficiency has been associated with neurodevelopmental compromise, poor academic performance, activity intolerance, and sleep disorders (specifically restless legs syndrome).

Epidemiology

In developing countries, dietary limitations (eg, minimal meat intake) combine with excessive iron losses (from cow's milk protein intolerance in some young infants and hookworm in many older infants and

children) to produce a high prevalence of iron deficiency. Normal hemoglobin levels vary with age and elevation above sea level, and anemia is defined as a sea-level hemoglobin concentration less than 10 g/dL at 4 to 6 months of age, less than 10.5 g/dL at 9 months of age, and less than 11 g/dL after a baby's first birthday.

Iron deficiency is assumed to be the cause of the anemia when it is associated with hypochromia and microcytosis or a low serum ferritin level. However, iron deficiency is 2.5 times more common than iron deficiency anemia in developing countries. Low serum ferritin levels suggest iron deficiency in the absence of an acute inflammatory condition; similarly, a low iron binding saturation suggests iron deficiency. Iron deficiency is common by whatever diagnostic criteria are used.

Three-fourths of infants in sub-Saharan Africa are anemic. About half of Asians and South Americans and one-third of North Africans are similarly affected; half of these anemic children are thought to be iron deficient. Iron deficiency is more common in resource-limited areas and former premature babies. The prevalence of iron deficiency is higher in infants and young children than in older children and adolescents. Overall, nearly half of the young children on this planet are thought to be iron deficient.

Clinical Presentations

Most young children in developing countries are iron deficient, but they rarely present for medical care due to their nutritional deficiency. Thus, screening (often by simply determining hemoglobin levels or hematocrits) is important and public health measures should be instituted in addition to managing individually diagnosed children.

Prevention

Prevention of iron deficiency should start before a child is born. Pregnant women should eat iron-rich foods and, in areas of risk, receive iron supplementation. Testing (or presumptive treatment) for hookworm is indicated in areas of high prevalence. At the time of birth, delayed cord clamping (approximately 2 minutes, until pulsations cease) allows for greater maternal-infant transfer of blood and iron.

Breastfeeding should be encouraged and supported for the first year of the infant's life. Premature and low birth weight babies should have iron supplementation (2–3 mg elemental iron per kg per day). Iron-rich foods should be added to the routine infant diet at about 6 months of age. Iron supplements should be considered for at-risk infants. Stool testing for helminths (or presumptive deworming) every 6 months during

childhood is advisable in lower-income countries. Widespread professional and lay education can help mobilize efforts to implement these interventions at community levels.

Treatment

Children found to be iron deficient should be treated with iron supplements to provide 4 to 6 mg elemental iron per kg per day for at least 3 months, and subsequent adequacy of dietary intake should be ensured. Anemic children can be presumptively treated with iron in areas with limited laboratory testing; an increase of 1 g/dL or more in hemoglobin concentration after 1 month confirms an iron-deficiency diagnosis. A lack of response to treatment (with known adherence to therapeutic regimen) could prompt a search for other causes of anemia. Blood transfusions are given when there are signs of cardiovascular decompensation due to the anemia, realizing that children with chronic anemia often become tolerant to hemoglobin levels in the 5 to 8 g/dL range.

Selenium

Importance

Rarely, selenium deficiency is seen in children with inadequate parenteral nutrition. Selenium deficiency is also seen as 3 clinical situations in distinct geographic areas of the world: central Africa in combination with iodine deficiency causing myxedematous cretinism; southwest China as a unique form of cardiomyopathy, Keshan disease; and southwest China as Kashin-Bek osteoarthropathy. These conditions are increasingly rare thanks to improved selenium nutrition.

Physiology

Selenium deficiency is uncommon except in a few areas of the world. Dietary selenium intake depends on local soil content, which determines how much selenium is in water, plants, animals, and milk. Selenium is necessary for the functioning of several enzymes and the metabolism of free radicals through glutathione peroxidase.

It is likely that selenium deficiency serves as a cofactor with other agents or conditions to produce unique clinical problems. It seems that coxsackievirus infection might interact with selenium deficiency to cause a unique cardiomyopathy in and around the Keshan province of China; the clinical presentation is similar to mitochondrial cardiomyopathies.[99] Combined selenium and iodine deficiencies affect cartilage integrity and longitudinal growth, but the exact mechanism by which selenium deficiency contributes to Kashin-Bek osteoarthropathy is unknown; in

fact, even the relevance of low selenium levels to this condition has been debated.[100]

Epidemiology

A belt running through several provinces of southwest China is associated with low selenium levels in soil, animals, and humans. Up to 100% of children show some signs of disease in some areas of China. Selenium levels are lower in parts of Scandinavia than in most other parts of the world. Northern regions of the Democratic Republic of Congo are also relatively selenium deficient. Children are more affected than adults, and poor pregnancy outcomes (miscarriages) are also seen with selenium deficiency during pregnancy.

Clinical Presentations

Selenium deficiency in Central Africa manifests itself by combining with prevalent iodine deficiency to produce myxedematous cretinism (rather than the more common spastic cretinism seen in other areas). Kashin-Bek osteoarthropathy presents as painful destruction of joint cartilage at about 5 years of age and progresses to multiple joints. Progressive joint deformity and stunting are common. Keshan cardiomyopathy occurs in children and presents with heart failure and dysrhythmia; it is often fatal, and myocardial necrosis is seen on autopsy.

Prevention

To prevent selenium deficiency in recipients of parenteral nutrition, the IV solution should include 2 mcg of selenium per kg per day. In endemic areas, prevention of selenium deficiency is effective with supplementation (usually 1 mg orally each week if <10 years; 2 mg orally each week if >10 years). Supplementation leads to significant reductions in overt disease and mortality in high-risk areas.

Treatment

Keshan cardiomyopathy is reversible with early treatment (100 mcg per day IV has been used).[101] Outcome studies are limited, but a diagnosis of selenium deficiency in a patient who is not critically ill should prompt supplementation using the same doses used for prevention.

Zinc[79]

Importance

Zinc deficiency contributes directly to morbidity and mortality due to infectious illnesses in impoverished communities around the world. It

is estimated that zinc deficiency accounts for 4% of childhood deaths and 1% of childhood disease in Africa, Asia, and Latin America.[102] Specifically, zinc deficiency was identified as an exacerbating factor in 2 of the most common killers of children: diarrhea and pneumonia. As a type 2 nutrient, zinc deficiency may prevent a child from recovering from malnutrition even if adequate calories are given.

Physiology

Zinc is an essential cofactor in a variety of metabolic pathways that greatly affect protein and energy metabolism. Zinc is readily available in meats, cheese, legumes, and grains. Deficiency affects transcription pathways and cellular synthetic functions, which result in problems with growth and resistance to infections.

Epidemiology

Zinc deficiency is widespread, especially in developing countries where generalized malnutrition is common. Most children in slums in some parts of Asia are zinc deficient.[103] It is estimated that one-fourth of the world's population is at risk of zinc deficiency.[102]

Clinical Presentations

Isolated severe zinc deficiency is rare and presents as perioral and perianal dermatitis, diarrhea, increased susceptibility to infection, and poor growth. Less-severe zinc deficiency is not characterized by the dermatologic findings but aggravates gastrointestinal and respiratory diseases in children who grow poorly.

Prevention

Adequate general dietary intake prevents zinc deficiency. Daily (20 mg) or weekly (70 mg) supplements are effective for children in deprived areas of the world. In areas where zinc deficiency is common, children with diarrhea recover better if they are concurrently treated with zinc (10 mg daily for 2 weeks if <6 months; 20 mg per dose for older infants and children).[102,104] Pre-illness zinc supplementation decreases the incidence of childhood pneumonia but likely does not alter the course of established respiratory infection.[105]

Treatment

Severe zinc deficiency responds within days to daily zinc supplements of 20 to 30 mg orally. Daily (1 mg/kg/d) and weekly (70 mg) supplements for mildly deficient young children have similar favorable effects.

MALNUTRITION: THE FUTURE

What We Know

It is said that Isaac Newton claimed he could only extend scientific knowledge "by standing on the shoulders of giants"; that is, by building on the foundation others laid for him. Like Newton, we are poised to extend the scientific and clinical conquest of malnutrition to greater levels of success. We do so, however, not by standing on the shoulders of giants but by rising above the collective experience of the starving masses who have gone before us. We learn from their tragic sacrifices and we implement better strategies to avoid the intolerable burden of childhood malnutrition.

Malnutrition is often an economic problem directly related to living in poverty. We know that more than 1 billion people on the planet are hungry.[1] We know that 2 million children, mostly in the resource-limited countries of Asia and Africa, die each year from malnutrition.[5,6,106] We know that up to half of children in developing countries experience subtle (and not-so-subtle) effects of generalized malnutrition or specific micronutrient deficiencies.[6] These children are sometimes crippled or blinded by their malnutrition. Other times, they are weakened and diseased. And sometimes, they look OK but fail to reach their developmental, academic, social, and economic potential because of their nutritional deficiencies. We know that families, communities, and countries are suffering from inadequate nutrition.

We know that poverty is a problem, yet we realize that much of the planet's population lives in luxury. We know that there are significant disparities in the allocation of resources, with 20% of the world's population garnering 75% of the planet's resources.[106] We know that more than half of the world's people live on less than the equivalent of $2.50 per day.[107] Yet we also know that there are ways to combat poverty—top-down,[108] community-up,[109] and social mobilization.[110]

However, we also know that malnutrition is complex. It is often a matter of poverty, but it is also often a matter of other social and political issues. It is affected by war. Armed conflict, for instance, diverts agricultural workers to soldiering, decreases security of gardens and food, and displaces families, all with resulting increases in malnutrition. Overall, nearly one-fifth of children in the developing world lack secure sources of daily food.[14]

We know that malnutrition is a health problem and that malnutrition aggravates and is aggravated by other health problems. We know

that major child killers such as diarrhea, pneumonia, malaria, and birth asphyxia are tangled up with malnutrition.[111]

We know how to define and diagnose various forms of malnutrition. We know how to assess and alter the course of malnutrition. We know how to use individual supplements and integrated systems to combat malnutrition.

And we know that we care. We are involved with this chapter and this book precisely because we want to get involved in solutions. To us, malnutrition is not merely an academic exercise but rather an active experience. We know that we must personally and collectively engage in the battle to improve individual and societal outcomes for people currently experiencing malnutrition, and we know that we must support ongoing efforts to prevent malnutrition in the next generation.

What We Need to Do

Aware of large issues and societal approaches to malnutrition, we must now work to help children who are suffering from generalized malnutrition or micronutrient deficiency. Affected children must be identified and monitored. Appropriate care for concurrent illnesses must be instituted. A holistic approach, as identified by WHO,[14] must be followed to help those most severely affected. We must consider the possibility of micronutrient deficiency while caring for asymptomatic and ill children in developing countries, and we must treat those deficiencies appropriately. Treating malnutrition is not glamorous or easy, but it is necessary. While working clinically with malnourished individuals, we must combat systems that foster malnutrition. We must advocate for food security, protection of children from the effects of armed conflict, equitable distribution of vaccines, development of improved water sources and better sanitation, and child-appropriate health policies. At the same time, we should partner with multinational organizations to improve distribution of resources. We should support research about micronutrients and cognition, food fortification and supplementation, and population-based implementation of nutritional programs.

The Next Generation

Science has advanced enough to adequately inform our prescriptions of care for malnourished children. We know what needs to be done for individuals and groups, but we must continually use evidence-based research to improve our care.[112] What mostly remains, however, is to learn to implement systems better to ensure that appropriate care reaches the most needy children. We must continue to work toward

systems that rectify existing disparities in the availability of adequate nutritional care and health interventions. Mostly, though, we must avoid paralysis of analysis. The children of our current and next generations need action—action that we are now able to undertake.

KEY POINTS

- Childhood malnutrition is a serious global health issue resulting from a multiplicity of complex and interrelated factors, including financial, geographic, political, cultural, and educational causes.
- Although Asia has typically been the area of highest prevalence of malnutrition, East Africa is currently experiencing the greatest increase in malnutrition disorders.
- Malnutrition increases morbidity and mortality associated with the most common causes of childhood illness, including diarrhea, acute respiratory infections, malaria, measles, and HIV/AIDS.
- Proper nutrition, often including supplementation of important micronutrients such as zinc and vitamin A, can reduce mortality from these common illnesses.
- Anemia in children living in underdeveloped countries is often multifactorial. Malaria should be considered in addition to dietary and helminth causes.
- Exclusive breastfeeding for the first 6 months of life reduces malnutrition in infants and reduces frequency and severity of numerous common childhood illnesses; as such, it is an important strategy for reducing the devastating effects of malnutrition.
- Malnutrition is arguably the most critical health issue facing children in the developing world, contributing to more than 50% of the mortality in children younger than 5 years.
- Malnutrition results in numerous metabolic abnormalities that form the basis for proven treatment strategies.
- Malnourished children should be identified and treated early in the course of their disease to prevent sequelae and mortality.
- Diagnosis of malnutrition should be based on multiple anthropometric measurements when available, developmental survey, and clinical signs of macronutrient and micronutrient deficiencies.
- Once identified, malnourished children should be placed in a community or hospital-based treatment plan as appropriately determined by appetite and presence of comorbidities.
- The WHO 10 steps are a proven beneficial strategy for treatment of SAM and should be strictly adhered to for inpatient treatment of malnutrition.

- Despite reductions in generalized malnutrition rates, micronutrient deficiencies continue to plague much of the developing world because of lack of diversity in diets, cultural issues, and lack of education concerning pediatric nutritive needs.
- Many of these nutritional deficiencies can be prevented simply by providing a balanced meal plan, including fresh fruits and vegetables and some animal products. In fact, children receiving adequate animal products in their diets rarely develop generalized malnutrition or micronutrient deficiencies.
- Adequate maternal micronutrient supplementation is important for preventing micronutrient deficiencies in newborns and breastfed infants.
- Treatment of micronutrient disorders requires acute replacement of the deficient nutrient as well as continued adequate dietary intake throughout childhood.

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CHAPTER

23

Common Infections

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INTRODUCTION

Infection is the leading cause of morbidity and mortality in children worldwide. More than 6 million children younger than 5 years died in 2012. Pneumonia, birth asphyxia, diarrhea, and malaria were among the most common causes. Most deaths were in the first year of life. Death rates were 16 times higher in sub-Saharan African countries than in developed countries. In Africa, respiratory infections, malaria, diarrhea, HIV, and tuberculosis (TB) are common causes of death. More than 90% of HIV-positive children live in Africa. Much of the mortality is confounded by malnutrition, which leads to stunted growth, weakened immune systems, and an increase in infections. Affected children often live in communities with inadequate sanitation and poor water quality, increasing the risk for parasitic infections, enteric fever, and diarrheal diseases.[1]

Because the morbidity and mortality associated with infections acquired in developing countries is significant, recognition and early treatment are imperative. Clinicians must differentiate between minor, self-limiting illnesses and diseases such as malaria, enteric fever, pneumonia, shigellosis, and meningococcal meningitis. In most instances, fever will not be the only manifestation of disease. Chills, sweats, headaches, fatigue, coughing, difficulty breathing, neck pain, malaise, vomiting, diarrhea, and abdominal pain may be present and help with clinical diagnosis. However, challenges remain. Malnourished and immunocompromised children with serious infections may not mount a febrile reaction or may have atypical clinical features.

This chapter provides a framework for health care professionals to assist with management of patients with common infectious diseases. Special emphasis is given to the approach to the febrile child, especially those who reside in developing countries and who traveled to non-endemic regions. Malaria, enteric fever, meningitis, respiratory infections, and dengue will receive specific attention.

APPROACH TO THE CHILD WITH A SUSPECTED INFECTION: DIAGNOSIS AND MANAGEMENT

Fever is a frequent manifestation of disease in children. In most cases, it is indicative of an infectious process. Fortunately, most are mild and self-limiting and require no medical intervention. However, in many parts of the world, fever may be the initial sign of a serious infection such as malaria, dengue, or enteric fever. In most countries, respiratory infections caused by viruses or bacteria are responsible for a significant degree of morbidity and mortality in children. Measles still remains an important cause. Of the estimated 6.9 million deaths in children younger than 5 years reported worldwide in 2011, two-thirds were caused by infectious diseases. While pneumonia was the leading cause of death (18%), diarrhea and malaria were responsible for 11% and 7% of deaths, respectively.

Stanfield provided one of the first comprehensive reviews detailing the diverse spectrum of etiologies for fever in children living in the tropics.[2] Bacteremia, malaria, meningitis, otitis media, pneumonia, diarrheal infections, and acute rheumatic fever were among the most common.[2] Diarrhea and malaria were the most common among hospitalized children returning from the tropics with febrile illnesses. A treatable cause for the febrile illness was identified in only 46% of children.[3] Dengue is a frequent cause of fever in parts of Asia and Latin America. Eight percent of ill children returning from international travel were found to have malaria; 69% of these children required hospitalization. Most cases were caused by *Plasmodium falciparum* following travel to sub-Saharan Africa. Only 1% to 2% had dengue and enteric fever.[4]

At times, clinical presentations in children will differ from those observed in adults. The well-described classical fever patterns associated with malaria in adults are rarely observed in children, in whom patterns are more erratic. It is important to remember that not all febrile illnesses represent an infection. Fever is frequently part of systemic juvenile idiopathic arthropathies, acute rheumatic fever, Kawasaki disease, and certain malignancies.

Access to diagnostic technology is limited in many parts of the world. Health care professionals have to rely on a review of symptomatology

and physical examination to determine the most appropriate therapy. Guidelines have been developed with the hope of identifying those patients who are most likely to benefit from specific therapies and whom will need to be referred for hospitalization.

Integrated Management of Childhood Illness (IMCI) guidelines were developed by the World Health Organization (WHO) and United Nations Children's Fund to assist clinicians in management of children with febrile illnesses. Their goal is to help identify those patients most likely to have malaria and other serious bacterial infections and provide prompt and appropriate therapy. They were mostly developed for regions of the world with limited access to care and therapies. However, IMCI guidelines are not a perfect tool because patients with coughing or breathing difficulty may be diagnosed as pneumonia. These findings can be observed in other non-respiratory problems such as typhoid, malaria, and bacteremia.[5–7]

In the IMCI guidelines, fever is defined as having a child with a history of fever, "feeling hot," or an axillary temperature of 37.5°C or above. A classification into a high or low malaria risk category determines if the child receives empiric antimalarial or antibiotic therapy. A runny nose or an exanthem diminishes the likelihood of malaria. Febrile children who are likely to have malaria would receive antimalarial therapy, and those with suspected bacterial infections would receive antibiotics.[6]

A test of the guidelines in a region of low malaria prevalence revealed that 78% of those with bacterial infections received antibacterial therapy, 100% of those with meningitis, 95% of those with pneumonia, and 95% of children with otitis media. Children with bacteremia, dysentery, or skin infections received therapy, but at a lower percentage—less than 50%.[8] In a study out of Papua New Guinea, the use of antibiotics in children with mild pneumonia did not appear to affect outcomes when compared with non-recipients.[9] In the study cohort, 54% of cases received an antibiotic when, according to IMCI guidelines, only 36% should have received treatment. Forty percent of patients were treated according to guidelines.

Using WHO guidelines can lead to the undertreating of children with bacterial infections. In an area of high malaria transmission, use of guidelines failed to identify close to one-third of children with invasive bacterial disease.[10] Caution is merited when using IMCI guidelines in the diagnosis of HIV infection. In a study by Diener and colleagues in Kenya, their use was associated with a median delay of 5.9 months in the diagnosis of HIV infection in the first year of life.[11]

Identifying a causative pathogen for a febrile illness is easier when the person traveled to an area where the pathogen is endemic and returned to a non-endemic area. Specific incubation periods are helpful in determining a possible etiology. A too-short or too-long incubation period could eliminate consideration of some conditions. However, this may not be possible for children living in endemic regions. Box 23-1 lists diseases according to incubation period. Incubation periods of fewer than 14 days would support the diagnosis of malaria, dengue, rickettsial infection, leptospirosis, and typhoid fever. Incubation periods longer than 14 days would rule out dengue. Incubation periods of various mosquito-borne viral infections frequently overlap with median incubation periods of 3 days (range 3–7 days) for chikungunya, with 75% of patients with dengue developing symptoms by day 7.[12] Known exposures to individuals with an infectious condition, such as measles or chickenpox, may help the clinician by providing a precise incubation period.

It is important to remember that more than 30% of febrile illnesses are caused by more "cosmopolitan-type" infections, such as acute otitis media, pharyngitis, infectious mononucleosis, soft tissue infection, and urinary tract infection.

Physical findings on examination may lead to a diagnosis. Purpura may suggest meningococcal disease; eschars and chagomas may support the diagnosis of rickettsioses or Chagas disease, respectively. The presence of lymphadenopathy, tonsillitis, and hepatosplenomegaly would suggest infectious mononucleosis, possibly by Epstein-Barr virus. A person with fever and polyarthritis in northern Australia may represent Ross River fever, but it may represent chikungunya viral infection in islands of the Caribbean. Vesicular and vesiculopustular exanthems can be observed with a multiplicity of different conditions, such as rickettsialpox, disseminated herpes simplex virus in a young infant, or chickenpox. Vesicular lesions are observed in patients with monkeypox. Endemic mycoses, such as coccidioidomycosis and histoplasmosis, can present with erythema nodosum. Persons with TB may have a similar exanthem. Regional lymphadenopathy with an eschar may suggest tularemia. Unfortunately, fever may be the only manifestation early in the illness; physical examination may still be of limited benefit. Box 23-2 provides differential diagnoses according to syndromic features. Signs and symptoms, such as meningismus, headache, vomiting, and photophobia, all suggest a central nervous system (CNS) infection such as meningitis. A diagnostic flow chart based on clinical manifestations is provided in Box 23-3 as a tool to assist clinicians in the management of children with suspected infections.

Box 23-1. Incubation Periods for Common Infections That Cause Fever

INCUBATION PERIOD <14 DAYS

- Malaria
- Dengue
- Rickettsial infections (eg, *Rickettsia africae, Ehrlichia*)
- Acute HIV retroviral syndrome
- Leptospirosis
- Enteric fever (ie, typhoid, paratyphoid fever)
- Diarrheal illnesses (eg, shigellosis, salmonellosis, campylobacteriosis)
- Brucellosis
- Viral respiratory infections (eg, influenza, hantavirus, respiratory syncytial virus)
- Endemic mycoses (eg, histoplasmosis, coccidioidomycosis, blastomycosis)
- Acute toxoplasmosis
- Relapsing fever
- Trichinosis
- Trypanosomiasis
- Viral hemorrhagic fevers
- Yellow fever
- Meningococcal sepsis and meningitis
- Pneumococcal sepsis and meningitis
- Enteroviral infections (including poliomyelitis)

INCUBATION PERIOD 2–6 WEEKS

- Malaria
- Enteric fever (ie, typhoid, paratyphoid)
- Hepatitis A and E
- Acute schistosomiasis (eg, Katayama fever)
- Leptospirosis
- Amebic liver abscess
- Q fever
- Acute HIV retroviral syndrome
- Tuberculosis
- Brucellosis
- Infectious mononucleosis
- Toxoplasmosis

INCUBATION PERIOD >6 WEEKS

- Malaria
- Tuberculosis
- Hepatitis B
- Visceral leishmaniasis
- Schistosomiasis
- Amebic liver abscess
- Brucellosis
- Visceral larva migrans
- Bartonellosis
- Histoplasmosis
- Coccidioidomycosis
- Paracoccidioidomycosis
- Filariasis
- Fascioliasis

Box 23-2. Febrile Syndromes

FEVER AND HEPATITIS
- Hepatitis A, B, and E
- Leptospirosis
- Infectious mononucleosis
- Amebiasis (eg, liver abscess)

FEVER AND EOSINOPHILIA
- Schistosomiasis (eg, Katayama fever)
- Ascariasis
- Strongyloidiasis

FEVER AND LYMPHADENOPATHIES
- Toxoplasmosis (mononucleosis-like)
- Epstein-Barr virus (mononucleosis-like)
- Cytomegalovirus
- Tularemia
- HIV (eg, acute retroviral syndrome)
- Brucellosis

FEVER AND ARTHROPATHIES
- Ross River virus
- Chikungunya virus
- Dengue
- Lyme borreliosis
- Pyogenic septic arthritis
- Acute rheumatic fever
- Human parvovirus B19

FEVER AND DIARRHEA
- Shigellosis
- Salmonellosis
- Amebiasis
- Campylobacteriosis
- *Clostridium difficile* enteritis
- Diarrheogenic *Escherichia coli* (eg, enterotoxigenic, enterohemorrhagic, enteroaggregative)
- Rotavirus

FEVER: CHRONIC, RELAPSING, RECURRENT
- Malaria
- Relapsing fever (eg, louse-borne, tick-borne)
- Enteric fever
- Brucellosis
- Q fever
- Leptospirosis
- Familial Mediterranean fever

FEVER AND HEMORRHAGIC MANIFESTATIONS
- Dengue
- Yellow fever
- Lassa fever
- Rift Valley fever
- Viral hemorrhagic fevers (eg, Machupo, Marburg, Ebola)
- Meningococcal

Box 23-2. Febrile Syndromes, continued

FEVER AND EXANTHEM (TYPE)

- Dengue (maculopapular)
- Chikungunya (maculopapular)
- Measles (maculopapular)
- Rubella (maculopapular)
- Rickettsial (maculopapular, eschar, petechial, vesiculopustular)
- *Neisseria meningitidis* (petechial, purpura)
- Enterovirus (maculopapular)
- Drug reactions (erythema multiforme)
- Varicella-zoster virus (vesicular)
- Histoplasmosis, coccidioidomycosis, blastomycosis (erythema nodosum)
- Tuberculosis (erythema nodosum, papulonecrotic tuberculids)
- Monkeypox (vesicular)
- Syphilis (maculopapular)
- Yellow fever (maculopapular)

FEVER AND CENTRAL NERVOUS SYSTEM DISEASE

- *Neisseria meningitidis* meningitis
- *Streptococcus pneumoniae* meningitis
- Enterovirus
- Coccidioidomycosis
- Malaria
- Arboviral meningoencephalitis
- Rabies
- Japanese encephalitis virus
- West Nile virus
- Tuberculosis
- *Angiostrongylus* (eg, eosinophilic meningitis)

FEVER AND ABDOMINAL PAIN

- Enteric fever (eg, typhoid, paratyphoid)
- Yersiniosis
- Adenovirus
- Liver abscess

FEVER, RESPIRATORY SYMPTOMS, AND PNEUMONIA

- Pneumococcal
- Influenza
- Respiratory syncytial virus
- Tuberculosis
- Histoplasmosis
- Coccidioidomycosis
- Adenovirus
- Legionellosis
- Q fever
- Plague
- Tularemia
- Diphtheria
- Anthrax
- Hantavirus

Box 23-3. Approach to the Child With a Suspected Infection Living in the Tropics

Step 1: Is the child febrile? Does the child have respiratory symptoms? Does the child have an exanthem?

Fever is defined as axillary temperature ≥37.5°C, history of fever, or "feels hot."

Step 2: Decide management of the child based on signs and symptoms.

Rule: **Before considering etiologies, clinicians must be familiar with specific conditions that are endemic to the region where they practice or at-risk activities that may lead to exposure and disease (eg, malaria, dengue, rickettsial infections, leptospirosis).**

I. RESPIRATORY SYMPTOMS OR FINDINGS

A. Nasal congestion, rhinorrhea, watery eyes, sore throat, ±coughing: **Upper respiratory tract infection, most likely viral**

Supportive care only—no antibacterial therapy needed

B. Sore throat, no coughing, no congestion, foul-smelling breath, pharyngitis/tonsillitis with exudates: **Streptococcal pharyngitis—tonsillitis likely**

Oral antibacterial therapy indicated—penicillin, amoxicillin

C. Coughing, tachypnea; may be accompanied by congestion, sore throat, ±wheezing; crackles on examination: **Pneumonia likely. Nasal congestion with wheezing: likely viral.**

Antibacterial therapy indicated—amoxicillin, amoxicillin-clavulanic acid, cephalosporin, macrolide

II. SKIN OR MUCOSAL FINDINGS

A. Nasal, congestion, coughing, maculopapular exanthem, ±Koplik spots: **Measles, highly probable**

Supportive care

B. Purpura, petechial exanthem; poor perfusion: **Meningococcal sepsis**

Intravenous fluids, intravenous antibacterial therapy: third-generation cephalosporin such as ceftriaxone

C. Eschars, ±regional adenopathy; ±petechial exanthem: **Rickettsial infection**

Antibacterial therapy, all ages—doxycycline

D. Jaundice, ±hepatosplenomegaly, ±adenopathy: **Hepatitis A and E likely. Hepatitis B and C possible. Acquired toxoplasmosis may have similar presentation.**

Supportive care

Box 23-3. Approach to the Child With a Suspected Infection Living in the Tropics, continued

E. Jaundice, hepatosplenomegaly, adenopathy, exudative tonsillitis: **Infectious mononucleosis due to Epstein-Barr virus or cytomegalovirus**

Supportive care; prednisone for marked tonsillar hypertrophy

F. Jaundice, hepatosplenomegaly, conjunctival suffusion, renal dysfunction, ±mental status changes: **Leptospirosis**

Antibacterial therapy—penicillin is agent of choice. Alternatives: erythromycin or doxycycline.

III. CENTRAL NERVOUS SYSTEM FINDINGS

A. Headaches, neck pain, vomiting, altered mental status, nuchal rigidity, ±seizures: **Acute bacterial meningitis likely**

Intravenous antibacterial therapy: third-generation cephalosporin such as ceftriaxone; supportive care

B. Chills, myalgia, sweats, absence of respiratory symptoms, altered mental status, seizures; malaria-endemic regions: **Cerebral malaria**

Antimalarial therapy, ±intravenous antibacterial therapy

IV. NONSPECIFIC FEBRILE SYNDROMES

A. Chills, myalgia, sweats, absence of respiratory symptoms; malaria-endemic regions: **Malaria**

Antimalarial therapy

B. Chills, myalgia, sweats, absence of respiratory symptoms; non–malaria-endemic regions: **Dengue**

Supportive care; watch for hemorrhagic/shock changes.

C. Chills, myalgia, sweats, exposure to freshwater, floods: **Leptospirosis possible**

Antibacterial therapy—penicillin is agent of choice. Alternatives: erythromycin or doxycycline.

D. Poor perfusion, signs of sepsis, no exanthems, no meningism, ±altered mental status: **Bacterial sepsis possible**

Intravenous antibacterial therapy, regimen based on local resistance patterns; supportive care

V. GASTROINTESTINAL SYMPTOMS AND FINDINGS

A. Abdominal pain, diarrhea with mucus or blood: **Bacterial enteritis possible. Shigellosis, salmonellosis (including enteric fever), or campylobacteriosis.**

Antibacterial therapy—azithromycin is preferred empiric agent. Ciprofloxacin could be used in regions with low resistance (eg, Africa).

Clinicians must be familiar with the epidemiology of infectious pathogens frequently observed in regions of interest. There are also epidemiologic variations within countries. For example, most of South Africa is malaria free, with the exception of the northeast regions around Kruger National Park. Approximately 10% of people who travel to a developing country experience a febrile illness during or after travel, which frequently requires medical consultation. Stays in sub-Saharan Africa and Southeast Asia-Pacific regions are most often associated with febrile illnesses. Tropical diseases account for close to 40% of febrile illness cases. A cause cannot be determined for one-fourth of patients.

Type of disease is greatly influenced by the country visited. Malaria (mostly by *P falciparum*) and rickettsial infections are the leading diagnoses associated with travel to Africa, while dengue and enteric fever lead with travel to Asia and dengue and malaria with travel to Latin America.[13] *P falciparum* malaria is the most frequent cause of hospitalization. In Thailand, dengue and leptospirosis were common causes of febrile illnesses.[14] In the Ecuadorian Amazon basin, leptospirosis, malaria, rickettsioses, and dengue were common causes of acute undifferentiated febrile illnesses.[15] Access to medical facilities with diagnostic and therapeutic capabilities could influence observed outcomes. In addition, parental responses to fever, especially in regions endemic with malaria, also influence how promptly effective therapy is initiated. While urban and rural mothers in Nigeria are aware that malaria causes fevers in children, urban mothers tend to respond better. However, rural mothers recognize childhood fever and danger signs better than urban mothers. Rural mothers frequently use leftover medicines from prior episodes.[16]

Many factors influence the likelihood of a sick child receiving effective therapy. Access can be impeded by lack and cost of transportation and medications and the need to care for other children, prepare food for others, and work. Access to medicines at home or from neighborhood shops or vendors may improve access to effective therapy.[17] Birthplace, feeding type, parental education, maternal visits to antenatal clinics, household economic status, and place of residence influence the incidence of fevers and resulting mortality. Children living in urban areas have a lower risk of fever than those living in rural regions.[18] Urban areas in developing countries may have a lower risk of malaria. Stays at higher elevations (>2,500 m) are associated with lower risk as well. Sleeping accommodations protected from mosquitoes by using bed nets reduced the incidence of malaria.

Vaccinations diminish the risk of yellow fever and Japanese encephalitis virus infection. When resources are available, an initial workup may consist of a complete blood cell count and differential, liver function tests, blood cultures for bacteria, stool culture, urinalysis, and thick and thin smears for malaria. Serologic testing may be needed to confirm dengue. Patients with a cough may require a chest film, and evidence of pneumonic infiltrates may require respiratory viral testing or sputum for Gram stain and culture or gastric aspirates for acid-fast bacilli cultures. A stool culture may be useful in patients with diarrhea, as determined by the duration and type of symptoms; some may require testing for *Clostridium difficile* toxin. Examination for ova and parasites may be useful in persons with chronic diarrhea. Antigen assays for *Cryptosporidium* and *Giardia* are particularly sensitive. Children with just watery diarrhea, with or without vomiting, with suspected rotavirus or norovirus gastroenteritis rarely require testing. Individuals with complaints of pharyngitis and evidence of exudative disease would benefit from rapid streptococcal antigen assay with a backup throat culture if necessary. Patients with symptoms suggestive of meningitis require a lumbar puncture. Some individuals may require diagnostic imaging with computed tomography (CT) scan or magnetic resonance imaging (MRI). Aspiration of joints may be required for children with suspected pyogenic septic arthritis. Tuberculin skin testing (TST) or interferon-gamma release assay (IGRA) may be needed as a way of confirming diagnosis of TB in a young child with atypical or complex disease. When differentiating between dengue, malaria, and typhoid, a normal C-reactive protein (CRP) is more likely seen with dengue. These patients are also more likely to have a normal white blood cell count. Patients with dengue and malaria are likely to have platelet counts less than 100,000/mm^3.[19]

SPECIFIC INFECTIONS OF GLOBAL IMPORTANCE

Malaria

Malaria is a mosquito-borne protozoan infection that involves erythrocytes. The most important species infecting humans are *P falciparum, P vivax, P ovale, P malariae*, and *P knowlesi*. The major vector is the *Anopheles* mosquito, which is endemic in many regions of the world, including the United States. Regions of the world with the most malarial transmission are sub-Saharan Africa, Southeast Asia-Pacific, Amazonian South America, and parts of Central America. *P knowlesi* is widely distributed in Malaysian Borneo, Peninsular Malaysia, and the Philippines. The spectrum of disease is variable, with many recovering without sequelae; however, mortality is estimated at 10%.[20,21]

More than 40% of the world's population is exposed to malaria. According to WHO estimates, 3.4 billion people are at risk of malaria. In 2012, 207 million cases occurred globally, resulting in approximately 627,000 deaths. Most deaths (77%) were in children younger than 5 years. Most cases and deaths occurred in Africa.[22] Most deaths were caused by *P falciparum* resulting from cerebral involvement, bacterial superinfection, and multiorgan failure. In addition, severe anemia is responsible for delayed growth and development. Unfortunately, regions affected by malaria are also plagued by HIV, TB, and typhoid fever. In a coastal city in Ghana, malaria infection was a contributor to the detrimental effect of socioeconomic deprivation and resulting low birth weight of neonates.[23]

Resistance to antimalarial agents in *P falciparum* contributed to its uncontrolled prevalence in Africa. Most *P falciparum* strains are resistant to chloroquine outside Central America. *P falciparum* is resistant to mefloquine in some Asian countries (ie, regions bordering Thailand, Myanmar, Laos, and Cambodia). Of greater concern, artemisinin resistance was recently found to be prevalent throughout mainland Southeast Asia.[24] *Plasmodium vivax* is the most prominent species outside Africa, especially in Asia where better diagnosis and antimalarial treatments are available, resulting in less *P falciparum*. However, resistance does not escape *P vivax*. Chloroquine resistance is reported in areas of Indonesia and Malaysia. *Plasmodium ovale* is rarely observed outside Africa. Recently, *P ovale* was detected in southeastern Bangladesh.[25]

In a study from The Gambia, the incidence of non-typhoid *Salmonella* infections decreased along with a decrease in the prevalence of malaria parasitemia, which suggests an association between the infections.[26]

Nonspecific clinical features are usually observed in children with malaria. Fever, vomiting, headaches, chills, myalgia, and anorexia are common. Gastrointestinal symptoms, such as diarrhea and abdominal pain and distension, are also observed. In one study, the absence of thrombocytopenia had a negative predictive value of 97% for malaria.[3] Other conditions, such as influenza, infectious diarrhea, typhoid fever, and dengue, may have similar complaints.

Severe malaria may result from cerebral involvement, acute respiratory distress syndrome, and multiorgan involvement. Most of these infected children will die unless they are hospitalized and promptly treated with effective support and antimalarial medications. Coma, seizures, metabolic acidosis, profound hypoglycemia, and shock are associated with high mortality.[27] While most of the serious complications are observed with *P falciparum,* severe malarial anemia in young infants is

seen more often with *P vivax*. Severe thrombocytopenia is also seen more often with *P vivax*.[28] Children with severe malaria have a lower mortality than individuals older than 50 years—6.1% versus 36.5%, respectively. Incidence of anemia and convulsions decreases with age, but the degree of hyperparasitemia, jaundice, and renal insufficiency increases with age.[29] Cerebral malaria is common in young children living in sub-Saharan Africa, where the incidence is 1 to 12 cases per 1,000 children per year. Mortality can be as high as 22%.[30]

While it is known that the sickle cell trait (hemoglobin genotype AS) protects against malaria, it is assumed that children with sickle cell disease are at increased risk of malaria when compared with children who do not have sickle cell disease. Evidence from a study in a rural area on the coast of Kenya could not support such a notion. However, children with sickle cell disease are more likely to die from malaria.[31,32]

Visualization of the parasite on blood smears has been the method of choice for malaria diagnosis for decades. Unfortunately, there is great variability of practitioners' ability to perform proper microscopy. In addition, a functioning microscope may be unavailable in some areas. Because many febrile illnesses share clinical features, overuse of antimalarial agents is a problem. Of interest, even when malaria was excluded, individuals with acute undifferentiated fever still frequently received antimalarial therapy.[33] Diagnostic tests have to be sensitive and accurate. Driven by this problem, the use of rapid diagnostic tests (RDTs) is becoming more widespread. In clinical settings where access to microscopy is not available, RDTs result in less overuse of antimalarial agents and improved focused use of antibiotics.[34] However, in the same study from Ghana, the use of RDTs at 4 peripheral clinics added very little if microscopy was available. In a laboratory-based study, RDTs performed better than the Giemsa-stained blood smears (GS). Rapid antigen capture assay (BinaxNOW Malaria test) had a sensitivity of 97% compared with 85% of GS, with a negative predictive value of 99.6% versus 98.2% with GS for all malaria.[35] Sensitivity was 100% for *P falciparum*. In regions of high endemicity, performing RDTs on all patients with suspected malaria was not cost-effective when compared with presumptive treatment of all febrile children.[36] In a low-transmission area, RDT use decreased drug costs and improved management of patients and compliance with test results.[37]

Other diagnostic methodologies may eventually replace GS in laboratory settings. Polymerase chain reaction (PCR) has become the gold standard for diagnosis. However, its availability is still limited in most resource-poor countries. In a study from Thailand, Pöschl and coworkers

compared loop-mediated isothermal amplification (LAMP) to nested PCR and microscopy.[38] Loop-mediated isothermal amplification is a molecular method that compares favorably with PCR but is cheaper, simpler, and faster. Using PCR as a gold standard, LAMP detected 100% of blood specimens with *P falciparum* with 100% specificity. Microscopy demonstrated 92% sensitivity and 93% specificity. Loop-mediated isothermal amplification performed just as well with specimens containing *P vivax,* while microscopy detected only 68% of positive specimens. The use of LAMP may eliminate the need for subjective interpretation of microscopic findings. However, its use as a field tool needs further study.

A newer version of LAMP, RealAmp is contained in a portable instrument that allows real-time monitoring of DNA amplification. In a field evaluation in India, when compared with PCR, RealAmp had a sensitivity and specificity of 94.8% and 100%, respectively, for detection of *P vivax*.[39] In Thailand, sensitivity and specificity were 100% and 96.7%, respectively. The fluorescent assay Partec Rapid Malaria Test may be easier to perform and provides quicker results compared with GS.[40] More widespread use of RDTs will change the way clinicians use treatment protocols. Individuals with negative RDT results would not require empiric treatment for malaria.

In 2010, WHO updated its guidelines for malaria treatment.[41] Artemisinin-based combinations are the recommended treatment for uncomplicated *P falciparum* malaria. Artemether-lumefantrine (AL), artesunate plus amodiaquine, artesunate plus mefloquine, and artesunate plus sulfadoxine-pyrimethamine are being used throughout the world. Of these, only AL (Coartem, Novartis, East Hanover, NJ) is licensed in the United States. Artemisinin derivatives should never be used as monotherapy. Artemisinin-based therapy is given for 3 days. Fever and parasite clearance is rapid with AL. The combination is generally well-tolerated. Diarrhea, abdominal pain, vomiting, and headaches were reported in fewer than 18% of recipients.[42] In a recent study from Tanzania, exposure to AL in the first trimester of pregnancy was found to be safe for the mother and fetus.[43] The use of dihydroartemisinin-piperaquine in Ugandan children for treating uncomplicated malaria resulted in delayed recurrence and prevented severe disease and hospitalizations.[44]

When compared with mefloquine alone, artesunate-mefloquine (AM) cleared parasitemia and reduced gametocyte carriage more rapidly in Nigerian children, with a lesser fall in hematocrit.[45] Of interest, individuals coinfected with *Plasmodium* and *Schistosoma* who received treatment with the combination AM for malaria had clearance of their malaria parasitemia and a reduction in schistosomiasis-related morbidity.

Therefore, AM appeared to be more effective than praziquantel.[46] In a trial in Bangladesh, an artesunate-azithromycin combination was found to be just as effective as an AL regimen. The combination was also well tolerated.[47]

Second-line antimalarial treatments may consist of artesunate plus tetracycline or doxycycline or clindamycin, or quinine plus tetracycline or doxycycline or clindamycin. These combination therapies are to be administered for at least 7 days. Atovaquone-proguanil (AP), AL, or quinine plus doxycycline or clindamycin are recommended for travelers returning to non-endemic countries where they develop malaria. In a recent study of French travelers with malaria, AP cured 99% of travelers with uncomplicated *P falciparum* malaria.[48] However, gastrointestinal adverse reactions such as nausea and vomiting were common. In approximately 4% of patients, therapy was switched to a different agent. In addition, another study demonstrated that AP had slower blood schizonticidal activity, resulting in early treatment failures in some patients. However, a combination of AP and artesunate was found to be a highly effective alternative.[49]

Severe malaria is always a medical emergency. Parenteral antimalarial treatment should be started immediately. Not all agents are available for use in developing countries. Therapy should be started with whichever effective antimalarial is first available. For children living in endemic regions, especially Africa, the following antimalarial agents are recommended: intravenous (IV) or intramuscular (IM) artesunate, quinine (IV infusion or divided IM injection), or IM artemether. Parenteral antimalarials are usually administered intravenously for a minimum of 24 hours and then switched to an oral regimen consisting of an artemisinin-based combination therapy, artesunate plus clindamycin or doxycycline, or quinine plus clindamycin or doxycycline, to complete the therapy. Quinidine can be used when parenteral quinine is not available. Artemisinin derivatives were found to be equivalent to quinine in the treatment of cerebral malaria in children.[50,51]

Delayed hemolysis is now recognized as a complication of parenteral artesunate.[52] Children with hyperparasitemia are at the greatest risk. There is a lack of correlation of its occurrence with the presence of sickle cell anemia or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Chloroquine combined with primaquine is the treatment of choice for chloroquine-susceptible *P vivax* infections. An artemisinin-based combination regimen is recommended for infections suspected to be caused by chloroquine-resistant *P vivax*. Primaquine is recommended for 14 days to eliminate the hepatic hypnozoite stage and prevent relapses.

Severe *P vivax* or *P knowlesi* infections should be treated with artemisinin-combination regimens. In Papua New Guinea, AL was found to be effective against *P falciparum* and *P vivax*. However, a high rate of *P vivax* recurrences were observed with this agent. The authors recommend co-treatment with primaquine.[53] To avoid medication-induced hemolysis, testing to rule out G6PD deficiency is advised before treating with primaquine.

Children with severe malaria presenting with respiratory distress and metabolic acidosis benefit from blood transfusions. Close monitoring for hypoglycemia is imperative. Seizures can be a complication of cerebral malaria or profound hypoglycemia. Unfortunately, in many countries, access to laboratory testing is limited, so many patients are monitored without testing. Newer bedside diagnostic (point-of-care) devices may prove beneficial, but testing strips and cartridges may still be too expensive for some facilities.[54]

Vector control, intermittent preventive treatments, and insecticide-treated bed nets are strategies used to reduce transmission and the effect of malaria on children. Sleeping under a bed net was found to protect against malaria.[55] However, a disturbing trend is being observed in some areas of Africa: an increase in a pyrethroid-resistance species of *Anopheles* mosquito. *Anopheles funestus* appears to survive longer and tends to spend more time inside dwellings, factors that are associated with increased malaria transmission.[56]

In endemic regions, febrile illnesses are always considered to be caused by malaria. Unfortunately, many receive antimalarial agents unnecessarily, and other non-malaria illnesses are not being treated appropriately.[57] Improvements in the availability of diagnostic testing would help solve some of these deficiencies.

Enteric Fever

Enteric fever, an infection caused by *Salmonella enterica* subspecies *enterica* serovar *Typhi* (typhoid fever) or *S enterica* subspecies *enterica* serovar *Paratyphi* A, B, C (paratyphoid fever), is a frequent cause of morbidity and mortality in many parts of the world. Most infections occur in Southern and Southeast Asia. Parts of Africa and Latin America are affected but at a lower frequency. In Asia, it is estimated that the incidence approximates 100 cases per 100,000 population. It is estimated that 22 million cases occur worldwide each year, of which more than 200,000 deaths result.[58,59] Of febrile episodes in Tanzania, typhoid fever was present in 3.7% of children.[60] Travelers to endemic regions are at risk; it is estimated that there are approximately 3 to 30 cases per 100,000 travelers of this febrile ailment each year.[61]

The major factor responsible for the magnitude of this problem is poor sanitary infrastructure resulting in substandard drinking water and contaminated food. Person-to-person transmission from chronic asymptomatic infections among inhabitants also contributes to the infection of susceptible individuals. Travelers visiting friends and relatives are at the highest risk of infection.

While fever, gastrointestinal symptoms (eg, vomiting, severe diarrhea, abdominal distension, pain), cough, relative bradycardia, rose spots, and splenomegaly are frequently regarded as features of typhoid and paratyphoid fever, many patients lack these, making diagnosis difficult if solely based on clinical features. Blood culture results are frequently positive; stool, less so. While liver enzymes are frequently elevated, leukocytosis is not always observed. However, leukocytosis is more frequently observed in children than adults.[62] Leukopenia and anemia are frequently associated with enteric fevers. Many suggest that bone marrow cultures have higher sensitivity; however, obtaining this type of specimen is more invasive and impractical under most circumstances in a developing country. Jaundice is frequently observed among children. In a study of travelers with enteric fever, clinical and laboratory features were indistinguishable between *S Typhi* and *S Paratyphi*, which suggests that milder disease is not always observed with *S Paratyphi* as originally thought.[58]

In studies from Pakistan, disease was more severe in children younger than 5 years. More than 95% of these children had fever, 20% to 41% had hepatomegaly, 5% to 20% had splenomegaly, 19% to 28% had abdominal pain, and 8% to 35% had diarrhea.[63,64] Severe disease resulted in more hospitalizations. Intestinal perforation was a rare complication observed in fewer than 1% of children. Cough was observed in approximately 15% of patients.[63] Thrombocytopenia and intravascular disseminated coagulation are markers of severe disease.[59] Relative bradycardia and rose spots are seldom observed in children. Febrile convulsions have been reported in children with enteric fever[65] and may be the presenting symptom in many children.[66]

The Widal test, a classic test that measures antibodies against O and H antigens of *S Typhi,* was associated with the diagnosis of typhoid fever. However, it lacks sensitivity and specificity and should no longer be performed. A false-positive test may lead to overtreatment and a delay in considering other conditions.[59,67] Use of the Widal test led to many unnecessary treatments in rural Kenya, where typhoid fever is still rare among children and significantly less frequent than other bacterial pathogens.[68] In one study, the positive predictive value was only 9.25%.[69]

While blood cultures and pathogen-specific serologic and PCR assays are the preferred methods for diagnosing enteric fever, diagnosis is still made using clinical criteria in most lower-income countries. Unfortunately, early features of enteric fever mimic other conditions such as pneumonia, malaria, sepsis, dengue, acute hepatitis, and rickettsial infections.

Chloramphenicol, amoxicillin, and trimethoprim-sulfamethoxazole (TMP/SMX) are no longer recommended as first-line agents because of a high frequency of treatment failures and resistance and high relapse rates. Relapse rates in children are only 2% to 4% after therapy, while carrier rates occur in fewer than 2% of infected children.[59] Antimicrobial resistance observed in many countries has influenced the choice of agent for treating typhoid and paratyphoid fevers. Ceftriaxone remains the recommended agent in the most severe cases in which parenteral therapy is indicated. While fluoroquinolones, such as ciprofloxacin, are generally associated with high cure rates, defervescence within a week, and lowered relapse and fecal carriage rates, isolates from many Asian countries demonstrate resistance, rendering them ineffective. Azithromycin appears favorable in the treatment of these. However, in a study from a tertiary-care pediatric hospital in western India, 63% of *S Typhi* cases were resistant to azithromycin, but 90% were susceptible to quinolones.[70] Ciprofloxacin remains the drug of choice for Africa.[71] For obvious reasons, attention to proper hydration, perfusion, and fever control are integral components of treating enteric fever.

Undoubtedly, improving the quality of drinking water and food will lead to the prevention of disease, but other strategies may be of benefit. Vaccinating children older than 2 years, who live in the slums in India, with the Vi capsular polysaccharide typhoid vaccine demonstrated a 61% protective effectiveness compared with a placebo. In children 2 to 5 years of age, the protective effect was 80%. Of interest, the level of protection was 44% among unvaccinated members of Vi vaccinee clusters.[72] A conjugate typhoid vaccine, Vi-CRM197, was found to be safe and immunogenic in randomized, observer-blind trials in Pakistan, India, and the Philippines.[73]

A multidrug-resistant *S Paratyphi* A emerged as an important pathogen in Asia. Azithromycin was found to be an effective alternative for non-severe disease in this region.[74] Infections from *S Paratyphi* A are becoming more frequent than *S Typhi* among travelers.[75] A similar trend has been observed in Nepal.[76]

Mixed infections with multiple pathogens occur in tropical endemic countries. Treatment against enteric fever should be considered

for children with unremitting fevers after completing adequate antimalarial therapy.[77]

Ileal perforations in the tropics are frequently considered to be associated with enteric fever. In one study, only 4.2% and 6.3% of ileal perforations were associated with *S Typhi* and *S Paratyphi* A, respectively.[78] In Nigeria, 50% of all admissions for typhoid-related ileal perforation were in children, with 62.5% of these occurring between the ages of 5 and 6 years.[79] Fever, vomiting, and abdominal tenderness and distension are suggestive of ileal perforation. Postoperative complications are common, such as surgical wound infection, intra-abdominal abscesses, ileus, and re-perforation. Mortality is high in children—40.9% in those younger than 5 years and close to 20% in children older than 5 years.[80]

Non-typhoid Salmonellosis

It is important not to forget that non-typhoid salmonellosis remains a frequent cause of invasive disease in many regions of the world, especially sub-Saharan Africa. Children younger than 3 years and those infected with HIV have the greatest burden. Mortality remains high, especially in children with bacteremia and meningitis. Seasonal peaks of disease correlate well with the rainy season, which leads to fecal contamination of drinking water. In many countries, investigators found an association of malaria and non-typhoid salmonellosis, which may lead to delays in treatment resulting in a rise in morbidity and mortality. Clinical features, such as fevers, anemia, and splenomegaly, are frequent findings in both conditions.[81] Christenson provides a comprehensive review of this group of infections and their management.[82] In a study from Taiwan, patients with non-typhoid salmonellosis frequently used proton pump inhibitors.[83] Eosinopenia is generally observed in patients with non-typhoid salmonellosis.[84]

Leptospirosis

Leptospirosis has become an important cause of febrile disease in urban communities within developing countries. Urine from wild and domestic animals is the source of human infection. Contact with infected animals, poor sanitation and water quality, flash flooding, and overcrowding are contributing to an increase in cases. Approximately 268 pathogenic serovars of *Leptospira* have been identified. *Leptospira interrogans* is the primary pathogenic species.[85] Jaundice and renal failure, known as hepatorenal syndrome or Weil disease, is the stereotypical presentation associated with leptospirosis; however, this condition represents a smaller number of cases. Hemorrhagic pneumonia and meningitis are also described with the infection and high mortality is associated

with these. *Leptospira* causes a nonspecific febrile illness in most cases. It mimics other diseases such as malaria and dengue.[86] In a low-income region of Dhaka, Bangladesh, leptospirosis accounted for 2% to 8% of acute outpatient febrile episodes.[87] Eighteen percent of dengue-negative individuals were found to have leptospirosis during a dengue outbreak in the same region in 2001.[88]

Visualization of leptospires by dark field microscopy, detection of specific antibody in serum, or DNA by PCR are the most frequently used methods for diagnosis. Unfortunately, most are impractical in regions with limited resources.

Penicillin for 5 days is the agent of choice for treatment. Erythromycin (5 days) and doxycycline (10 days) are alternative agents.

Dengue

Dengue is an acute febrile illness caused by a flavivirus transmitted by the mosquitoes *Aedes aegypti* and *A albopictus*. Disease is frequently associated with high fever and intense joint and muscle pain. Hemorrhagic complications and shock have also been reported. Dengue remains a common cause of hospitalizations in Southeast Asia. In a Vietnamese study, dengue was responsible for one-third of febrile illnesses presenting to a public primary care clinic. The presentations were highly nonspecific; most were not suspected clinically. Approximately 32% of the cases without a clinical diagnosis were positive by serologies; this was mostly among children younger than 15 years. In patients with acute dengue, other diseases were suspected clinically, such as pharyngitis, typhoid fever, tonsillitis, leptospirosis, and hepatitis.[89] Febrile seizure, macular rash, petechiae, and thrombocytopenia were presenting clinical features of infants with dengue. However, asymptomatic infections were 6 times higher than symptomatic cases.[90] The majority of children with symptomatic dengue have fever (93%), rash (79%), headache (84%), and eye pain (67%). Sixty-five percent of patients complain of joint aches.[91]

Dengue is frequently characterized by acute onset of fever and 2 of the following symptoms: retro-orbital pain, rash, headaches, myalgia, arthralgia, leukopenia, or hemorrhagic manifestations, such as positive tourniquet test, bleeding gums, thrombocytopenia, petechiae, or purpura or ecchymoses.[92] Mixed infections with dengue do occur in endemic regions. Of 602 children admitted to a hospital in Mumbai, India, 30 had malaria, 11 had enteric fever, and 7 had mixed infections; 27 children had leptospirosis. Clinical features were shared among these infections. However, contact with floodwater, myalgia, and conjunctival suffusion were more often associated with leptospirosis. Abdominal pain, rash, and bleeding manifestations were more associated with dengue.[93]

The acute febrile phase of dengue usually lasts 3 to 7 days. However, in some affected individuals, signs and symptoms such as body pain, headaches, fatigue, and exanthems may persist weeks after the initial febrile illness.[94] Severe dengue has been described in pediatric travelers returning from the Caribbean.[95]

Dengue has been diagnosed in parts of south Texas along the United States–Mexico border where vectors are found. In addition, imported cases are frequently reported in mainland United States.[96,97] In 2009 and 2010, an outbreak of dengue was reported in Key West, FL, the first cases in the region since 1934.[98]

Acute and convalescent serologic tests are necessary for diagnosis. Polymerase chain reaction assay is also available through the Dengue Branch of the Centers for Disease Control and Prevention.

In endemic regions, it may be difficult to differentiate between malaria, dengue, and chikungunya virus as the cause of a febrile illness. Patients with chikungunya virus are more commonly afflicted by severe arthralgia. Individuals with malaria are more likely to have elevated CRP and hyperbilirubinemia.[99]

Clinicians caring for children in the tropics where dengue is endemic should become familiar with WHO guidelines on the management of dengue, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).[100] Treatment is supportive. No effective antiviral therapy is available at this time. Dengue hemorrhagic fever and DSS are frequent severe complications. Promptly recognizing signs of DHF and DSS and initiating appropriate treatment are critical for reducing fatalities. Massive capillary leak is usually observed after the child becomes afebrile (days 3–6). Close monitoring is necessary at this stage of illness. A drop in platelet count accompanied by rising hematocrit usually precedes shock. Persistent vomiting along with abdominal pain are signs of impending shock. Thrombocytopenia below 100,000/mm^3 with a hematocrit rise of 20% or more, with spontaneous bleeding, is indicative of DHF (grade 2 using a dengue classification scale). Signs of circulatory failure and shock confirm DSS (grade 3–4). The use of crystalloid oral and IV fluids and colloids are critical components of management of DHF and DSS.[101] Aspirin and nonsteroidal anti-inflammatory agents should be avoided.

Ebola Virus Disease

On March 23, 2014, the WHO was officially notified of an outbreak of infections caused by Zaire Ebola virus (EBOV) in the country of Guinea in West Africa. Within several weeks, infections were reported in Sierra Leone and Liberia. Since the initial infections were detected in December 2013, 21,296 cases were reported as of January 14, 2015, resulting in

8,429 deaths.[102] While several cases have been reported in the United States, Europe, and other countries in Africa (a total of 35 cases), the majority of cases have occurred in 3 countries in West Africa. Between July and October 2014, an unrelated outbreak of 69 cases with 49 deaths was detected and contained in the Democratic Republic of Congo.[103]

Ebola viruses belong to the *Filoviridae* family of viruses. In addition to Marburg virus, infections by these viruses are associated with significant morbidity and high fatality rates. Contact with fruit bats or nonhuman primates is presumed to initiate human infections, which later spread among humans by contact with infectious body fluids. In the current epidemic, the first case of EBOV in Guinea was in a 2-year-old boy.[104] His source of infection is still unknown.

Five different strains of EBOVs have been described. Zaire and Sudan EBOV have been responsible for most outbreaks of EBOV infections, with the largest outbreaks occurring in Uganda (2000, 2011), Sudan (1976, 2004), and Democratic Republic of Congo (1995). The largest of these outbreaks occurred in Uganda in 2000 through 2011 with 425 reported cases.[105] Reston EBOV has been described in the Philippines with a suspected swine reservoir and infections among macaque monkeys. Only asymptomatic human infections have been reported with this virus.[106] Tai Forest EBOV has been detected in only one patient. Bunyalivirdae EBOV was responsible for an outbreak in Uganda in 2007 and 2008.[107]

While the 2 initial cases of EBOV in Guinea were in 2- and 3-year-old siblings, the majority of cases have occurred in adults.[102,104,108] The majority of patients have been in the range of 15 to 44 years of age with a case fatality rate of greater than 70%.[108] More than 3,000 children younger than 14 years have been affected by EBOV, with an infection rate 3 to 4 times less than in persons older than 14 years.[102] In an outbreak of Ebola hemorrhagic fever in Uganda in 2000, approximately 40% of hospitalized patients were children or adolescents[109]; the mean age was 8.2 years. Forty percent of these children died. In past outbreaks, children comprised 9% to 41% of total cases.[110] In the current epidemic, approximately 14% of cases have been in children. It is thought that fewer cases occur in children because most are kept away from sick and dying friends and relatives, resulting in less transmission.[111]

The incubation period of most infections has been approximately 11 days.[108] Most patients have fever, fatigue, vomiting, loss of appetite, diarrhea, abdominal pain, and myalgia. Hypoperfusion, followed by renal and hepatic dysfunction, are the cause of death in most fatal cases. Metabolic acidosis and diarrhea-associated hypokalemia are common.

In prior outbreaks, hemorrhagic findings, such as bleeding from gums and the gastrointestinal tract, were common. However, in the current epidemic, hemorrhagic findings have been uncommon. For this reason, the term Ebola hemorrhagic fever is not used to describe this epidemic.

Aggressive prevention of intravascular volume depletion and complications of shock is the mainstay treatment of Ebola virus disease. Various experimental therapies have been used in infected patients. Blood transfusions of convalescent plasma of Ebola survivors and monoclonal antibodies have been used to block or neutralize the virus. Hyperimmune globulin, prepared by purifying and concentrating plasma of immunized animals or previously infected humans with high titers of neutralizing antibody, has also been proposed as therapy. Antiviral agents, such as brincidofovir and favipiravir, have also been used in a number of patients. Because there is a lack of controlled trials, it is unclear if any of these therapies are effective. Vaccine trials with 3 test vaccines are underway to determine if these will be effective in stopping current and future epidemics. Attention to infection control measures and use of personal protective equipment are known to be effective in preventing the spread of EBOV within homes and hospitals.

Chikungunya Virus

Chikungunya virus, an alphavirus in the *Togaviridae* family, has been spreading in many regions of the world, most recently in the Caribbean and the Americas. Major outbreaks have been described in Africa, Southeast Asia, countries surrounding the Indian Ocean, and in the islands of Martinique, Dominican Republic, and Puerto Rico.[112] There is great concern that chikungunya virus may spread to Europe.[113] Various *Aedes* species are capable of transmitting this virus. *Aedes aegypti* and *A albopictus* are responsible for human-to-human transmission.[114] Most of the clinical features of chikungunya virus infection resemble dengue. An incubation period of 2 to 4 days (range 1–12 days) is followed by an abrupt onset of high fever, headache, back pain, myalgia and arthralgia. Joint pain can be severe. Ankles, wrists, and phalanges are commonly affected. Joint involvement usually resolve within 1 to 2 weeks. In approximately 12% of patients, arthralgia can be observed up to 3 years after initial infection.[114] A maculopapular exanthem mostly involving the thorax has been described. Other manifestations of chikungunya virus infection include retinitis, iridocyclitis, meningoencephalitis, and Guillain-Barré syndrome (GBS). Treatment is supportive.

Rickettsial Infections

Scrub and murine typhus in children is frequently misdiagnosed as enteric fever because children frequently lack classical features. Nonspecific features, such as fever, tachypnea, and hepatosplenomegaly, are reported.[115]

Species of rickettsiae are significant causes of zoonotic infection and are increasingly recognized as pathogens in travelers.[116] *Rickettsia rickettsii* causes Rocky Mountain spotted fever and is endemic in North America and parts of South America. Patients with Rocky Mountain spotted fever typically present with fever, petechial rash, and headache with evidence of systemic inflammation. However, they rarely have any evidence of a prior tick bite. In contrast, many rickettsioses acquired abroad present with a systemic illness and "inoculation eschars" at sites of previous tick bites.[116] A patient presenting with a systemic illness, eschars with regional lymphadenopathy, and rash is likely infected with a species of *Rickettsia*.

African tick-bite fever appears to be the most common rickettsial disease in travelers. The bacterium is transmitted from the bite of the cattle tick and the typical presentation is fever, headache, and eschars with lymphadenopathy. Vesicular rash with blisters in the mouth can also be seen. Travelers engaging in wild game safaris are at elevated risk of infection.[116]

Mediterranean spotted fever is acquired in Europe, Africa, and Asia and presents similarly to African tick-bite fever. Murine typhus (*Rickettsia typhi*) is transmitted from its rodent host to humans via fleas, and coastal regions are the most frequently infested areas. No eschar develops after infection and the clinical course is often benign, nonspecific febrile illness.

Contact with the larvae of certain species of mites (chiggers) in Southeast Asia can lead to infection with *Orientia tsutsugamushi* and the clinical disease scrub typhus. An inoculation eschar is common along with fever and lymphadenitis. Treatment is required for this potentially fatal disease.

Diagnosis of rickettsial infection can be difficult; the best option is acute and convalescent antibody serology. It should be recognized, however, that cross-reaction between rickettsial species is common. Doxycycline therapy should be given in suspected cases.

Community-Acquired Bacteremia

Community-acquired bloodstream infections are common in Africa. In a meta-analysis of studies from 1984 to 2006, incidence

of community-acquired bacteremia (CAB) in infants younger than 1 year was estimated at 1,457 cases per 100,000 children, 100 in children younger than 2 years and 505 in children older than 5 years.[117] Twenty-six percent of all in-hospital deaths were in children with CAB, with 70.5% of these occurring in the first 2 days of hospitalization.[117] HIV infection and malnutrition may have been contributing factors. Bacteremia was responsible for more deaths in young infants than malaria. Twenty-nine percent of infections were caused by *S enterica*; approximately 58% of these were non-typhoid. The most common isolate in children was *Streptococcus pneumoniae* (18.3%). Other common pathogens were *Staphylococcus aureus* and *Escherichia coli*. In patients with HIV, *Mycobacterium tuberculosis* was isolated when mycobacterial culture techniques were used. *E coli* and *Streptococcus agalactiae* (group B *Streptococcus*) were the most frequently isolated pathogens in infants younger than 60 days in a rural hospital in Kilifi, Kenya.[118] *S pneumoniae*, non-typhoid *Salmonella* species, *Haemophilus influenzae*, and *E coli* were common in children older than 60 days.

Blood cultures should be obtained in all febrile children with malaria. In a study from Nigeria, bacteremia was detected in 38.2% of infants and malaria parasitemia was found in 46.1%. *E coli, S aureus,* and *Klebsiella* were the most commonly isolated bacteria.[119] Empiric antibacterial therapy should be administered to all children being treated for malaria when laboratory facilities are not available. Fifty percent of febrile individuals had a positive blood culture result, when malaria was excluded, in a study from 3 rural hospitals in Ghana. The median patient age was 15 years. *Salmonella* was the most frequently isolated pathogen; 59% were *S Typhi*. Most isolates were resistant to chloramphenicol, TMP/SMX, and ampicillin.[120] Similar findings were found in a study from Mozambique.[121]

Central Nervous System Infections

Infections of the CNS have a devastating effect on the well-being of infants and children. Acute morbidity, mortality, and long-term neurologic sequelae account for most of the complications encountered with this group of infections. While viruses are responsible for most cases of meningitis, bacteria such as *S pneumoniae, H influenzae* type b (Hib), and *Neisseria meningitidis* inflict much of the mortality and morbidity associated with the disease. In countries with adequate economic resources and active vaccination programs for infants, bacterial infections caused by Hib are rare and are mostly relegated to unvaccinated children. In addition, invasive infections by *S pneumoniae* have been significantly

reduced since the introduction of universal vaccination of infants with pneumococcal conjugate vaccines. In many countries, neonatal infections by *Streptococcus agalactiae* (GBS), *E coli,* and other gram-negative bacilli continue to be a common occurrence. Young infants and children, adolescents, and adults with splenic deficiency, such as sickle cell anemia and thalassemia, are at risk of infections by encapsulated organisms such as *S pneumoniae,* but *Salmonella* species can also be responsible for great morbidity. Among viruses that cause CNS disease, enteroviruses, human herpesviruses, and arboviruses are the most common. Through the use of PCR, we have a better grasp of their clinical presentations and epidemiology. With the exception of human herpesviruses, infections are self-limiting. West Nile virus was recently introduced into industrialized countries around the world. Enterovirus 71 and coxsackievirus A6 have been spreading. Enterovirus 71 has been responsible for hand-foot-and-mouth syndromes, as well as myocarditis and meningoencephalitis.[122] Coxsackievirus A6 is mostly responsible for an erythematous vesiculopustular exanthem that accentuates in areas of eczema.[123] Yeast such as *Cryptococcus neoformans* and *C gattii* are well-recognized pathogens of immunocompromised hosts, such as those with HIV/AIDS, and those who are young or old. Infections by parasites are rare. Infections by *Angiostrongylus* species, associated with the consumption of freshwater crests or contaminated vegetables, are well described.[124–126] Central nervous system infections caused by *Toxoplasma gondii* are almost exclusively observed in individuals with compromised immune systems. Coinfections are well described during malarial infections. In Vietnam, *Streptococcus suis* was responsible for 24% of infections in individuals older than 14 years. Japanese encephalitis virus was more common in children younger than 14 years. Tuberculous meningitis was confirmed in 2% of pediatric patients.[127]

Plasmodium falciparum, Trypanosoma brucei subspecies (*gambiense* and *rhodesiense*), *T cruzi,* and HIV have tropism for the CNS.[30] They are responsible for a variety of neurologic manifestations of disease. Further details of these is beyond the scope of this chapter.

Fever, headaches, vomiting, altered mental status, nuchal rigidity, photophobia, and seizures are clinical features frequently associated with CNS infections. Young infants and children may lack most of these classic signs and symptoms, especially early in the disease. Young infants may require a lumbar puncture even if classic features are lacking. Nonspecific features such as lethargy, fever, vomiting, and decreased appetite and activity are more common. A high degree of suspicion is required. It is not uncommon to confuse meningitis with malaria.[128]

Seizures were frequently thought to be malaria. This may result in a delay in taking a patient to a health care facility for diagnosis and care.

The presence of cerebrospinal fluid pleocytosis with a predominance of polymorphonuclear cells with elevated protein and hypoglycorrhachia is highly indicative of a bacterial process. Gram stain is positive in more than two-thirds of patients with bacterial meningitis. Lymphocytic predominance is more commonly observed in viral infections. Cerebrospinal fluid eosinophilia is highly suggestive of a parasitic CNS infection.

In countries with limited resources, microbiology laboratories may not be available for routine use. Alternative methods to confirm causative pathogens are generally needed. In a study of children with acute meningitis in which *S pneumoniae* was the predominant pathogen, the use of Gram staining and latex agglutination bacterial antigen detection was able to confirm 85% of cases.[129] When cultures were included, 100% of cases were detected.

Before the introduction of conjugate vaccines, meningitis infection by Hib and *S pneumoniae* was most commonly observed in infants between the ages of 6 and 11 months. In most countries, invasive infections by these pathogens occurred in children younger than 5 years. However, these organisms are usually not common pathogens in the first month of life.

Distribution of pathogens according to age determines the choice of antimicrobial therapy. In the first month of life, ampicillin and a third-generation cephalosporin (with the addition of an aminoglycoside such as gentamicin) is the preferred regimen for the patient with suspected neonatal meningitis. In infants and children older than 2 months, a third-generation cephalosporin such as ceftriaxone or cefotaxime is the recommended treatment. These would appropriately cover most common pathogens such as *N meningitidis* and *S pneumoniae*. In regions of the world where penicillin and third-generation cephalosporin resistance is prevalent, the addition of vancomycin is recommended. A third-generation cephalosporin would be appropriate therapy for infections caused by Hib. In the overlapping weeks between the neonatal period and 2 months of age, GBS, gram-negative enteric bacilli, Hib, and *S pneumoniae* can be prevalent organisms. A combination regimen of ampicillin plus third-generation cephalosporin (plus vancomycin, if indicated) is recommended. In children with meningitis caused by Hib, *N meningitidis,* and *S pneumoniae,* 5 days of ceftriaxone was found to be adequate therapy.[130] However, in the United States, most clinicians treat *S pneumoniae* meningitis for at least 10 days and *N meningitidis* for 7 days.

While the prompt administration of antimicrobial therapy is critical for the rapid sterilization of cerebrospinal fluid with the ultimate goal of reducing neurologic sequelae, it is imperative that attention be given to the hemodynamic status of the patient and control of increased intracranial pressure. A concern over the development of inappropriate secretion of antidiuretic hormone (SIADH) may lead some clinicians to restrict fluids. However, before this can be done safely, the patient should receive adequate amounts of fluids and electrolytes to reestablish intravascular stores that may be affected by third spacing secondary to sepsis or insensible losses due to infection. Close monitoring of urine output and weight gain and measurement of electrolytes (when feasible) may help detect the presence of SIADH. Seizures in the first several days of illness are not unexpected. Anticonvulsants may be required for some patients. The presence of generalized seizures in the first 4 days of illness usually does not lead to long-term neurologic sequelae. Most patients will only require anticonvulsant therapy for a few months after the initial presentation.

Severe and profound hearing loss and motor impairment appear to be the most common neurologic sequelae observed in a study from Niger.[131] Some investigators proposed corticosteroids as a mean of reducing the incidence of neurologic sequelae, especially hearing deficit. While randomized placebo-controlled trials in children with mostly Hib meningitis suggest benefit, its role in other types of meningitis is less clear.[132,133] Adult studies show a reduction in mortality in patients with pneumococcal meningitis.[134] Studies demonstrate that clinical benefit is mostly achieved if dexamethasone is administered at least 30 minutes before the antibiotic. It is still unclear if dexamethasone benefits all patients with meningitis.[135] Early studies of corticosteroid use as adjunctive therapy in patients with neonatal meningitis, viral meningitis, meningococcal meningitis, and meningitis occurring in countries with limited resources failed to demonstrate a beneficial effect.[136] However, in recent studies, use of dexamethasone in neonatal meningitis resulted in a lower fatality rate in recipients.[137] Dexamethasone is considered an integral part of treatment for TB meningitis. Its use has shown to decrease mortality and long-term neurologic sequelae. Other adjunctive agents, such as glycerol, have demonstrated beneficial effects in some patients.[138] However, its use in children with meningitis in Malawi failed to show benefit.[139]

Vaccination of susceptible populations, such as young infants and children, is the most important means of reducing the incidence of invasive infections, such as meningitis. Access to conjugate vaccines may be limited in most countries with limited resources.

The introduction of Hib conjugate vaccine in developing countries has had the desired effect in reducing disease.[140] The introduction of a group A meningococcal conjugate vaccine (MenAfriVac, Serum Institute of India Ltd, Pune, India) in Burkina Faso and Mali was intended to eliminate epidemics of group A meningococcal meningitis.[141] However, in parts of sub-Saharan Africa, serogroup shifting has been observed, as serogroup X is becoming a prominent pathogen.[142] This has not been observed following Hib vaccination. However, in developed countries with active pneumococcal conjugate vaccination, shifting to non-vaccine types has been widely observed, which required the development of new vaccines with broader protection coverage. A similar approach will be required in countries yet to initiate vaccination programs.

In many developed countries, mothers in premature labor or known to be colonized with GBS receive intrapartum antibiotics such as penicillin. This strategy has effectively reduced the incidence of early-onset disease such as sepsis and pneumonia. Unfortunately, late-onset disease that frequently presents as bacteremia or meningitis is not affected by intrapartum prophylaxis. In some communities, *E coli* has become the most common bacterial neonatal pathogen. Antimicrobial prophylaxis with rifampin may be recommended in households with young children exposed to a child with Hib meningitis. Close contacts of patients with meningococcal infections should receive rifampin or ceftriaxone as prophylaxis.

Neonatal meningitis is most common in the developing world. Mortality is much higher than in developed countries (40%–58% versus 10%).[143] The WHO estimates 5 million neonatal deaths each year, with most of these occur in the developing world. It is estimated that neonatal meningitis is responsible for 50,000 deaths each year. The risk of meningitis is highest during the neonatal period. Infections by GBS appear to be less common in developing countries; however, the true epidemiology is still unclear in many countries.[144] Gram-negative bacilli and *S pneumoniae* are frequently reported as important pathogens. In most countries, infections by *Listeria monocytogenes* are uncommon. In most developing countries, a combination of penicillin, an aminoglycoside, and a third-generation cephalosporin is recommended as initial empiric therapy. In developing countries, most neonatal infections consist of bacteremia, meningitis, and respiratory tract infections. The most common bacterial pathogens are *E coli, Klebsiella* species, *S aureus,* and *S pyogenes*.[145] In Malawi, non-typhoid *Salmonella* was responsible for 16% of neonatal meningitis.[146] Of interest, 30% of these cases were caused by

GBS. In Asia, 54% of neonatal gram-negative bacillary pathogens were resistant to third-generation cephalosporins and gentamicin.[147]

Brain abscesses are uncommon in children. Most are seen in children with congenital heart defects and in older children with sinusitis. Extension from the frontal or sphenoid sinuses is frequently implicated.[148] On occasion, extension from the middle ear or mastoids is to blame. Depending on the site of origin, microbial pathogens may vary. Most infections originating from the sinuses are polymicrobial with viridans streptococci, such as *S intermedius* and anaerobes being the main culprits.[148,149] Hematogenous-related brain abscesses are usually observed in children with congenital heart disease and endocarditis; *S aureus* is a common pathogen.[150] Otic-related infections are usually caused by multiple organisms, including *Pseudomonas aeruginosa*. Adults with HIV and other types of immunosuppression are particularly at risk of infection.[151] Neonates with meningitis caused by *Cronobacter sakazakii, Citrobacter koseri,* and *Enterobacter cloacae* are frequently complicated by brain abscesses.[152,153]

Most patients with a brain abscess will have headaches. Fever and altered states of consciousness are less common. Symptoms may last days to weeks. Some patients may present with seizures. An enlarging abscess will lead to more symptoms. Focal neurologic deficits may be observed with advanced disease. Some patients may present with focal frontal headaches accompanied by swelling of the forehead and periorbital edema as initial symptoms and signs of Pott puffy tumor, a complication of frontal sinusitis. It is not uncommon to observe early frontal lobe cerebritis and contiguous epidural abscess that later progress into a brain abscess.

Computed tomography with contrast and MRI are quite sensitive in detecting intracranial infections. While blood and cerebrospinal fluid culture results are positive in some patients, direct stereotactic aspiration of the abscess or contiguous infected sinus is necessary to identify all offending pathogens. Large single abscesses (>2.5 cm in diameter) usually require neurosurgical drainage. Patients with multiple abscesses can generally be treated with antibiotics alone. However, if a larger abscess is present, this could be drained. Patients with extensive surrounding edema with shifting of brain structures, herniation, and severe symptoms will require surgical intervention.

Initial empiric antimicrobial therapy should be broad and must cover streptococci, anaerobes, and staphylococci. Vancomycin, metronidazole, and a third-generation cephalosporin are generally first-line therapy. If the abscess has its origin in the middle ear, perhaps cefepime

should be a substitute for cefotaxime or ceftriaxone because it has better coverage against *P aeruginosa*. Meropenem can be an alternative agent. In the immunocompromised host, the antibiotic regimen may need the addition of an antifungal agent and possibly TMP/SMX to cover *Nocardia* species. Duration of therapy is greatly influenced by resolution of the infection. Most abscesses require at least 6 to 8 weeks of antibiotic therapy.

Musculoskeletal Infections

Osteomyelitis and septic arthritis in children are frequently caused by *S aureus*. In some communities, methicillin-resistant *S aureus* (MRSA) is the most common cause of osteomyelitis. In a study from India, MRSA was responsible for 55% of culture-positive cases of bone and joint infections.[154] *Streptococcus pyogenes* is common in children with a history of trauma or chickenpox. Septic arthritis can be caused by Hib and *S pneumoniae* in unvaccinated and under-vaccinated children. *Kingella kingae* is responsible for musculoskeletal infections in children younger than 4 years.[155–157] *H influenzae* type b is an uncommon cause of osteomyelitis; most infections are caused by the hematogenous seeding of a long bone or associated joint. The metaphysis is the primary focus of infection. The femur, tibia, and humerus are the most commonly affected bones, while hips, knees, elbows, and ankles are the most frequently affected joints. Involvement of vertebral bodies or flat bones is less common. Some organisms may have tropism for certain sites as spine and sacroiliac joints, such as *M tuberculosis* and *Brucella* species, respectively.

In some developing countries, microbial flora may vary compared with higher-income countries. *Enterobacteriaceae* were the most common isolated osteomyelitis pathogens in Lahore, Pakistan.[158] One-third of patients had this group of organisms, followed by *S aureus* (29.5%) and *P aeruginosa* (15.5%). Mixed infections, at times with anaerobes, were also reported. Most of these patients appeared to have chronic disease. Some patients with chronic infection are known to have a history of open fractures. In another study, mixed aerobic and anaerobic infections were common (68%).[159] While most cases of chronic osteomyelitis occur in adult males, it is important to recognize the consequence of poorly treated acute infections.

Children with suspected musculoskeletal infections present with pain at the site of infection, usually accompanied by swelling and redness. Limitation in range of motion can be observed in the affected joint or in a contiguous joint. Refusal to bear weight is a common feature as well. Fever is seen in most patients. Most children will have elevated inflammatory markers such as erythrocyte sedimentation rate and CRP. Normal

assays along with the absence of high fevers and toxicity would be more suggestive of a transient synovitis. Most untreated children will have a positive blood culture. Aspirates of bone and joint fluid will frequently yield a pathogen. In young children in whom *K kingae* may be a likely pathogen, inoculation of fluids and tissue into BACTEC bottles results in greater yields when compared with conventional methods.[156] Infected joint fluid has elevated white blood cell counts greater than 10,000 per mm^3 with a predominance of polymorphonuclear cells and elevated protein and decreased glucose. Infections in young infants in the first 2 months of life frequently present with pseudoparalysis and pain with movement of the affected limb. Multiple sites are frequently involved. Many of these infants will otherwise lack signs of systemic toxicity, such as fever, in spite of having positive blood cultures. *Streptococcus agalactiae* (GBS) and *S aureus* are the most common pathogens in this age group, followed by *E coli* and other gram-negative rods.

Infections by MRSA are frequently complicated by prolonged fevers, subperiosteal abscesses, deep vein thrombosis, prolonged hospitalizations, chronic osteomyelitis, and need for multiple surgical debridements. *Bartonella henselae* can cause osteomyelitis in any bone. Infections generally appear as lytic lesions within the bone. Some of these patients may complain of bone pain at the site, accompanied by fever and a history of exposure to cats. On occasion, *S aureus* can cause a subacute infection known as primary subacute hematogenous osteomyelitis (known as Brodie abscess). These patients have an afebrile presentation generally characterized by a persisting dull pain at the site of the infection that may last weeks to months. These infections usually occur on long bones and have the appearance of a lytic lesion with surrounding sclerosis. Radiographic findings may suggest a bone tumor. Chronic bone pain and chronic draining sinuses may suggest a chronic bone infection. Chronic infection is generally related to poorly treated acute infections or a failure to recognize the acute process. In Uganda, 3.5% of surgical procedures were in patients with osteomyelitis; one-third of these patients were children 10 to 14 years of age.[160] Sequestrectomy was the most frequent surgical procedure performed in these children.

Fungal musculoskeletal infections are uncommon and generally secondary to direct inoculation of bone or joint or caused through hematogenous dissemination from a remote site. In North America, *Blastomyces dermatitidis* is perhaps the largest cause of fungal bone disease. Infections are generally associated with living in a specific geographic region around the Great Lakes between the United States and Canada. Coccidioidomycosis caused by *Coccidioides immitis* or *C posadasii*

is responsible for serious infections in individuals residing or traveling in regions of southwestern United States and northern Mexico. Bone involvement is also observed with this fungal infection.

Trauma to extremities, especially legs, may lead to bone and joint infections. Type of injury will determine the offending pathogen. Puncture wounds through sporting shoes may lead to *P aeruginosa* osteochondritis of the foot. Injury with mechanical devices such as lawn mower blades and agricultural equipment are generally polymicrobial and may contain multiple gram-negative bacilli such as *Serratia marcescens, Stenotrophomonas maltophilia,* and *Enterobacter cloacae*.[161,162] Molds such as *Fusarium, Pseudallescheria boydii,* and *Aspergillus* can also be participants. These types of infection required broad-spectrum antimicrobial therapy, surgical debridement, and, at times, amputation.

Diagnosis of acute osteomyelitis is confirmed by the use of radionuclide scans (bone scan) and MRI. In recent studies, MRI was superior to bone scan in detecting bone pathology. In addition, MRI better defines the presence of contiguous myositis, subperiosteal, and soft tissue abscesses. Radiographic bone changes generally take 10 to 14 days to appear. Magnetic resonance imaging and ultrasounds are useful in defining the amount of fluid in suspected infected joints. Computerized tomography has been used in lieu of MRI. In communities with limited resources, MRI or CT may not be available. Antimicrobial therapy should be started in patients with suspected infections. If possible, radiographs can be performed 2 weeks later to determine if bone changes are present. While aggressive surgical debridement of infected joints is practiced in many developed countries, not all joints require such an approach. Some joints may just require an initial aspiration followed by antibiotic therapy.

Initial empiric antimicrobial therapy should cover most likely pathogens. Vancomycin plus an antistaphylococcal penicillin (nafcillin or oxacillin) or clindamycin are frequently recommended. It is important to remind clinicians that clindamycin resistance among isolates of MRSA may be as high as 18% in some communities. In India, MRSA isolates were found to be resistant to various commonly used antibiotics: TMP/SMX, 80%; erythromycin, 83%; clindamycin, 54%; and ciprofloxacin, 61%.[154] Twenty-four percent of methicillin-susceptible isolates were resistant to TMP/SMX, while 34% were resistant to clindamycin. Cefazolin is an alternative for treating methicillin-susceptible isolates. Beta-lactams offer a more effective reduction in microbial burden in methicillin-susceptible *S aureus* infections. In young infants at risk for Hib, *S pneumoniae,* and *K kingae,* vancomycin plus a third-generation cephalosporin

or ampicillin-sulbactam is a better option. Subperiosteal abscesses and infections of the hip joint must be promptly drained. Uncomplicated infections of the bone can be treated with antibiotic courses as short as 2 to 3 weeks. Patients with complicated bone infections, especially those caused by MRSA, require at least 6 weeks. Most children with septic arthritis will require 2 weeks of therapy. Children with subacute and chronic infections will require longer antibiotic courses, up to 12 weeks. Some recommend suppressive therapy for years.[163] Some chronic infections may benefit from antibiotic-impregnated beads placed directly in the debrided site. Infections by *B henselae* may not require therapy.

Respiratory Infections

Acute respiratory infections are a leading cause of child mortality worldwide. Infants and children living in countries with limited resources are at greatest risk. Poverty, overcrowding, malnutrition, micronutrient deficiency, and other chronic infections predispose children to severe disease and higher mortality. The precise magnitude of the problem is lacking for many developing countries. In recent years, surveillance centers have been established to address the need for data. *S pneumoniae* is the most common bacterial cause of pneumonia in developing countries. The presence of bacteremia is a contributing factor to the severity of the disease. However, infections by viruses can be just as severe in the young compromised infant. Respiratory syncytial virus was a common cause of severe pneumonia in Kenya.[164] At a surveillance center in Guatemala, persons with acute respiratory infections were tested for common respiratory viruses (respiratory syncytial virus, influenza, parainfluenza, adenovirus, human metapneumovirus), *Chlamydophila* (*Chlamydia*) *pneumoniae, Mycoplasma pneumoniae,* and *S pneumoniae*.[165] As in other developing countries, most acute respiratory infection cases (60.4%) occurred in children younger than 5 years. Viruses were found in 52.6% of tested individuals, and approximately 72% of those individuals were younger than 1 year. Respiratory syncytial virus was the most commonly detected virus.

Respiratory infections are common among travelers. Influenza and parainfluenza viruses are among the most common pathogens. In a GeoSentinel study of travelers, influenza was reported frequently during the months of December through February in the northern hemisphere.[166] Travel duration of longer than 30 days increased the risk of influenza infection and lower respiratory tract involvement. Persons visiting friends and relatives were 6 times more likely to acquire influenza.

Most acute respiratory infections involve the upper respiratory tract. Otitis media, pharyngitis, and sinusitis are common in children.

Exudative tonsillitis in the absence of coughing is highly suggestive of a streptococcal infection. Antibiotic therapy would be merited. In many countries, point-of-care antigen detection assays are used to confirm the diagnosis. Throat cultures are still recommended for patients with negative antigen assays. Acute bacterial sinusitis is diagnosed by the use of clinical criteria. The persistence of upper respiratory tract symptoms, such as rhinorrhea and congestion for more than 10 days, accompanied by fever and coughing, supports the diagnosis.[167] This group of patients will also benefit from antimicrobial therapy. Most acute sinus and ear infections are caused by *S pneumoniae, Moraxella catarrhalis,* and *H influenzae*. Amoxicillin-clavulanic acid may be the preferred agent for most young children who are recipients of a complete series of pneumococcal conjugate vaccines. Under most circumstances, radiographic imaging of sinuses for diagnostic purposes is not indicated and its routine use is discouraged.

While most lung infections in infants and children are caused by viruses, bacterial coinfections are common. Fever, coughing, and tachypnea are common features in young children. The presence of stridor, wheezing, rhinorrhea, and congestion would suggest a viral pathogen such as parainfluenza or influenza.[168] Inspiratory crackles on auscultation suggest the presence of pneumonia. With these findings and symptoms, most patients do not require a chest radiograph. *Streptococcus pneumoniae* and *S aureus* are common causes of bacterial pneumonia. *Haemophilus influenzae* is also responsible for lung disease. Parapneumonic effusions and empyema are common complications. While IMCI provides guidelines for the diagnosis and management of pneumonia, in some countries, the use of guidelines by some nonphysician clinicians has been suboptimal. In one country, the diagnosis of pneumonia was correctly made in only 30% of cases, and appropriate care was only offered in 25% of cases.[169] Only approximately 40% of patients with severe pneumonia were hospitalized. The IMCI guidelines are undergoing revisions to improve the diagnosis and management of patients with pneumonia.[170] Bibasilar pneumonia in an older child suggests an atypical pathogen such as *M pneumoniae* and *C pneumoniae*. A macrolide would be indicated for this type of pneumonia. Outpatient antimicrobial treatment of most episodes of bacterial pneumonia can be accomplished with amoxicillin. Ampicillin or aqueous penicillin G should be used as the IV agent of choice for the completely immunized hospitalized child.[171] Ceftriaxone is the preferred agent for unvaccinated children. Coverage for *S aureus* is indicated in patients with empyema or other suppurative complications. Adding vancomycin or linezolid to the initial empiric therapy is

recommended in countries with a high prevalence of MRSA. Drainage of empyema is highly recommended.

Health care–associated pneumonias are a great burden to most institutions. High morbidity and mortality are associated with these types of infection. Most of these infections occur in children and adults requiring mechanical ventilation. *Pseudomonas aeruginosa, S aureus, Enterobacter cloacae,* and other gram-negative bacilli are responsible for most infections. Choice of antimicrobial therapy will be influenced by the susceptibility pattern of each respective health care facility. Agents such as piperacillin-tazobactam, cefepime, and meropenem are commonly used as initial empiric therapy.

In countries with a high incidence of HIV, *Pneumocystis jiroveci* pneumonia may present as an acute illness with tachypnea and evidence of hypoxemia. Migration of parasites, such as hookworms, through the respiratory tract may lead some clinicians to consider an acute respiratory infection. However, associated infiltrates are usually migratory and transient, and frequently there is the presence of eosinophilia in the peripheral blood smear. The presence of pulmonary infiltrates along with hilar or mediastinal lymphadenopathy may represent TB or an endemic mycosis such as histoplasmosis. Chronic lung infiltrates may present a chronic lung disorder such as cystic fibrosis.

Tuberculosis

Tuberculosis accounts for 8 million deaths annually around the world. In some countries, coinfection with HIV has a significant influence on response to therapy and mortality.[172,173] In most cases, an adult with symptoms or risk factors is usually involved. An adult with HIV accompanied by fever, fatigue, chills, night sweats, weight loss, coughing, and hemoptysis is a perfect source for *M tuberculosis*. Children are generally infected by a contagious adult. Three species form part of the *M tuberculosis* complex: *M tuberculosis, M bovis,* and *M africanum*. *M bovis* is distinguished from *M tuberculosis* by its resistance to pyrazinamide. *M africanum* is rare in the United States. Clinically, they all resemble each other.

The incidence of TB in the United States is much higher in foreign-born children and US-born children with foreign-born parents.[174] Most infected US-born children are exposed in the United States. Most are infants and Hispanic and diagnosed through contact investigations. One-third of children have extrapulmonary TB. Meningeal and miliary disease were more common in infants, as they represent dissemination. When screened, approximately 90% of children had a positive TST. Multidrug resistance (resistance to isoniazid and rifampin) was detected

in approximately 2% of children, while approximately 11% of children had isoniazid resistance. All children with pyrazinamide-resistant isolates had Mexican parents, which suggests that *M bovis* was the most likely pathogen in this group. Two-thirds of children were symptomatic with fever and cough, which was observed in more than half of the patients. A median of 52 days elapsed from onset of symptoms to initiation of treatment.

Cavitary pulmonary infiltrates, a "trademark" of pulmonary TB in adults, is rare in young children. When seen in children, it is usually in the adolescent years. Nonspecific pulmonary infiltrates, pleural effusion, military disease, hilar, and mediastinal lymphadenopathy have been observed in pediatric pulmonary TB.[175] Cervical lymphadenitis can also be observed in TB. Diagnosis of TB in children is greatly influenced by a history of exposure. Gastrointestinal and renal TB are rare in children. Chronic abdominal pain is reported with *M bovis*.

Spinal TB is still prevalent among children in developing countries.[176] Spondylitis with thoracolumbar vertebral body wedging and collapse and anterior vertebral scalloping are radiographic features commonly observed in patients with TB osteomyelitis of the spine.[172] Hydrocephalus, basilar inflammation of the brain, meningeal enhancement, and ischemic parenchymal infarcts are features that support the diagnosis of TB meningitis. Infection of the CNS results from the hematogenous spread of the organism, generally from the lungs.[177]

Tuberculosis is a rarely reported travel-related infection. Acquiring this infection is not easy. It is greatly influenced by duration of contact with the contagious individual and degree of contagiousness of that individual, as those with cavitary lung disease are more likely to infect others. In the United States, a large number of pediatric infections are observed among refugees, immigrants, and contacts of foreign-born individuals. At one point, more than 80% of pediatric infections were related to travel.[174] Staying with parents and relatives in high-prevalence regions was the major risk factor for these pediatric travelers.

Once TB is clinically suspected, confirming the diagnosis can be a challenging endeavor. Tuberculin skin testing with purified protein derivative and IGRA are frequently used to support the diagnosis. However, false-positive TST may result from a patient's receipt of BCG vaccine or from infection with a non-TB strain of mycobacteria. Testing by IGRA is limited to children 5 years and older. False-negative results are usually observed in children younger than 5 years. In addition, parasitic infections and malnutrition may alter the results of TST and IGRA, rendering their interpretation difficult.[178,179] The organism can be cultured

from lung tissue and sputum (in older children and adolescents), bronchial alveolar lavage, lymph node tissue, and gastric aspirates.

Once TB is suspected or confirmed, therapy can be initiated with a combination of medications that may include isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. Based on susceptibility patterns in the community, adjustments must be made to accommodate for resistance.[180] Depending on the disease presentation and treatment and susceptibility patterns, therapy may last 6 months to a year. Readers are recommended to consult an up-to-date source for specifics on the treatment of TB.[175] In many countries around the world, BCG vaccination takes place in early infancy with the goal of preventing disseminated disease. Many countries have established programs for the screening of at-risk individuals with the goal of instituting treatments for latent TB infection. Isoniazid has been the main agent for treating latent TB infection. However, in recent years, an increase in isoniazid resistance has led some to consider other agents, such as rifampin.[181] Local variations in the treatment of latent TB infection will be influenced by resistance patterns in the community.

KEY POINTS

- Febrile illness remains an important cause of morbidity and mortality in children around the world.
- Prompt recognition of etiology and institution of appropriate supportive care or antimicrobial therapy are critical as the means of improving prognosis.

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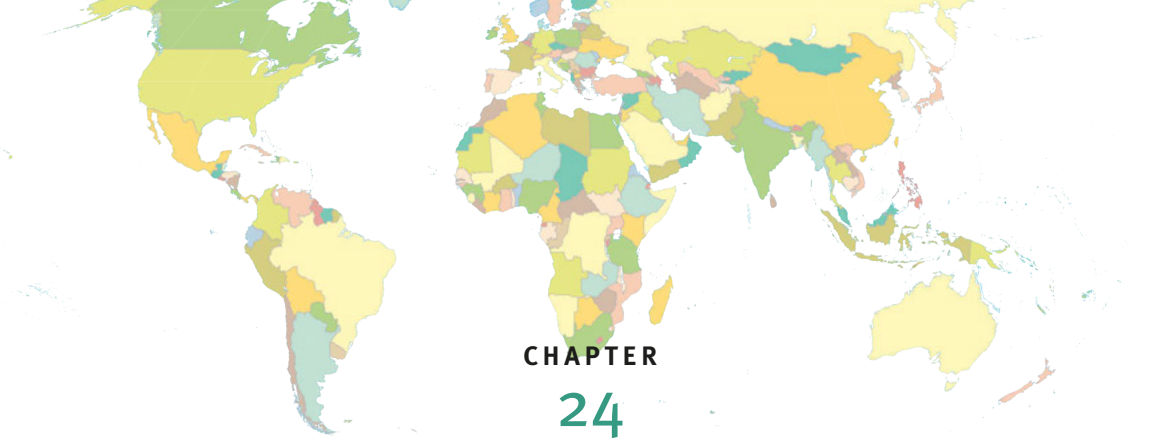

CHAPTER

24

Gastrointestinal Infections

John C. Christenson, MD, FAAP

INTRODUCTION

Respiratory and diarrheal infections, malaria, and tuberculosis (TB) are among the most common causes of morbidity and mortality in children in developing countries. Five of the 10 leading causes of death around the world affect children.[1,2] Approximately 6.6 million children younger than 5 years died in 2012. Close to 80% of these deaths are caused by infectious, neonatal, or nutritional conditions. Only neonatal deaths and respiratory infections surpass gastrointestinal (GI) infections as causes of infant mortality.[2,3]

Diarrhea is the main reason for hospitalization in pediatric age groups. It is estimated that more than 1 billion cases of diarrhea occur each year in developing countries.[4,5] Approximately 2 million children younger than 5 years die each year from GI infections caused by rotavirus, cholera, diarrheagenic *Escherichia coli,* typhoid fever, and dysentery, representing approximately 19% of total child deaths. Although globally there has been a 47% decrease in deaths compared with 1990, child mortality remains high in many parts of the world. Africa and southeast regions combined contain 78% of all diarrheal deaths, with 73% of them concentrated within 15 developing countries.[6] Malnutrition, immune deficiencies such as HIV/AIDS, dehydration, malaria, pneumonia, and infection by invasive enteropathogens such as *Shigella, Salmonella,* and *Entamoeba histolytica* are considered risk factors for fatal diarrhea. In Haiti, diarrhea was responsible for approximately 34% of hospitalizations and 11.5% of in-hospital deaths in children 5 years and younger.[7]

Fortunately, through improvements in infrastructure and rotavirus vaccination programs, many developing countries are seeing decreases in GI infections.[8] The introduction and use of oral rehydration solution (ORS) has also contributed to a decrease in mortality.

Because most morbidity and mortality is associated with diarrheal disease, parts of this chapter present a comprehensive understanding of the epidemiology and appropriate management of diarrheal disease in the developing world and the means to prevent it. Other GI infections, including hepatitis, with a focus on enterally transmitted hepatitis viruses A and E, will be covered.

EPIDEMIOLOGY OF ACUTE DIARRHEA IN CHILDREN

Rotavirus, enterotoxigenic *E coli* (ETEC), and *Shigella* remain the most important pediatric enteropathogens.[4,9] They are frequently associated with acute diarrhea, resulting in the passage of loose stools for fewer than 14 days. Other organisms, such as *Salmonella, Campylobacter,* adenovirus, *Clostridium difficile,* norovirus, astrovirus, *Cryptosporidium,* and *Giardia,* are associated with acute disease in the immunocompetent and well-nourished host. Most other viruses, with the exception of rotavirus and norovirus, are infrequent causes of acute diarrhea.[10] While norovirus-related outbreaks are well described in magnitude of numbers, rotavirus dwarfs all other viral enteropathogens. However, with widespread use of rotavirus vaccination, this epidemiologic fact may change with time. In recent years, norovirus has become a prevalent pathogen responsible for one-fifth of all acute gastroenteritis cases.[11] Based on surveillance studies from centers in sub-Saharan Africa and South Asia, most cases of moderate-to-severe diarrheal disease in children are caused by rotavirus, *Cryptosporidium,* ETEC-producing heat-stable toxin (ST-ETEC), and *Shigella*. Most deaths due to diarrhea occur in the first 2 years of life (~88%). Infections with ST-ETEC and enteropathogenic *E coli* in infants and *Cryptosporidium* in toddlers 12 to 23 months of age were associated with the greatest risk for dying.[12]

Community outbreaks of non-typhoid salmonellosis and shigellosis are common because both have low infective doses at approximately 100 and less than 200 colony-forming units (CFUs), respectively.[10] Norovirus attack rates can be high because they cause vomiting and produce large-volume stools that contain large amounts of the virus and can spread easily in areas with poor hygiene. This makes norovirus a highly infectious enteric pathogen. In addition, the low inoculum (<100 viral particles) required to produce infection also facilitates new cases. Noroviruses are responsible for most epidemic gastroenteritis outbreaks throughout

the world. Most seroepidemiologic studies may have underestimated its true prevalence.[13]

Diarrhea is the most common problem reported among travelers.[14] Acute GI illness was most common in travelers to North Africa and South-Central Asia.[15]

Mortality is much higher in younger children. As previously stated, the availability of ORS significantly diminished mortality observed in high-risk groups. While incidence of diarrhea has not changed in some regions, mortality clearly has. Invasive pathogens, such as *Shigella, Salmonella, Campylobacter,* and *E histolytica,* are more prone to cause mortality than organisms that are traditionally responsible for dehydration, such as rotavirus, cholera, and diarrheagenic *E coli*.

Dysentery remains a common problem in the tropics. The most common causative organism is *Shigella dysenteriae* type 1. The organism readily spreads from person to person through fecal-oral transmission. *S flexneri* is also frequently isolated. Mortality has been reported as high as 15% in some Latin America communities.

Vibrio cholerae O1 continues to cause worldwide disease. Mortality for this organism is estimated to be approximately 2%. Large epidemics still occur in many places of the developing world, including circulation of new strains, such as O139. In 2013, 47 countries reported cases of cholera for a total of 129,064 cases.[16] This represents an estimated disease burden of 1.4 to 2.3 million cases per year worldwide. Close to 50% of cases occur in Africa.[17] Cholera remains endemic in portions of India, Pakistan, Democratic Republic of Congo, Somalia, Afghanistan, and many countries of Southeast Asia. Outbreaks of cholera among poverty-stricken and displaced people in Zimbabwe and Haiti have been ongoing for many years.[18,19] In 2005, 78% of countries reporting indigenous cases of cholera were in sub-Saharan Africa.[20] The number of cases in Africa is close to 100 times higher than those reported in Asia and 16,600 times higher than incidences in Latin America. In that same year, case fatalities in Africa were 3 times higher than in Asia, with no reported deaths in Latin America. Since the beginning of the epidemic in November 2010, 703,510 cases of cholera have been reported in Haiti, resulting in 393,912 hospitalizations and 8,562 deaths.[21] In neighboring Dominican Republic, 31,628 suspected cases have been recorded. Farming and disruptions in sanitation in impoverished environments, such as refugee camps full of displaced people caused by economic or political turmoil, are frequent associations.

Cholera has always served as an indicator of unsafe drinking water, poor sanitation, and inadequate health care.[20] In Latin America,

investments to improve drinking water, sanitation, and health care not only reduced the number of cases and associated mortality but also decreased hepatitis A virus (HAV) and typhoid fever cases. In addition to clean water, access to ORS significantly decreased the mortality rate associated with this infection. The introduction of ORS in South Asia decreased the case fatality rate from 30% to less than 1%.[17,19] If cholera is to be eliminated, improvements in sanitation and water quality must occur in Africa. When ORS is not available, mortality remains high.[22] It is estimated that approximately 17% of the world's population lacks access to safe water and 42% lacks proper sanitary facilities. While vaccination has not succeeded in preventing all cases of cholera, improvements in sanitation have had demonstrable beneficial effects. Other pathogens, such as *Shigella*, *Salmonella*, *Campylobacter*, *Aeromonas,* and *Plesiomonas*, and protozoa and helminthic parasites were also common in impoverished areas with poor environmental sanitation.[23]

Studies demonstrate that lack of micronutrients, such as zinc, which is extensively lost in the stool of cholera victims, may lead to acrodermatitis enteropathica. While zinc supplementation will prevent this complication, it also reduces stool volume and shortens the duration of diarrhea.[24,25]

Accessibility to ORS, zinc supplementation, and basic health care will need to be enhanced. Along with these improvements, increased breastfeeding and measles vaccination rates contributed to the decrease in diarrhea-related infant mortality in Brazil.[26] Brazil can serve as a model to other countries. Before these interventions, infants exclusively receiving powdered milk or cow's milk were approximately 14 times more likely to die from diarrhea than those who were exclusively breastfed.[27] In addition, mass vaccination programs with effective vaccines against cholera will have beneficial effects, especially in regions with high prevalence of HIV infection.[20,28]

While it is well known to parents that ORS and feedings are essential for children with diarrhea, many affected children are still not receiving them. In a study, 52% of children received reduced or no food during diarrheal episodes.[29] This was frequently observed in children younger than 3 years. This trend had been increasing. In recent years, the percentage of children receiving ORS, recommended home fluids, and increased fluids during illness (as recommended by World Health Organization [WHO] guidelines) was 68% overall in surveyed countries. However, of greater concern, ORS use was less than 1% in Rwanda and 32% in Kenya and Nigeria. The reason for this decline in appropriate diarrheal management appears to be multifactorial. A shift in attention

toward HIV/AIDS, malaria, and TB treatment and prevention strategies may have diminished focus on diarrhea management. Creation of integrated approaches to care at the level of health care facilities and with health care workers appears to have resulted in gaps in the promotion of basic diarrhea management at the community level. In addition, limited resources at home caused by an inability to work because of TB, malaria, or HIV/AIDS appears to be a contributing factor. Increased knowledge may be beneficial, but it does not always lead to better clinical practices.[17]

The vicious cycle of severe GI infections leading to malnutrition is frequently seen in the developing world. Maternal and childhood undernutrition leads to approximately 3.5 million deaths and is responsible for 35% of the disease burden in children younger than 5 years.[28] Gastrointestinal infections and diarrhea impair not only weight and height gains but also physical and cognitive development. Malnourished children will have slower recovery from diarrheal episodes and be unable to catch up with non-malnourished children in height and weight. Malnourished children will have lower IQ scores compared with non-malnourished children.[28,30] Cognitive impairment due to diarrhea equates to nearly 10 IQ points. A decrease in cognitive abilities, as well as disease burden, affects the individual's ability to benefit from education and dramatically affects disability-adjusted life year (DALY) rates. Fitness impairment leads to approximately 17% decreased work productivity.[30]

It is estimated that 34% of disease burden in children is attributable to the environment. Most disease burden is associated with contaminated water and poor sanitation.[31] Environmental contributors to diarrheal diseases are closer to 94%. In rural Pakistan, higher prevalence of diarrhea was associated with lack of maternal education and exclusive breastfeeding, roundworm infection, and multiple young children in the home. Among predictors of mortality, severe malnutrition and non-breastfeeding are the most common.[32] Child mortality secondary to diarrheal diseases in Matlab, Bangladesh, was lowest in the postharvest months of February, March, and August, compared with the "hungry" months of September and October.[33] This effect was only observed in homes with no maternal schooling. Additional studies from the same region showed diarrheal deaths peaking in the hot-wet season.[34] In Ecuador, poor sanitation and unimproved water were highly associated with increased diarrheal risk, especially during periods of high rainfall.[35]

It is not uncommon to find patients infected with multiple pathogens at the same time. In a study in Mexico City, 52% of patients were infected with more than 1 enteropathogen, notably *E histolytica, E dispar,*

and *Salmonella*.[36] In Nigeria, approximately 36% of patients had multiple pathogens; among these were ETEC, enterohemorrhagic *E coli*, enteroaggregative *E coli* (EAEC), *Salmonella*, *Shigella*, and *E histolytica*.[37]

CHILDREN WITH PERSISTENT OR CHRONIC INFECTIONS

Diarrhea

Children with persistent diarrhea and malnutrition were more likely to die during their third year of life. *Persistent diarrhea* is defined as a diarrheal episode that lasts 14 days or more.[38]

In Matlab, Bangladesh, 49% of diarrheal deaths were in malnourished children with persistent diarrhea.[39] Most enteropathogens, bacterial, viral, or parasitic, are associated with persistent diarrhea and enteropathy. Prior malnutrition, recurrent infections, suboptimal or delayed diarrhea treatment, and micronutrient malnutrition are all contributing factors for persistent diarrhea.[38,40]

Postinfectious malabsorption syndromes are partially responsible for the malnutrition and failure of growth in young infants. This is prominently observed once mothers stop breastfeeding and exclusively rely on farmed or purchased goods and contaminated water for hydration. In populations with moderate malnutrition, low weight for age and diarrhea itself are risk factors for recurrent and persistent diarrheal diseases.[29] Recurrent diarrhea is not infrequent. Children may experience an average of 3 to 10 episodes per year.[4] Persistent diarrhea may occur in some children, prolonging increased stool output for more than 14 days; this can be observed mainly with parasitic infections and in immunocompromised children. Pathogens, such as measles, and enteric viruses, such as norovirus, are also responsible for malabsorption problems. Rotavirus is the leading cause of acute gastroenteritis in children younger than 5 years. Approximately 5% of infected children will die as a result of the infection and resulting severe dehydration. Infections may lead to malabsorption and resulting chronic diarrhea in survivors.

Patients infected with *Salmonella enterica* subspecies *enterica* serovar *Typhi* and *S enterica* subspecies *enterica* serovar *Paratyphi* are likely to develop prolonged infections and suffer from severe enteric fever.[41] Parasitic infections with *Cryptosporidium* and *Giardia* frequently lead to chronic diarrhea in the immunocompromised and malnourished host.

Enteroaggregative *E coli* has emerged as an important diarrheal pathogen. Acute and persistent diarrhea, and even asymptomatic infections, have been reported with this enteropathogen.[42,43] Patients with EAEC infections frequently present with watery diarrhea and at times with mucus, low-grade fever, nausea, and tenesmus. Adherence fimbriae

allow attachment of bacteria to epithelial cells, which leads to a biofilm formation that allows infection to persist.[44] The release of toxins results in secretory diarrhea. In 2011, an EAEC strain, O104:H4, was associated with a large outbreak of hemorrhagic colitis and hemolytic uremic syndrome (HUS) in Germany.[45] Persistent diarrhea is common in young infants. Community and nosocomial outbreaks have also been reported. It appears that a large amount of bacteria (at least 10^{10} CFU) is required for diarrheal illness. The incubation period is approximately 8 to 18 hours. The illness is self-limiting in most hosts and only requires ORS and supportive care. Urinary tract infections are also recognized with this group of enteric pathogens.

Gastritis

Helicobacter pylori is a common cause of gastric and peptic ulcer disease. The prevalence in lower-income countries is much higher than in higher-income countries, 80% to 90% versus 10% to 50%, respectively. Infection rates are closely associated with low economic status, poor sanitation, overcrowding, and poor hygiene. Of interest, infected children are more often infected with other enteral pathogens; this supports a fecal-oral route of transmission. Not surprisingly, in Bangladesh, infections by this organism appear to occur more often in children after they are weaned from human milk.[46] Among Burmese refugees in Australia, 80% of tested individuals had evidence of *H pylori* infection.[47]

Enteric Fever

Enteric fever is a common systemic infection observed in the developing world. It can be caused by *Salmonella enterica,* which includes 2 serotypes, *S Typhi* and *S Paratyphi* A, B, or C. *Salmonella Typhi* is estimated to cause approximately 22 million infections worldwide every year with 200,000 deaths; *S Paratyphi* is responsible for 5.4 million illnesses.[48] While it was initially thought that *S Paratyphi* caused a milder disease than typhoid fever, recent experience supports the opposite.[49] The Indian subcontinent has the highest incidence of enteric fever. Enteric fever is prevalent worldwide, but incidence of typhoid and paratyphoid fever is only low in those countries where public health and sanitation have been improved.

Tropical Enteropathy

Contaminated environments and recurrent GI infections will lead to chronic enteropathies and malabsorption syndromes such a tropical enteropathy (tropical sprue),[50–53] which lead to vitamin (B_{12}), fat, amino acid, and micronutrient deficiencies.[54] Most of these enteropathies

are subclinical.[55] In developing countries, 26% of preschool-aged children are underweight. More than 50% of childhood deaths are associated with being underweight[56–58]; these children are more likely to die from pneumonia, measles, malaria, and diarrhea.[59] This is frequently associated with infections caused by a multiplicity of different viral, bacterial, and parasitic pathogens. No single organism can be identified as a cause in all cases. Reports from parts of South America, the Caribbean, and Southeast Asia have enteropathy rates much higher than areas of Northern Africa, Southern Europe, and parts of Africa.[52,53] While infectious agents are a frequent trigger for this condition, there appears to be a genetic predisposition for it, specifically in the presence of histocompatibility antigens AW19 or AW31.[52] Bacterial colonization through the adhesive properties of bacteria, such as *E coli*, *Salmonella*, and *V cholerae,* is responsible for much of the observed disease, especially the blunting of intestinal villi with increased lymphocytic and plasma cell infiltrations. Blunting of villi is in part responsible for the malabsorption observed in these patients. Patients with more of a colonic involvement are unable to absorb the necessary fluids to prevent diarrhea, which makes chronic diarrhea common. As a consequence of malabsorption, weight loss is a prominent feature, followed by malnutrition and vitamin B_{12} and folate deficiencies. With mucosal injury to the bowel, there is an increase of gut hormones such as enteroglucagon, which is responsible for reduced small intestine transit time, leading to further intraluminal bacterial colonization, perpetrating further mucosal injury.[52] This vicious cycle can be eliminated by eradicating bacterial overgrowth with antimicrobial agents and healing the mucosal lining with folates. In addition, an adequate diet, in combination with antimicrobial therapy and folates, is usually necessary.

Other Enteric Pathogens

Malabsorption is frequently observed in the immunocompromised host, such as those affected by HIV, because chronic infections with organisms such as *Cryptosporidium parvum, Isospora belli,* and *Giardia* often occur in this population. While rare, intestinal TB may also be responsible for chronic diarrhea and malabsorption.

PARASITES AND OTHER GASTROINTESTINAL PATHOGENS

Parasites

Parasites frequently cause diarrhea in developing countries. Recurrent infections may lead to chronic diarrhea, malabsorption, anemia, micronutrient deficiencies, and malnutrition.[60] Chronic infections are

common in the immunocompromised host with HIV/AIDS and malnourished children. Intestinal parasites were observed in approximately 47% of children with diarrhea in Delhi.[61] *Cryptosporidium, Giardia intestinalis,* and *E histolytica* were the most commonly found. Intestinal parasites were found in 19% of the examined population in a national prevalence study from Iran; *G intestinalis* was the most common.[62] The highest infection rates were found in rural children between 2 and 14 years of age. Helminths, such as *Ascaris lumbricoides* and *Trichuris trichiura,* were found less frequently.[61–63] Additional studies confirmed the importance of *Giardia* and *Cryptosporidium* as parasitic enteropathogens.[64–68] The prevalence of hookworms, *Schistosoma mansoni,* and *Ascaris lumbricoides* was 15% or higher in displacement camps within Sierra Leone.[65] In addition to *Shigella, E histolytica, G intestinalis,* and *S mansoni* were frequently found in the stool of patients with bloody diarrhea in Tanzania.[69] Among children with parasitic infections, Nigerian children with large parasite burdens were shorter in height and had lower weights than noninfected children.[70] As in most countries, geophagia or pica is associated with nematode intestinal parasitic infections.[71] Prevalence of enteric parasites in Haiti was significantly higher in the rainy season than the dry season.[72]

Parasitic infections associated with chronic inflammation are also associated with cancer. Chronic infections of the urinary bladder with *S haematobium,* the portal venous system of the liver with *S mansoni* and *S japonicum,* and the hepatobiliary tract with *Opisthorchis* or *Clonorchis* may lead to various types of malignancies. Early diagnosis and treatment and measures to prevent infection will help reduce incidence of these cancers.

Hepatic and Biliary Infections

Hepatic and biliary infections are frequently associated with poor sanitation and contaminated food and water. A diverse number of pathogens, such as HAV and hepatitis E virus (HEV), are frequently associated with these conditions. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequently transmitted perinatally but are also transmitted through contact with contaminated body fluids. These agents can be responsible for jaundice seen in acute infections. Dengue, acute schistosomiasis (Katayama fever), human herpesvirus, and enteroviruses could also be responsible for acute jaundice. Infections such as leptospirosis, typhoid fever, syphilis, and malaria are also responsible for jaundice in the tropics. In some instances, chronic liver disease will develop specifically in those with HBV and HCV. Venoocclusive and portal hypertension have been observed in patients with chronic infections with schistosomiasis.

Splenomegaly and bleeding varices will be ultimate complications. Biliary tract disease is usually related to parasitic organisms, such as ascariasis, clonorchiasis, and opisthorchiasis. Early diagnosis is imperative because chronic infections of the biliary tract may lead to pancreatic carcinomas and cholangiocarcinomas. Organisms such as *E histolytica* can also cause liver abscesses that would present with right upper-quadrant pain, hepatomegaly, and fever. These patients may have a history of a preceding diarrheal illness, fever, or jaundice.

APPROACHING THE CHILD WITH DIARRHEA

Oral Rehydration Fluids

Dehydration is responsible for most morbidity associated with acute diarrhea. Promptly replacing fluids and electrolytes is critical in the management of this condition by reversing dehydration but also replacing ongoing fecal losses. Fluids can be administered intravenously or with ORS in the severely dehydrated child. Different ORS formulations have been suggested, but because glucose-based ORS (G-ORS) is inexpensive and easy to prepare, it remains the standard recommended ORS for managing the dehydrated child with diarrhea. Rice-flour–based ORS preparations have demonstrated a slightly better reduction in stool output than G-ORS in the first 6 hours of treatment, but this benefit did not persist after 12 hours of treatment. Overall, they appear to have an efficacy similar to G-ORS.[73]

Since 1978, the recommended WHO and United Nations Children's Fund (UNICEF) ORS preparation was a formulation containing 90 mEq/L sodium with an osmolarity of 311 mOsm/L. While effective in replacing fluid losses, the preparation had no effect on stool volume or duration. The formulation was considered hyperosmolar because of its sodium content; thus, hypernatremia was a great concern. This was particularly so in young infants and children with non-cholera diarrhea. So work on a new formulation was deemed necessary.

In a clinical trial in Bangladesh, a formulation containing 60 mmol/L sodium with an osmolarity of 250 mOsm/L (reduced-osmolarity solution) was found to be equally effective as the WHO solution containing 90 mEq/L sodium but with no significant hyponatremia in any treated patients.[74] In a similar study, using a 75 mmol/L sodium formulation (245 mOsm/L) for patients with acute diarrhea resulted in a 33% reduction in the need for intravenous (IV) fluids; results were similar to the standard WHO formulation at the time.[75] In a meta-analysis of existing studies, reduced-osmolarity ORS, when compared with standard WHO ORS, was associated with fewer unscheduled IV fluid infusions, reduced

stool volumes, and less vomiting with no increase in hyponatremia episodes.[76] Since 2002, the WHO formulation has contained 75 mEq/L sodium and 75 mmol/L glucose with an osmolarity of 245 mOsm/L.[77–79]

In the United States, maintenance ORS such as Pedialyte (Abbott Laboratories, Abbott Park, IL) containing 45 mmol/L sodium with an osmolarity of 250 mOsm/L is frequently used as ORS in children with diarrhea. Although the sodium content is lower than the WHO formulations, they were found to be as effective as ORS in a non-comparative study.[80]

When used appropriately, ORS effectively corrects mild to moderate dehydration in infants and children with acute gastroenteritis. Oral rehydration solution can minimize the need for IV fluid infusions even in higher-income countries with good access to health care.

Assessing and Treating Dehydration

In the child with diarrhea, the initial step in management is to quickly assess the degree of dehydration. Important questions to ask include, how many stools per day? What is the volume of the stools? Is the child vomiting? Clinicians caring for infants and children with diarrhea in lower-income countries will find excellent resources to assist them in the care of these patients.[77,78] Most children could be treated at home; however, medical evaluation of an infant or child with acute diarrhea is recommended if the infant is younger than 6 months, has preexisting medical conditions, or is highly febrile (≥39°C); there is visible blood in the stool; and there are signs of toxicity or severe dehydration (Table 24-1). Mental status changes (eg, lethargy, irritability, unresponsiveness), persistent vomiting that interferes with taking oral fluids, and a suboptimal response to or an inability to take ORS should also trigger a medical evaluation.[77]

Management of acute diarrhea is based on the degree of dehydration. Oral rehydration solution can be used for rehydration but should be initiated promptly after onset of diarrhea (within 3–4 hours). Once dehydration is corrected, an age-appropriate diet should be restarted. Breastfeeding should not be interrupted. If diarrhea continues, an appropriate amount of fluid should be given to match ongoing losses. In the child with minimal or no dehydration, treatment is targeted at providing adequate fluid while continuing age-appropriate diet. In general, for each gram of stool output, 1 mL of fluid should be administered. Alternatively, 60 to 120 mL of ORS should be given for each diarrheal stool or vomiting episode if the child weighs less than 10 kg. In the child weighing more than 10 kg, 120 to 140 mL ORS is needed. In the child with mild to moderate dehydration, at least 50 to 100 mL/kg

Table 24-1. Assessment of Dehydration for Infants and Children

SYMPTOM	MINIMAL OR NO DEHYDRATION (<3% LOSS OF BODY WEIGHT)	MILD TO MODERATE DEHYDRATION (3%–9% LOSS OF BODY WEIGHT)	SEVERE DEHYDRATION (>9% LOSS OF BODY WEIGHT)
Mental status	Well; alert; interactive	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or non-palpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal; tears present	Slightly sunken; tears decreased	Deeply sunken; tears absent
Oral mucous membranes	Moist	Dry	Parched
Skin turgor	Instant recoil	Recoil in >2 sec	Recoil in >2 sec
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Adapted from Hahn S, Kim S, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. *Cochrane Database Syst Rev.* 2002;(1):CD002847; and King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52(RR-16):1–16.

body weight of ORS should be given within 2 to 4 hours to replace existing fluid deficit. An additional amount is given to replace ongoing losses. In the severely dehydrated child, a 20 mL/kg body weight IV bolus of lactated Ringer solution or normal saline should be given until perfusion and mental status normalize, followed by appropriate fluids (5% dextrose, half normal saline) at twice the maintenance fluid rates. If IV access is not available and the child is unable to drink, ORS can be administered by nasogastric tube for the child who needs fluids to replace losses (20 mL/kg/h for 6 hours, for a total of 120 mL/kg).[78] Intravenous fluids of 5% dextrose, one-fourth normal saline, with

20 mEq/L potassium chloride, can also be administered. Oral rehydration solution can be initiated if the health care facility is more than 30 minutes away.

The US Agency for International Development (USAID) Micronutrient Program offers a simplified method of computing fluid needs for the first 4 hours of treatment in infants and children with diarrhea (Table 24-2). After the first 4 hours of rehydration, the child is reassessed for signs of dehydration and additional fluid needs are calculated. Health care professionals and families need to be educated on the proper use of ORS.[81]

The child with severe dehydration needs to receive fluids promptly, preferably IV fluids. While referral to a health care facility with the capability to administer IV fluids is indicated, fluid administration should not be delayed. Whenever possible, give more fluids than needed. If the infant can breastfeed, continue to do so, but do so more frequently and for longer periods. Oral rehydration solution or clean water (previously boiled) can be given to older children. Approximately 50 to 100 mL of fluid (¼ large cup) should be given with each loose stool in children younger than 2 years; older children can receive double that amount.[77] Soft drinks, sweetened tea, juices, and coffee should not be given, as they are likely to increase stool output. Caregivers need to monitor adequacy of fluid intake in children who are sent home. Children should return to the clinic for reevaluation if they are passing more stools, are persistently thirsty, have sunken eyes, have decreased urine output, do not seem to be getting better, are febrile, and are not eating or drinking well.

Diagnostic Testing

Once the correction of dehydration is underway, carefully assessing stool characteristics (ie, watery versus bloody) and other clinical features (eg, high fevers, abdominal pain) will help determine the cause of the diarrhea, which will dictate additional therapies if needed.[78] Use of smears for fecal leukocytes as an initial screen has been recommended. Patients

Table 24-2. US Agency for International Development Micronutrient Program Fluid Needs for the First 4 Hours of Treatment for Dehydration

AGE[a]	≤4 mo	4–12 mo	1–2 y	2–5 y
Body weight, kg	<6	6–<10	10–<12	12–19
Amount of fluid, mL[b]	200–400	400–700	700–900	900–1,400

[a] Use of child's age only when weight is not available.

[b] Rough calculation of fluids: weight of child (in kilograms) multiplied by 75.

with positive smear results would be more likely to have a bacterial pathogen for which a stool culture would be ordered. Unfortunately, studies have demonstrated variable results in patients with bacterial enteric infections. Sensitivity of the fecal leukocyte test in patients with shigellosis was 73%, while for most other bacterial pathogens it was approximately 50% at best.[82] Bacterial stool cultures, rotavirus, and *Giardia* or *Cryptosporidium* antigen detection assays, and materials for the examination of other fecal parasites, are commercially available in most countries. However, some health care facilities within developing countries may lack these because of limited resources; clinical assessments of the patient will usually dictate the management pathway.

A diagnostic GI panel (FilmArray, BioFire, Salt Lake City, UT) can detect up to 22 GI pathogens including EAEC, ETEC, Shiga toxin–producing *E coli* (STEC), norovirus, *E histolytica, G intestinalis,* and *C difficile*.[83]

Antimicrobial Therapy

Overemphasis on antimicrobial therapy and other medications will have limited effect on infantile diarrhea-related mortality. In developing countries, most patients with diarrhea do not require antimicrobial therapy. Most guidelines recommend antimicrobial therapy only in suspected cases of cholera or dysentery.[78,84] In most instances, an ongoing outbreak leads to treatment recommendations. Most diarrheal illnesses are self-limiting, and antibiotic therapy is costly and leads to resistance or infections with *C difficile*.

In addition to hydration fluids, the patient with bloody stools (when dysentery is suspected in an area) should receive 5 days of antibacterial therapy against *Shigella*.[78] The precise cause of bloody diarrhea would require a stool culture with at least 2 to 3 days of incubation and workup for results. The identification of diarrheagenic *E coli,* with the exception of STEC, requires the use of polymerase chain reaction technology.[85]

While routine use is generally discouraged, certain infections should be treated with antimicrobial therapy.[77,78] In addition to shigellosis, antimicrobial treatment of the following conditions should also be considered: giardiasis, cholera, amebiasis, salmonellosis in the young febrile infant or infant with a positive blood culture and signs of dissemination, or the compromised host with *Campylobacter* or certain types of diarrheagenic *E coli* (eg, ETEC, EAEC).[86]

Widespread use of antibiotics leads to resistance. In a study from rural western Kenya, among stool specimens from 3,445 persons, 32% yielded at least one bacterial pathogen.[87] *Shigella,* the most commonly isolated pathogen (16% of all illnesses), was susceptible to frequently used agents

in the community in less than 25% of occasions. Most persons were treated with an antibiotic to which their isolate was resistant. In data from an active surveillance community-based study in the Peruvian Amazon, *Shigella,* the most common cause of symptomatic disease, was resistant to ampicillin in 73% of isolates, 62% to chloramphenicol, 79% to trimethoprim-sulfamethoxazole (TMP/SMX), and 83% to tetracycline.[88] Ninety-seven percent of isolates were susceptible to ceftriaxone, 84% to azithromycin, and 97% to ciprofloxacin. In a similar study from Gaza, Palestine, high-level resistance was observed among isolates of *Salmonella* and *Shigella*.[89] In this region, ampicillin and TMP/SMX were no longer recommended agents for the empiric treatment of childhood diarrhea. Similar high-level resistance has been reported in Nepal and Tanzania.[69,90]

In Thailand, most isolates of *Campylobacter* are resistant to ciprofloxacin and more than 90% of *Shigella* isolates are resistant to TMP/SMX.[91] While azithromycin has become the recommended agent for treating *Campylobacter,* resistance to this agent is increasing. Similar findings have been observed among children with *Campylobacter* diarrhea in rural Egypt.[92]

Treatment is not routinely indicated in uncomplicated *Salmonella* enteritis.[93,94] When necessary, azithromycin or a third-generation cephalosporin, such as ceftriaxone, is the agent of choice for treating diarrhea, especially in children.[95,96] A single dose of azithromycin is effective for treating cholera.[97–99] A fluoroquinolone, such as ciprofloxacin or levofloxacin, is considered an alternative in patients with shigellosis, ETEC, or EAEC.[84,100] Ciprofloxacin and a poorly absorbable antibiotic, rifaximin, have been shown to be effective against EAEC among travelers. Unfortunately, multidrug-resistant isolates of EAEC have been recognized in Africa.[101]

Treatment of rotavirus gastroenteritis has been supportive with emphasis on correcting and preventing dehydration. There are no existing antiviral agents effective against this pathogen or any other virus responsible for diarrhea. However, in a double-blind, placebo-controlled trial from Egypt, a 3-day course of nitazoxanide was found to significantly reduce the duration of rotavirus disease in hospitalized pediatric patients.[102] Nitazoxanide is an anti-infective medication with broad activity against *Giardia, Cryptosporidium,* and *C difficile.* In vitro, the agent inhibits replication of various types of viruses, including rotavirus.[102] In a clinical study, nitazoxanide and probiotics were shown to reduce the duration of hospitalization for treatment of acute diarrhea due to rotavirus.[103]

Antibiotics and Hemolytic Uremic Syndrome

In the United States and other higher-income countries, clinicians are advised not to give antibiotics empirically to children with bloody diarrhea because this therapy may increase the risk of HUS if the child is infected with *E coli* O157:H7 (also known as STEC O157). In a study by Wong and associates in Seattle, WA, antibiotic treatment of children with *E coli* O157:H7 infection increased their risk for HUS (relative risk, 17.3).[104] In Minnesota, the use of ß-lactams to treat O157 infections was associated with development of HUS.[105] These studies prompt the questions, should a practitioner in a developing country have the same concern when evaluating a child with bloody diarrhea? Is there STEC O157 in developing countries? While the precise prevalence is not well known, data are available from some countries.

In Thailand, approximately 7% of food samples yielded STEC O157, but with no isolations from diarrheal specimens.[106] In 1992, there was a large outbreak of bloody diarrhea by *E coli* O157:H7 in Swaziland in southern Africa, which was associated with drought, carriage of the organism by cows, and heavy rains contaminating surface water.[107] In 1996, an outbreak of hemorrhagic colitis occurred in the Central African Republic. Initially it was suspected to be caused by viral hemorrhagic fever; however, an enterohemorrhagic strain of STEC was implicated after further investigation.[108] The major contributing risk factor was the consumption of locally made meat pies with smoked zebu meat. In an analysis of existing studies, approximately 8% of participants with STEC and *Shigella dysenteriae* type 1 developed HUS.[109]

In 2011, an epidemic of STEC O104:H4 was observed throughout Europe, with 4,100 cases reported in the European Union and Germany and France being the most affected countries.[110,111] Several imported cases were reported in other non-European countries, including the United States. Hemolytic uremic syndrome was observed in 900 cases. Fifty infected persons died of the infection and its complications. Asymptomatic infections appear to be the common event. Contaminated fenugreek sprouts appeared to be the source of the epidemic.[110,111]

Without proper microbiologic laboratory surveillance, clinicians may assume *Shigella* dysentery is the cause of bloody diarrhea and treat the child with an antimicrobial agent. Making the distinction from cholera is not difficult, as profuse watery diarrhea is characteristic of cholera, while bloody stools and severe abdominal pain are uncharacteristic. Empiric use of antibiotics without laboratory confirmation may lead to HUS if the patient is infected with STEC. Most US laboratories test

for *E coli* O157:H7. Non-O157 STEC is being reported more often.[112] Hemolytic uremic syndrome has also been associated with these strains. Unfortunately, not all laboratories routinely test for these organisms. Hemolytic uremic syndrome is not only limited to STEC, as cases have been reported after infections by *S dysenteriae*.[113,114]

Zinc Supplementation

Increased stool zinc loss is frequently observed in patients with diarrhea. Studies link milder zinc deficiencies with childhood diarrhea. Patients receiving supplementation have improved outcomes in acute or chronic diarrhea. Zinc supplementation may even have a prophylactic effect. In randomized, controlled trials from Bangladesh, India, and Nepal, children with cholera or other causes of acute diarrhea who received zinc supplementation had significantly shorter durations of diarrhea and reduced stool output.[24,25,115,116]

In a review paper by Scrimgeour and Lukaski, the authors argue that in light of rising antimicrobial resistance around the world, along with a lack of effective antidiarrheal vaccines, the use of zinc supplementation could have a beneficial effect in diminishing morbidity associated with diarrheal disease.[24] The current USAID, UNICEF, and WHO recommendations for zinc supplementation are based on an analysis of available randomized, controlled trials.[78] Children with acute diarrhea should receive 20 mg per day of zinc for 10 to 14 days. Infants younger than 6 months should receive 10 mg per day.[24,84] There is evidence that zinc supplementation may prevent certain parasitic infections as well. In Sazawal and associates' trial in India, the clinical benefit of zinc supplementation was greater in children with stunted growth than in those with normal growth.[116] Use of zinc supplementation was found to be highly cost-effective. In contrast, the role of zinc supplementation in children with acute diarrhea in the developed world requires further study.[115]

Conflicting data have emerged in recent years. In a study from South Africa, the use of zinc alone or in combination with vitamin A or other micronutrients did not reduce diarrhea or morbidity related to respiratory infections.[117] Years earlier, a study from Tanzania demonstrated that vitamin A significantly reduces the risk of severe watery diarrhea but only among children with HIV-related wasting disease and malnourishment.[118]

Probiotics

Probiotics, such as human *Lactobacillus casei* strain GG and *Saccharomyces boulardii*, have demonstrable beneficial effects in treating rotavirus gastroenteritis.[115,119] Analysis of many randomized, placebo-controlled trials

confirms that probiotics significantly reduced antibiotic-associated diarrhea and acute diarrhea caused by multiple organisms.[120] However, most of these studies were performed in higher-income countries. It is unclear how beneficial these supplements would be in malnourished children. More studies are needed before they can be recommended for routine use in children with diarrhea from lower-income countries.[121] In a review of published data, the use of *Saccharomyces boulardii* for the treatment of childhood diarrhea demonstrated a significant reduction in duration of diarrhea.[122] In a randomized, double-blind, placebo-controlled trial in previously healthy children attending child care centers in Mexico, daily administration of a probiotic containing *Lactobacillus reuteri* had a significant effect in reducing incidence and severity of diarrheal and respiratory tract infections.[123]

Antidiarrheal Medications

Antidiarrheal agents such as kaolin-pectin and diphenoxylate-atropine (Lomotil) have been used in children with acute diarrhea. However, no beneficial therapeutic effect was observed in a placebo-controlled trial in Guatemala.[124] Similar results were noted in a study from Sweden.[125] Diphenoxylate-atropine use in young children has been associated with severe complications, such as paralytic ileus, vomiting, abdominal discomfort, and lethargy; its use in children should be avoided.[126–128]

Bismuth subsalicylate (BSS) has been shown to decrease duration of diarrhea in children.[129,130] In a randomized, placebo-controlled study from Peru, infants with acute diarrhea who received BSS had significant reductions in total stool output, total intake of ORS, and hospitalization.[130] A similar study from Chile demonstrated identical findings.[129] In both studies, blood levels of bismuth and salicylates were measured and found to be below toxic levels. In patients with diarrheal infections caused by ETEC, BSS was found to be very effective in diminishing the duration of diarrhea and reducing symptoms such as nausea and abdominal pain.[129,130] In addition, BSS-treated individuals cleared ETEC from their intestinal tracts quicker than untreated persons.[131] Of interest, even BSS-treated university students with shigellosis did not experience a prolonged course of diarrhea.[132] Children with chronic diarrhea have also benefited from BSS.[133,134] This raises the question of why BSS is not used more often for treating diarrhea. The relationship between use of salicylates (especially aspirin) and Reye syndrome dampened any desire for using this medication in children.

Adults frequently use loperamide for relief of diarrheal symptoms. It is generally well tolerated. In young children with acute diarrhea, especially those younger than 3 years, loperamide use has been associated

with paralytic ileus, drowsiness and lethargy, and even death.[135,136] It appears that a malnourished, moderately to severely dehydrated, systemically ill child with or without bloody stools is at the highest risk for these adverse events. However, despite its known safety profile, some children have benefited from the medication.[137,138] However, at this time, risks outweigh potential benefits and its use is not recommended for young children.

Use of loperamide for treatment of diarrhea in children has been discouraged. In a Cochrane review by Li and colleagues, the use of loperamide as an adjuvant to oral rehydration was associated with a shorter duration of diarrhea and improved outcomes. Most children appear to tolerate the medication well. However, the agent should be avoided in children younger than 3 years because incidence of death, ileus, and lethargy is higher in this group.[136] Children with severe colitis and infections by *C difficile* and who are severe dehydrated should not be treated with the agent.

PREVENTING GASTROINTESTINAL INFECTIONS

Rotavirus

While improvements in the quality of water, housing, and sanitary infrastructures and use of antimicrobial therapy have reduced the frequency of GI disease caused by other enteric pathogens, the magnitude of rotavirus infection had remained unchallenged. However, in recent years, the introduction of live, attenuated rotavirus vaccines has resulted in a significant reduction in the number of cases of severe gastroenteritis in countries where the vaccine was introduced. A decrease in infant deaths secondary to gastroenteritis has already been observed in some developing countries.

The first rotavirus vaccine (RotaShield, Wyeth Lederle Vaccines SA, Belgium, EU) was licensed in the United States in 1998 but was withdrawn a year later because of concerns over increased risks of intussusception. There are currently 2 vaccines available commercially in the United States and many other countries. A pentavalent vaccine (RV5), RotaTeq (Merck, Whitehouse Station, NJ), and a monovalent vaccine (RV1), Rotarix (GlaxoSmithKline, Research Triangle Park, NC), were found to be highly effective (98%–100%) in preventing severe gastroenteritis; both demonstrated reductions in diarrhea-related hospitalizations.[139,140] No increase in cases of intussusception was observed in these initial randomized, placebo-controlled studies. However, in postmarketing surveillance, rotavirus vaccination with RV5 in US infants was associated with approximately 1.5 excess cases of intussusception per

100,000 recipients after a first dose.[141] In another study, the attributable risk of intussusception after receiving 2 doses of RV1 was estimated to be 5.3 cases per 100,000 infants vaccinated.[142]

In 2006, WHO recommended use of rotavirus vaccines in the United States and Europe. In the 2007–2008 season, reduction in diagnosed cases of rotavirus were greater than expected despite there not being a full year of vaccination, indicating that any degree of vaccination may induce some herd immunity. Based on these findings, in 2009, WHO extended its recommendations for rotavirus vaccine to be included in all national vaccination programs around the world. The WHO prioritized efforts in nations where diarrheal disease accounts for more than 10% of childhood mortality. Studies from Latin America and Africa have demonstrated significant reductions in hospitalizations, diarrhea-related health care visits, and, in one study, diarrhea-related deaths.[143,144]

In resource-limited settings, there have been concerns that the vaccine may not be as immunogenic as in the developed world. This may be due in part to host and environmental factors, such as malnutrition with poor absorptive capacity, interference by human milk antibodies, or concurrent enteric infections. However, studies in El Salvador show that one dose confers approximately 50% protection and has its greatest effect in the 2- to 6-month age range when the risk of death is greatest.[145] Overall vaccination programs there showed 40% to 50% reduction in admissions for gastroenteritis from rotavirus in the 2008–2009 season and approximately 76% protection overall. Additional studies in India, which accounts for 23% of worldwide deaths due to rotavirus, show that 44,000 deaths, 293,000 admissions, and 328,000 outpatient visits were prevented by the national rotavirus immunization program, saving about US $20.6 million per year.[146] Additional studies confirm the benefits of vaccination.[147–149] A new monovalent human-bovine rotavirus vaccine (116E) was tested in a randomized, double-blind, placebo-controlled trial in Indian infants. Vaccine efficacy against severe gastroenteritis was 53.6%, and 56.4% in the first year of life.[150] This vaccine was developed in India through a government-led public-private partnership.[151]

Rotavirus Vaccines and Adverse Events

Adverse events from vaccination are very few. A possible increase in intussusceptions is the most discussed and studied major concern. Recently, post-licensure surveillance from Brazil and Mexico demonstrated a slight increase in cases of intussusception in association with receipt of RV1.[143] The combined annual excess of 96 cases of intussusception in these countries (with 5 deaths of intussusception) needs to be put in perspective with the fact that the vaccine prevented approximately

80,000 hospitalizations and 1,300 deaths attributed to diarrhea each year. No increase in intussusception was observe in a small study from Jamaica.[152]

Vaccination in immunocompromised hosts, especially those with severe combined immunodeficiency, has been shown to cause severe gastroenteritis with protracted viral shedding.[153] No increase in adverse events was seen in HIV-positive patients when compared with the general population; the maximum time of viral shedding postvaccination was approximately 7 days, the same as in HIV-negative patients. There was no effect on the immunosuppressive effects of primary HIV disease.

Vaccine Use in Developing Countries

Reducing the need for hospitalization by half still has a significant effect on disease and health care expenditures. It should be the priority of health care systems worldwide to develop vaccines that will prevent enteric infections. Vaccines against ETEC, *Shigella,* and *Campylobacter* and a more effective vaccine against typhoid fever and cholera would have significant effects on disease burden. These are high priorities within WHO.[154]

Various typhoid fever vaccines are commercially available around the world. An injectable formulation such as Vi capsular polysaccharide vaccine and an oral form of the live, attenuated vaccine (Ty21a) are available in the United States. Vaccine efficacy has been extremely variable, ranging from 19% to 96% with an average vaccination efficacy closer to 50%. Many endemic countries have vaccination programs targeting typhoid fever. To maintain immunity, revaccination every 2 to 3 years limits their clinical utility in countries with limited resources. Many countries lack the necessary funds to maintain an active immunization program. However, if made available, effective vaccines against rotavirus, typhoid fever, ETEC, and *Shigella* would significantly affect the morbidity and mortality of young children around the world.[154]

OTHER PREVENTIVE MEASURES

Once again, the vicious circle of malnutrition and diarrhea becomes evident. Preventing diarrhea prevents malnutrition; preventing malnutrition prevents diarrhea. In most tropical lower-income nations, the peak of diarrheal disease is usually during the summer months, which is related to the warmest rainy seasons. Lower maternal education, use of untreated water sources, poor water storage practices, and underweight are key determinants for the risk of shigellosis. A reduction in diarrheal disease in the developing world could be achieved through the implementation of a community education program, emphasizing

the benefits of vaccination, providing information to parents and health care professionals on how to use ORS, and introducing a zinc supplementation program.

Building well-maintained water treatment plants, installing sewage systems, and providing clean water will significantly reduce the number of diarrheal cases. Chlorine disinfection, solar disinfection, ceramic infiltration, and concrete biosand filters can help reduce the number of diarrheal cases in children.[155] It is estimated that 24% of the global burden of disease is attributable to environmental factors—94% in the case of diarrheal disease. This is in contrast with respiratory infections and malaria, in which the percentages are 41% and 42%, respectively.[31]

Appropriate management of animal feces and agriculture practices would also have an effect. Teaching people to minimize contact with freshwater by using rubber boots when working in irrigation canals would be beneficial in preventing schistosomiasis. Proven strategies in reducing incidence of diarrheal disease include provision of safe and clean water, availability of sewage systems, improvements in personal and food hygiene, and avoiding the use of human manure for fertilizing fields and crops. Extending the duration of breastfeeding in young infants and controlling the fly population will also help reduce the frequency of diarrheal disease.

Migration of rural inhabitants to frequently overcrowded impoverished urban or suburban areas creates favorable conditions for the spread of parasites and other enteric pathogens. Strategies to periodically reduce parasitic burden through deworming, especially school-aged children, should be implemented.[156–159] In the urban slums of Lucknow, India, 17.5% of preschool children had intestinal parasites.[160] People also need to be taught good food safety and distribution measures. Food handlers at a municipal market had 1 or more parasitic infections.[161] Of greater concern, meat and vegetables sold at the market were frequently contaminated with parasites (>65% of samples).

Chronic or recurrent infections with EAEC, *Cryptosporidium,* and *Giardia* have a great effect over malnutrition, growth, and development. An increase in the quality and amounts of nutrients improves intestinal growth and barrier function of the GI tract, hence reducing the likelihood of future enteric infections. Supplements of glutamine, arginine, vitamin A, zinc, and other micronutrients enhance GI tract health.

Early childhood diarrhea has greater disabling effects on children, leading to growth and fitness impairment, which leads to decreased work productivity later in life. Populations with moderate malnutrition,

low weight for age, and diarrhea itself are associated with increased diarrhea risk. Studies from Egypt validated these findings.[162]

An analysis of studies shows that administering antibiotics to children in countries with low and middle incomes has a beneficial effect on linear growth. This promoting effect may be secondary to the treatment of clinical or subclinical infection or modulation of intestinal flora.[163] In a study from Malawi, the use of chloroquine-azithromycin as a combination therapy for malaria resulted in a reduction in respiratory and GI infections among recipients.[164]

Mass-scale campaigns focused on hygiene and preventive health could potentially help reduce parasitic infections. In developed nations, routinely treating immigrants from developing countries with albendazole would reduce DALYs and health costs and prevent hospitalizations and deaths.[165]

In contrast with higher-income countries, enteropathogens still pose a great challenge to health care professionals and promoters, governmental officials, and the population at large. Preventive measures do work. Building infrastructure and educating people on how to prevent disease is still the way to achieve success.

Enteric parasitic infections and diarrhea have been shown to reduce immunogenicity and efficacy to vaccines, especially oral polio. It is imperative that we prevent and treat these infections.[166]

Hepatitis

Viruses are responsible for most cases of hepatitis throughout the world. Hepatitis A is the most common cause of acute viral hepatitis in children, followed by HEV.[167] Prevalence of hepatitis viruses among children has been found to be influenced by socioeconomic status. Children of high social class have lower seropositivity to HAV than poorer children.[168] Infections by HAV were common in the first 5 years of life in countries with limited resources, poor sanitary infrastructure, and poverty. Most of these infections are anicteric and asymptomatic, resulting in limited morbidity and, more importantly, immunity against infection at an older age when symptomatic disease was more likely. In some countries, improvements in living infrastructure resulted in a shift of HAV infection to older ages, where infections are more likely to be symptomatic. In a study from Turkey, 29.5% of children were HAV IgG-positive. In the age group of 1 to 2 years, 21.4% were positive, while at 14.1 to 18 years, 52.4% were positive.[169]

In India, one-third of cases of viral hepatitis were caused by HAV; many of these infections were in adults.[170] In Bangladesh, 100% of

children 6 years and younger were seropositive for HAV. Chronic carriage with HBV was found in 19% of persons tested. Antibodies to HCV and HEV were detected in 13% and 53% of persons, respectively.[171] Coinfections with hepatitis viruses are common in developing countries. In a study from Egypt, HEV-specific IgG was detected in patients with detectable antibodies to HBV (~57%), HCV (52%), and HAV (~34%).[172] In many developed countries, universal use of vaccination against HBV significantly diminished transmission of HBV among the population. The introduction of HAV vaccination in the United States resulted in a decrease in reported outbreaks and epidemic activity. In the United States, routine vaccination for HAV is initiated at 1 year of age, with expected catch-up of older children. However, HCV remains an important problem in most countries. Most HCV infections in children in the United States are perinatally acquired.

Hepatitis A virus and HEV are transmitted by the fecal-oral route, while HBV and HCV are acquired from contact with infectious body fluids. Various studies support the notion that 20% to 80% of all new HBV infections result from unsafe injections. Similar practices are also responsible for a high prevalence of HCV infections in some developing countries.[173]

It is estimated that 170 to 210 million people are infected with HCV worldwide. Approximately 3 to 4 million new cases occur each year. Prevalence of HCV in children is higher in developing countries (1.8%–5.8%) compared with the United States and Europe (0.05%–0.36%).[169] Reuse of needles and syringes, poorly screened blood transfusions, and poorly sterilized injection materials are major risk factors for HCV acquisition in many of these countries. Infections of HBV and HCV are generally not clinically apparent until later in life, when they are more likely to be detected. Frequently, they are suspected when serum chemistries demonstrate elevated liver enzymes and further workup determines the causative agent. Other pathogens, such as adenovirus, Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* can cause hepatitis.

In France, children who travel to endemic areas have a higher seroprevalence to HAV than those who do not travel (12% versus 2%).[168] Travel for more than 7 days, aged 14 to 16 years, and having a mother born in the endemic area were associated risk factors for infection. In a study of Israeli travelers, 1% were diagnosed with acute hepatitis. Two-thirds of infections were caused by enterically transmitted hepatitis viruses. Hepatitis E was detected in 39% of cases, followed by HAV in 27% of cases.[174] Acquiring HBV and HCV during travel is rare.

Similarly to HAV, most infections of HEV are subclinical.[173] It is a major cause of hepatitis in many tropical and subtropical countries of Asia, the Middle East, and northern Africa. Contact with contaminated water during heavy rainfalls and floods and swine is associated with infection. An outbreak in urban Bangladesh that resulted in 17 deaths was caused by sewage contamination of municipal drinking water.[174] Several HEV genotypes are responsible for human disease. Genotype 1 is responsible for most epidemic and sporadic cases in Asia and Africa, while genotype 2 is mostly observed in outbreaks in Mexico and Western Africa. Genotypes 3 and 4 are responsible for sporadic cases around the world. Hepatitis A virus and HEV are single-stranded RNA viruses. In contrast with HAV, most infections with HEV are acquired in early adulthood. There is currently no vaccine against HEV. Fewer than 10% of children younger than 10 years have antibodies against HEV, while 76% of individuals have antibodies against HEV by adolescence.[2,12] Seroprevalence was higher in children of lower socioeconomic status. Hepatitis E virus is hyperendemic in some countries, such as Egypt, where it is responsible for 22% of acute hepatitis in children younger than 10 years. The incubation period of HEV is similar to HAV at 15 at 60 days. When present, a prodrome consisting of nausea, vomiting, abdominal pain, and diarrhea or constipation appears 2 to 5 days before an icteric phase that usually lasts 10 to 14 days. Hepatomegaly and elevated liver enzymes can be observed for up to 6 weeks. Of interest, splenomegaly, ascites, and spontaneous bacterial peritonitis was observed in approximately one-third of patients.[167] While clinical features and route of transmissibility of HAV and HEV are similar, in contrast to HAV, HEV may lead to chronic infection and perinatal infections may result in serious infections in the newborn and mother.[175] Acute hepatic failure is rare in children. However, severe hepatitis is observed in approximately 20% of women during pregnancy and is associated with high mortality. In an outbreak in Bangladesh, deaths were reported more commonly in women.[171] Miscarriage and perinatal death were 2.7 times higher in pregnant women with jaundice. Chronic HEV (elevated liver enzymes and viremia) is mostly limited to immunocompromised hosts. Mother-to-fetus transmission of HEV has been documented in infected mothers in their third trimester. These may lead to fulminant hepatic failure, severe hypothermia, hypoglycemia, and death.[176,177]

Treatment for HAV and HEV is generally supportive. Ribavirin and pegylated interferon alfa-2a has been used in some patients with chronic HEV. There are no data of its use in children. There are recommended regimens for treating chronic HBV and HCV.[178, 179] Unfortunately,

many antiviral regimens are expensive for persons in countries with limited resources.

In developed countries, vaccination for HBV is started at birth and is usually completed by 6 months of age. Actively screening mothers during the prenatal period identifies chronic carriers that may lead to perinatally acquired infections. These preventive strategies have significant reduced the number of cases of HAV and HBV in children in the United States. Universal vaccination with HAV vaccine is routine practice in the United States starting at 1 year of age. In other countries, such as Brazil, this practice has been found to be cost saving.[180]

KEY POINTS

- Diarrhea and other GI infections are a leading cause of morbidity and mortality among young children around the world.
- Poor sanitation, contaminated water sources, inadequate access to primary health care, lack of maternal education, and lack of breastfeeding are major risk factors for diarrheal disease.
- Oral rehydration solution and zinc supplements are major components for treating acute diarrhea in lower-income countries.
- Antimicrobial therapy is only useful in shigellosis, parasitic infections, cholera, and immunocompromised hosts.
- Typhoid fever and HAV and HEV are acquired by consuming contaminated food and water.

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CHAPTER

25

Respiratory Conditions

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INTRODUCTION

Respiratory disease is a major cause of morbidity and mortality for all children but disproportionately burdens those in the developing world. As many as 95% of all clinical pneumonias may occur in developing countries.[1] In 2013 the World Health Organization (WHO) reported that 1.1 million deaths in children younger than 5 years are attributable to pneumonia, making pneumonia the single leading cause of death in this age group.[2] Many experts believe that gains can be made toward reducing the burden of respiratory disease through improving provision and distribution of existing prevention and treatment techniques that are validated and proven effective. However, many challenges hinder receipt of these interventions at the local level in much of the developing world.

Major population-specific barriers include recognizing the severity of disease, timely access to care, and availability of preventive measures, which include addressing vaccination use, malnutrition and micronutrient deficiencies, the effect of air pollution, and the burden of coinfection. Barriers specific to the delivery of health care include assessing disease severity, appropriately providing effective antibiotics, and, when possible, providing supportive care for dehydration, malnutrition, and hypoxemia. Addressing these barriers in a resource-poor setting is a daunting task. Fortunately, the international research community

provided guidelines for care that, when tailored to the local situation, have the potential to save millions of lives.[3]

UPPER RESPIRATORY TRACT INFECTION

Children presenting with new-onset cough or increased work of breathing are a treatment dilemma in many lower-income countries. Delay in appropriate treatment for children who may have a lower respiratory tract infection can lead to a life-threatening situation. On the other hand, many children with respiratory symptoms are uninfected or will have a self-limited course.

As in higher-income countries, most upper respiratory infections are viral and likely to be self-limited, although malnutrition and concurrent infections (eg, diarrhea, malaria) can weaken a child's immune system and predispose the child to more significant diseases. Viruses, such as respiratory syncytial virus (RSV) and parainfluenza viruses, typically begin as an upper respiratory process but can quickly progress to involve the lower respiratory tract, resulting in significant signs and symptoms of distress (eg, wheezing, stridor, retractions), even in otherwise healthy children.[3]

LOWER RESPIRATORY TRACT INFECTION

Bacterial pneumonia leads to significant morbidity and mortality in children, particularly for those younger than 5 years. *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Staphylococcus aureus* are the 3 most important pathogens leading to hospitalization and death for children with pneumonia.[4,5] Vaccination against *S pneumoniae* and *H influenzae* type b has substantially reduced invasive disease with these pathogens in developed countries and also shows promise in reducing infections in resource-poor settings where the distribution of these immunizations is still limited. Fortunately, the creation and more recent expansion of Gavi, the Vaccine Alliance, is improving access to these vaccines in the poorest countries.[6] Tuberculosis (TB) is also a significant contributor to childhood pneumonia in high endemic areas, comprising approximately 8% of cases and a higher proportion that lead to death.[7–9]

Among hospitalized children, studies have shown evidence of a viral etiology in about two-thirds of illnesses that WHO criteria classify as pneumonias.[10,11] Of these, RSV, influenza, and rhinovirus are the most common. Less is known about viral infections that do not lead to hospitalization. Other viruses commonly implicated for lower respiratory tract infections are metapneumovirus (now suspected to be a frequent cause of childhood lower respiratory infection after RSV),

adenovirus, and parainfluenza.[8,12] Seasonal and pandemic influenza are major health threats throughout the world. Vaccination coverage is variable in the developing world, and it is likely that coverage will remain inadequate without major funded initiatives despite strong recommendations.[13]

In lower-income countries, a significant proportion of viral pneumonia is complicated by concurrent bacterial infection, as a viral infection itself predisposes an individual to bacterial pneumonia.[14] Studies in developing countries report variable rates of mixed bacterial and viral pathogens of 8% to 40%. Prolonged or more severe symptoms warrant consideration of a mixed infection. Of note, influenza infection has been shown to interact with *S pneumonia* and *S aureus,* causing severe pneumonia that is sometimes necrotizing.[15,16] Vaccination against *S pneumoniae* has been shown to have the added benefit of reducing hospitalization for pneumonia in which a respiratory virus such as influenza was identified and may play a role in decreasing morbidity and severity of influenza outbreaks because of the virus' association with pneumococcal pneumonia.[17,18]

Bronchiolitis, most often from RSV, can be difficult to manage in a resource-poor setting and continues to contribute to childhood death from respiratory causes. Much research focusing on bronchiolitis has taken place in higher-income countries, whereas adequate research on its effect in the developing world is lacking.[19–21] The presence of viral symptoms and wheezing on auscultation can help differentiate viral bronchiolitis from pneumonia and potentially avoid overuse of antibiotics.[14] However, health care practitioners must be aware of the major complications of dehydration, hypoxemia, and superimposed bacterial infection, with predisposition to reactive airways disease and recurrent infections as delayed consequences.[22]

Assessment and Classification

Laboratory evaluation (eg, complete blood cell counts, erythrocyte sedimentation rate, C-reactive protein) and chest radiography are useful when available for improving diagnostic accuracy; however, their ability to improve sensitivity and specificity of a pneumonia diagnosis may not be significant enough to warrant the excess cost.[23] Their value is increased for cases in which important management decisions must be made, such as when anemia or TB is suspected. Because there is minimal research on respiratory infections that are managed in the outpatient setting in the developing world, health care professionals must rely on a careful clinical assessment, combined with a standardized management

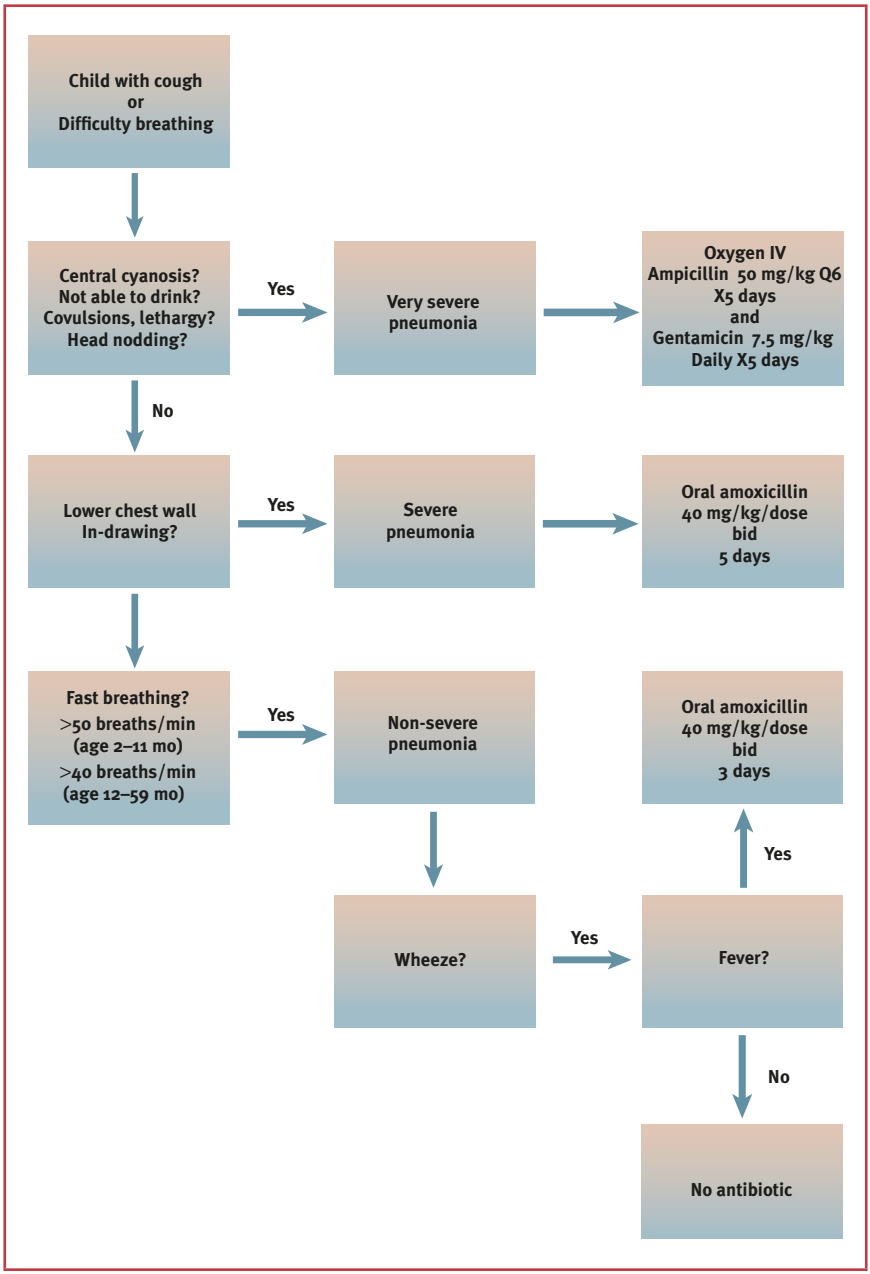
approach, to maximize identification and timely treatment of the child who will progress to severe disease.

The WHO published guidelines for classifying and managing lower respiratory tract infections are adapted in algorithm form in Figure 25-1. These guidelines rely on first-level health practitioners' ability to assess the Integrated Management of Childhood Illness (IMCI) danger signs (ie, unable to drink or breastfeed, vomits everything, convulses, lethargic, or unconscious). These signs have good sensitivity and reduce mortality in resource-poor settings by prompting early initiation of antibiotics and referral, as they define very severe illness.[24–27]

Once these danger signs are ruled out, WHO classification criteria require practitioners to measure respiratory rate and presence of lower chest wall in-drawing (retractions specific to the lower chest). When tachypnea is absent, WHO recommends symptomatic care only with instructions for the caregiver to watch for danger signs.[28] The presence of tachypnea (respiratory rate >50 breaths/min for infants 2–12 months of age and >40 breaths/min for children 1–5 years of age) defines pneumonia according to these guidelines. There has been some doubt cast on the predictive value of tachypnea in the diagnosis of pneumonia among children in US emergency departments.[29–31] However, because these studies relied on the use of radiography as the gold standard—a practice that has also been called into question and is not routinely available worldwide—the WHO guidelines remain in effect for the global population discussed in this text.[32,33] Recent data suggest that ultrasound may be useful in diagnosing pneumonia and that accessing this modality may be a more feasible option than radiography in some places.[34–36] In addition, training first-line health care workers in auscultating a wheeze and measuring fever has also been suggested and can help reduce overuse of antibiotics in cases of non-severe pneumonia.[28]

Tachypnea with the addition of lower chest in-drawing or grunting in a calm child represents severe pneumonia. Presence of the IMCI danger signs, coupled with difficulty breathing, tachypnea, and lower chest wall in-drawing, defines very severe pneumonia and warrants intravenous (IV) antibiotics and referral to an inpatient facility. Other factors to consider when basing management decisions on respiratory rate are fever and high altitude, which may elevate the rate, and poor nutritional status, which may depress the rate.[37]

Figure 25-1. Pneumonia Classification and Treatment Algorithm



Derived from World Health Organization. *Recommendations for Management of Common Childhood Conditions: Evidence for Technical Update of Pocket Book Recommendations.* Geneva, Switzerland: World Health Organization; 2012. http://www.who.int/maternal_child_adolescent/documents/management_childhood_conditions/en. Accessed June 9, 2015.

Management

Non-severe Pneumonia

Given the significant morbidity and mortality attributed to pneumonia, the efforts of the last 2 decades largely focused on the identification and management of severe pneumonia. Recently, there has been a helpful focus on managing non-severe pneumonia for first-level practitioners. The most recent recommendations take into account the need for improved diagnostic accuracy, an increased knowledge of antibiotic effectiveness, and the influence of HIV, TB, and malaria on outcomes.

The WHO recommendation for first-line therapy for non-severe pneumonia is amoxicillin at a dose of at least 40 mg/kg per day in 2 divided doses for 3 days. This recommendation is based on strong evidence that considers cost and effectiveness. Updated WHO guidelines suggest that auscultating a wheeze in an afebrile, clinically stable child can be safely treated without antibiotics. The authors of the WHO panel suggest a 5-day course in non-severe pneumonia occurring in areas with high HIV prevalence. Co-trimoxazole (8 mg/kg of trimethoprim in 2 divided doses) is an alternative first-line treatment; however, resistance is an emerging concern with this agent.[28] Treatment failure is defined as "lower chest-wall in-drawing, central cyanosis, stridor while calm, or IMCI-defined danger signs (the child being unable to drink or breastfeed, vomits everything, has convulsions, is lethargic or unconscious) at any time during a child's illness or a persistently raised respiratory rate at 72 hours (48 hours in an area of high HIV prevalence)."[38] This recommendation provides a more objective means of defining failure that has some validation; however, more research is needed.[38,39]

In the event of treatment failure, defined as development of IMCI danger signs or no improvement in respiratory rate within 48 hours, the health care practitioner should first determine if referral for more intensive care is necessary.[28] Children with a persistently elevated respiratory rate but who do not need immediate referral should be assessed for the cause of treatment failure. A systematic approach using a defined algorithm has proven benefit, although there is currently not a validated algorithm to address treatment failure. The authors of the WHO recommendations suggest an algorithm that includes assessing delivery barriers of the medication, the need for bronchodilators, and the presence of TB, HIV, and malnutrition. Other factors should also be considered, such as anemia, reactive airways disease, cardiac conditions, foreign bodies, non-susceptible pathogens, and complications of pneumonia, such as empyema.[38,40]

The recommendations for second-line antibiotic treatment for those children who do not require a referral are directed toward broadening coverage and addressing common resistance mechanisms. Changing therapy to amoxicillin-clavulanic acid at 80 to 90 mg/kg of amoxicillin in 2 divided doses for 5 days is recommended with suspected antibiotic failure. Alternatively, erythromycin may be added at 50 mg/kg in 4 divided doses for 5 to 7 days for children older than 3 years if an atypical bacterial pathogen is suspected. Children who received cotrimoxazole as a first-line treatment should be switched to amoxicillin for a 5-day course. While these recommendations are logical, they are not validated.[38]

Severe Lower Respiratory Tract Infections

When possible, timely referral for more intensive treatment has the potential to save many lives.[26] Clinicians should be aware that tachypnea is the most sensitive means of diagnosing severe pneumonia in developing countries, with additional signs of chest in-drawing and auscultatory findings enhancing specificity.[41] In cases of severe pneumonia (tachypnea with lower chest in-drawing), oral amoxicillin of at least 40 mg/kg/dose twice daily for 5 days should be used as first-line treatment for children 2 to 59 months of age.[24] The clinician caring for children who have not responded to initial therapy must keep in mind a broader differential diagnosis, reasons for antibiotic failure, and special considerations for children with HIV and other coinfections.[38] Specific treatment guidelines for treating severe pneumonia should be followed in children infected with HIV/AIDS.

Timely referral of children with very severe lower respiratory tract infection to a clinical location that can provide supportive care is of primary importance. These children often have expanded needs for hydration, nutritional support, and supplemental oxygen. For very severe pneumonia in children 2 to 59 months of age, first-line treatment consists of ampicillin 50 mg/kg (or penicillin G potassium or sodium 50,000 units per kg intramuscular [IM]/IV) every 6 hours for at least 5 days and gentamicin 7.5 mg/kg IM/IV once a day for 5 days. Failure of first-line therapy warrants reevaluating the child's condition and considering a change in therapy. Ceftriaxone should be used in children with severe pneumonia as a second-line agent in the event of first-line treatment failure.[28] A Cochrane review found that antibiotic treatment with a combination of penicillin and gentamicin intravenously was more efficacious for severe illness than chloramphenicol alone. The review also demonstrated evidence that high-dose (80–90 mg/kg/d) oral

amoxicillin is as effective as injectable penicillin for those who can tolerate the oral route.[42]

For pneumonia, hypoxemia is known to be a predictor of severe disease and a risk factor for death. Pulse oximetry is recommended to determine the presence of hypoxemia because it is more accurate and requires less training than use of clinical signs alone, although availability has historically limited its use.[31] More recently, oximeters are becoming more affordable and numerous studies have found them to be sustainable in low-resource settings, leading WHO to feel that the cost is justified.[28] The best clinical predictor of hypoxemia is the presence of lower chest in-drawing, supporting the use of WHO classification of severity.[43] If oximetry is not available, the following clinical signs could be used to guide the addition of oxygen therapy: central cyanosis, nasal flaring, inability to drink or feed, grunting with every breath, and depressed mental state. However, WHO strongly recommends that these signs alone not be relied on for detection of hypoxemia due to the unreliability of clinical signs without pulse oximetry.[28] Supplemental oxygen has been shown to save lives but unfortunately is not routinely available to many children admitted to hospitals with severe respiratory illness.[44–46] Providing supplemental oxygen is a difficult task in many parts of the world, but the increased attention on reducing mortality related to respiratory illness led WHO to state that effective oxygen delivery systems should be a universal standard of care and made more widely available.[28] In a systematic review by Subhi and colleagues, the median prevalence of hypoxemia among hospitalized children with acute lower respiratory tract infection was 13%; however, there was wide variation among the studies, with more severe disease consistently correlated to hypoxemia.[47] Use of nasal prongs is the preferred oxygen delivery method for children when considering effectiveness, safety, cost, and availability; however, nasopharyngeal catheters are acceptable with adequate nursing supervision when nasal prongs are not available.[48] Face masks or head boxes are not recommended. Oxygen delivery should be guided by pulse oximetry with thresholds depending on the altitude. The WHO recommends that children living at or below 2,500 m above sea level should receive oxygen therapy if their oxygen saturation is less than 90%. At altitudes higher than 2,500 m, 87% may be used as a threshold for giving oxygen therapy. This excludes oxygen therapy in preterm neonates who are at risk for hyperoxia-related complications. Children receiving oxygen therapy should be closely monitored using pulse oximetry, and therapy should be discontinued when oxygen saturation remains above the recommended levels and the child remains stable for at least 15 minutes

on room air.[28] Oxygen concentrators play an increasingly important role in areas where oxygen cost and availability are concerns. Bubble continuous positive airway pressure (CPAP), using oxygen concentrators and low-resistance nasal prongs, or CPAP with high-flow nasal cannula oxygen therapy using a flow generator, humidifier, and blender, have also been suggested in some settings.[49] However, use of these modalities is limited because they require electrical power. Appropriate and timely referral to centers that have the ability to provide oxygen may be the only option for many health care practitioners.

Pleural effusions are a relatively common complication of severe pneumonia and are associated with poor social conditions.[50] A Brazilian study found radiologically determined pleural involvement in 25% of children younger than 5 years who were hospitalized with severe pneumonia.[51] There is controversy, even in higher-income countries, over the management of significant intrathoracic complications of infections, such as empyema, although a procedural approach (ie, chest tube placement or operative management) is preferred when possible.[52]

Differential Diagnosis

While bacterial and viral pathogens are the most common cause of respiratory symptoms in children, other, more unusual pathogens, as well as noninfectious etiologies, must also be considered.

Parasitic Infections

Parasitic infections may manifest with respiratory symptoms by direct pulmonary involvement with the organism (eg, *Echinococcus,* amebiasis) or inducing an inflammatory response during the migratory phase through the lungs (eg, ascariasis, hookworms) or with a hypersensitivity syndrome, such as tropical pulmonary eosinophilia (eg, *Wuchereria bancrofti, Brugia malayi*). The potential organisms vary by geographic region. Treatment may be possible with appropriate antimicrobials, although surgical cyst resection is often necessary for a cure with certain pathogens.[53]

Pertussis

The typical persistent cough is a common presentation of *Bordetella pertussis* infection in older children. While whooping cough is often self-limited and preventable by vaccination, it does lead to 195,000 deaths globally in children per year.[54] Many older children and adults carry the infection symptomatically or asymptomatically. Younger children are at higher risk of complications from the disease, such as post-tussive vomiting, seizures, encephalopathy, brain damage, conjunctival hemorrhage,

and rectal prolapse. Young infants sometimes present only with apnea or sudden death and are at particular risk for pulmonary hypertension.

Prevention has been successful with vaccination; however, infections persist even in communities with high vaccination rates. Waning post-vaccination immunity is felt to be the reason for continued transmission despite good vaccine coverage in young children. As a result, many countries instituted a booster dose in adolescence to improve control.

Antibiotic treatment for active infection is helpful if provided in the first week after onset of illness. Macrolides (eg, azithromycin, erythromycin) are the antibiotics of choice; trimethoprim-sulfamethoxazole is an alternative agent. Prophylaxis with a macrolide antibiotic is warranted for vulnerable individuals, such as young infants and pregnant women, provided the antibiotic course is initiated within 3 weeks of exposure to the index case.[55]

Atypical Bacterial Infections

Atypical bacterial organisms, such as *Mycoplasma pneumoniae, Moraxella catarrhalis,* and *Klebsiella pneumoniae,* are believed to account for fewer than 10% of pneumonias; however, this speculation is based on limited research in resource-poor settings.[38] These organisms should generally be considered when first-line therapy fails, assuming adequate adherence to the regimen.

Asthma

The prevalence of asthma varies widely throughout the world.[56] With the exception of Latin America, higher-income countries have higher asthma rates than lower-income countries, which has been attributed to the effects of an overly clean environment (hygiene hypothesis). However, there is evidence that the prevalence of asthma is increasing worldwide.[40] The prevalence of reactive airways disease in Latin America nears that of higher-income countries and appears to be a different epidemic with nonatopic phenotypes predominating, which may be a result of previous viral or parasitic infections.[57]

A history of previous respiratory disease and audible wheeze should prompt consideration of a bronchodilator trial, particularly in the absence of fever. A child who responds to bronchodilator treatment is likely to benefit from treatment of the reactive component and avoidance of inciting exposures. Children with a history of acute wheeze and evidence of bronchoconstriction should be treated with inhaled salbutamol/albuterol using a metered dose inhaler and spacer. In cases of persistent symptoms, an inhaled corticosteroid should be added. Oral

salbutamol/albuterol should not be used except when inhaled salbutamol/albuterol is not.[40] Excess antibiotics may be avoided, although the possibility of superimposed infection should be considered with persistent symptoms.

Stridor

A child presenting with respiratory distress and extrathoracic noisy breathing that worsens on inspiration (ie, stridor) suggests an upper airway obstruction. Viral-induced croup is the most common cause in children between the ages of 3 months and 3 years, affecting 3% of children a year.[58] Treatments with proven benefit for viral croup include dexamethasone 0.6 mg/kg intramuscularly or orally and nebulized epinephrine. Humidified air is also commonly used, but no benefits were shown in studies within emergency departments, which suggests that severe illness may not respond.[59]

The introduction of *H influenzae* type b vaccine markedly reduced the incidence of epiglottitis. It remains a concern in under-vaccinated areas and can be life threatening. Epiglottitis classically presents with severe stridor in an ill-appearing child. The airway may be significantly compromised and instrumentation of the oropharynx should be avoided. When possible, sedation and intubation is the recommended course of management of severe epiglottitis.[60] Bacterial tracheitis is also a serious respiratory infection that can become severe enough to require lifesaving airway management. From a study in Taiwan, the most common presenting symptoms were cough, fever, dyspnea, and hoarseness. The most common etiologies were alpha-hemolytic streptococcus, *Pseudomonas,* and *S aureus*. One-fifth of the children required intubation.[61]

Stridor in young children, especially infants, may indicate an anatomic or neuromuscular predisposition to respiratory compromise. In resource-poor settings, this evaluation may rely on clinical suspicion, although examination for dysmorphisms, abnormal airway anatomy, neuromuscular tone, and assessment of development are helpful. Finally, clinical suspicion for a foreign body as a cause of stridor or respiratory distress is important to avoid delays in diagnosis and management. A chest radiograph, including inspiratory and expiratory films, should be obtained to look for air trapping. Lateral decubitus films are an alternative option for young infants suspected of having a foreign body and may demonstrate air trapping in the dependent lung (ie, the side with the foreign body will not deflate when placed in the dependent position).

Non-respiratory Etiologies

Cardiac Disease

Heart disease is often difficult to manage in lower-income countries and may go undetected until a child presents with respiratory symptoms. In lower-income countries, rheumatic heart disease remains a major threat to children and young adults, comprising up to 60% of cardiac disease for these age groups. Good progress has been made in reducing mortality in a few locations (eg, Cuba, Egypt, Martinique, Guadalupe) that instituted prevention programs. However, significant mortality, morbidity, and economic burden are persistent worldwide. Congenital heart disease and sequelae from other infectious diseases, such as myocarditis, pericarditis, and those related to Kawasaki disease, may also lead to pulmonary manifestations.[62]

Other

Ingestions (eg, aspirin, hydrocarbons), pneumothoraxes, and metabolic or endocrine causes (eg, acidosis, fever) should remain on the clinician's differential to avoid misdiagnosis and delay in management.

Risk Factors for Increased Morbidity and Mortality

Malnutrition

Malnourished children are at higher risk of death from lower respiratory tract infections. A weakened immune system and respiratory drive contribute to this higher mortality. Children with malnutrition are also more likely to have gram-negative bacteria or TB as the causative agents.[63] As such, it is prudent to refer malnourished children to a hospital for parenteral antibiotics and the consideration of TB infection.[64]

Young Infants

In addition to vulnerabilities associated with age, a broader range of bacterial pathogens is implicated in lower respiratory tract infections in infants younger than 3 months. Antibiotic coverage for gram-positive (*S aureus, S pneumoniae, S pyogenes,* group B streptococcus) and gram-negative (*Escherichia coli, Salmonella, H influenzae, Klebsiella*) organisms is indicated. The combination of ampicillin and gentamicin provides adequate coverage in most cases. A concern with this regimen is poor efficacy against *S aureus* and that an antistaphylococcal antibiotic should be added to the treatment regimen in the event of treatment failure after 48 hours.[64]

HIV

The presence of coinfection with HIV may predispose children to more severe disease and infection with atypical organisms. The HIV epidemic greatly increased the burden of respiratory disease, particularly in sub-Saharan Africa. The pneumonia mortality rate for children with HIV is 3 to 6 times greater than in uninfected children.[50] HIV-infected children have a higher percentage of bacterial pneumonia and are more likely to be infected with atypical organisms such as *Pneumocystis jiroveci* and gram-negative organisms, although *S pneumoniae* remains the most common bacterial etiology.[9] In addition, those with HIV are also more likely to have severe disease from viral infections.[8] Therefore, children with HIV must be given special consideration for broader antimicrobial coverage and more aggressive supportive care when initial treatment fails.[64] Co-trimoxazole prophylaxis is recommended for children with HIV and children born to HIV-infected mothers.[65]

Malaria

A fever often warrants treatment for malaria in endemic areas. The presenting symptoms of malaria may also include cough and increased work of breathing, making a single diagnosis difficult. Research in regions with a high rate of malaria indicates that ill children with this presentation may often have malaria and pneumonia, suggesting that treatment for both infections in the outpatient setting is a reasonable consideration.[65,66] For hospitalized children with clinical symptoms compatible with malaria and severe pneumonia, basic routine parasitologic and microbiologic methods, combined with chest radiography, should help differentiate the 2 processes. A recent study in hospitalized children in Mozambique, fulfilling IMCI criteria for malaria and pneumonia, revealed that only a small fraction of these children had confirmed malaria. The children with malaria were typically older and admitted during the rainy season or had a history of previous severe malaria episodes compared with children with pneumonia.[67]

Measles

Pneumonia is a well-known and severe complication of measles. A Cochrane review indicates that antibiotic treatment can decrease the incidence of pneumonia; however, guidelines for the type of antibiotic or duration of treatment cannot be derived from this review.[68] Vitamin A supplementation has also shown to improve outcomes for children infected with measles and the complication of pneumonia.[69] Therefore, WHO recommends vitamin A daily for 2 days for all children with acute measles.[70]

Chronic Cough

The WHO defines *chronic cough* as a cough that is present for 2 to 3 weeks.[71] Common causes of chronic cough in higher-income countries, such as chronic sinus disease (postnasal drip), asthma, and gastroesophageal reflux, are also likely to be common in lower-income countries. These conditions may be elucidated with a thorough history; however, the differential can be quite broad when diagnostic capabilities are limited. Toddlers and older children with a persistent cough warrant consideration for infectious causes such as rhinosinus disease (viral and bacterial), pneumonia, and *B pertussis* infection.

Tuberculosis should always be considered in endemic areas because it is associated with high morbidity and mortality. Children comprise one-fifth to one-quarter of TB cases in resource-poor countries, which results in significant morbidity and mortality because of the increased propensity for disseminated disease in children younger than 5 years. Diagnosing TB in children is problematic because they are more likely to present with an extrapulmonary manifestation and are rarely sputum positive. Gastric aspirates, chest radiographs, and a placed purified protein derivative are helpful when results are positive, although false negatives are common. The combination of infection with HIV and TB has led to a synergistic increase in mortality. It is prudent to maintain a high level of suspicion in TB-endemic areas.[72]

Geographic-specific fungal and parasitic organisms should be considered as causative agents. As discussed, asthma, allergic rhinitis, irritants (eg, passive smoke, indoor use of fossil fuels), chemical aspiration, foreign bodies, and heart disease may present with a prolonged cough. Patients refractory to treatment also warrant consideration for systemic disease, such as immunodeficiency, cystic fibrosis, and sickle cell.

The young infant with a persistent cough may have infectious causes with greater morbidity and mortality in this age group. Viral disease may be more severe (eg, RSV, metapneumovirus) and lead to prolonged symptoms. *B pertussis* infection may present with severe coughing spells and their associated complications, although infants 3 months and younger sometimes present with only apnea or sudden death. The severity of this infection in infants underlines the importance of immunization for all who are in contact with them. The newborn with persistent symptoms should also be considered for anatomic abnormalities such as vascular anomalies, laryngeal cleft, and pulmonary malformations. Gastroesophageal reflux is a common etiology of chronic cough for infants but is usually a diagnosis of exclusion.

Prevention

As is true in much of the practice of medicine, adequate preventive methods exist that could greatly reduce the burden of respiratory disease in the world if adequately used. Preventive education efforts on awareness of the presence and severity of disease, vaccination, attention to nutrition, micronutrient supplementation, and prevention of HIV transmission all have the potential to reduce mortality related to respiratory disease.

Seeking Care Early

Delay in seeking care occurs for multiple reasons, including geography, cost, cultural beliefs, and awareness. A joint statement by the United Nations Children's Fund and WHO reports evidence that a large percentage of ill children present late for care or not at all throughout the world.[73,74] Early intervention with case management by community health workers shows impressive reductions in childhood mortality.[26,73] To be successful, local health care workers should be able to recognize and treat uncomplicated pneumonia and know when to refer for higher care.

Education efforts were also extended to the family level with a focus on cough and fast or difficult breathing. Caregivers in various cultural settings often diversely interpret signs of respiratory distress. Education efforts for these caregivers show good short-term retention, particularly if local terminology is used. There are multiple reports on successful interventions to improve the management of pneumonia based on educating primary caregivers. The use of respiratory timers is helpful in these efforts.[65,73]

Vaccinations

Highly effective vaccines exist for many infectious etiologies that lead to the high death toll related to pneumonia. Knowledge of local population immunization coverage is essential for a clinician to provide adequate care. Diphtheria, pertussis, and tetanus; measles; *H influenzae* type b; and pneumococcal conjugate vaccines all greatly reduce the effect of childhood pneumonia.[75,76]

Coverage varies throughout the world, particularly for the newer *H influenzae* type b and pneumococcal conjugate vaccines.[77] As discussed, pneumonia is the most common cause of death in children with measles.[65] Reducing measles with vaccination will also reduce mortality from pneumonia. Measles vaccination rates have improved over the past several years. According to WHO, in 2012 an estimated 84%

of children received the first dose of measles vaccine before or by their second birthday.[70]

Nutrition

As noted previously, nutritional support is necessary for the acutely ill child to overcome the infection, and addressing nutritional needs for all children in the community will decrease the risk of mortality related to pneumonia overall.[78]

Breastfeeding

The WHO reports that infants who are exclusively breastfed for the first 6 months of life are 5 times less likely to die from pneumonia. Extended breastfeeding continues to offer protection beyond 6 months of life.[65] The excellent nutrition and strengthened immune system that breastfeeding provides are incredibly valuable to the infant in this critical period.

Micronutrient Deficiencies

Zinc and vitamin A are the 2 micronutrients shown to adequately reduce the burden of disease caused by pneumonia. Zinc intake early in the course of severe pneumonia has been shown to decrease the duration, severity, and number of treatment failures in children with pneumonia; however, this has been debated due to several studies that suggest that zinc does not improve outcomes.[79–81] Vitamin A supplementation only improves outcomes for pneumonia associated with measles; no effect is seen with pneumonia not associated with measles.[69]

Reducing Exposures

Indoor air pollution from heating and cooking fires is a common environmental exposure that contributes to respiratory problems such as asthma. Biomass fuel is common in developing countries; many lower-income families use biomass fuel for indoor heating and cooking without adequate ventilation. These fuels cause more than 1.5 million premature deaths worldwide and disproportionately affect women because of traditional occupational roles. Exposure to cooking smoke from biomass combustion is linked to many conditions, including asthma and acute lower respiratory tract infections. A WHO review estimates that indoor air pollution accounts for 3.7% of disease in lower-income countries with high mortality, making it one of the top 10 contributors to disease.[82]

Outdoor air pollution is also a growing problem in large urban areas of lower-income countries and for those who live close to roads.[83] As

in higher-income countries, atmospheric pollution has a greater visible effect on the young, elderly, and ill. Strong associations have been made between air pollution metrics and respiratory symptoms.[84,85] The burden of respiratory disease on a community correlates with worsening air pollution.[86] The growing evidence on the health effects of air quality in the dense cities of the developing world indicates that it is a major contributor to morbidity and mortality.[87] Special attention should be given to the management of chronic respiratory disease for travelers to urban areas, as even short-term exposure can have detrimental health effects.[88]

Tobacco smoke exposure is also a growing concern in lower-income countries. The relative burden of disease related to tobacco is likely to increase with expanded marketing.

Fungus in the home contributes to respiratory disease as a causative or exacerbating agent for rhinitis, asthma, hypersensitivity pneumonitis, and allergic bronchopulmonary aspergillus.

Hand Washing

Attention should be given to techniques aimed at reducing physical transmission of inciting organisms. Hand-washing programs are shown to reduce respiratory tract infections as well as diarrhea and other infections in high-risk settings.[89] Minimizing transmission is an important educational focus for health care professionals, caregivers, and children.

KEY POINTS

- Respiratory conditions are a major cause of death in children younger than 5 years.
- Tachypnea is the most sensitive means of diagnosing childhood pneumonia in developing countries (>50 respirations/min for infants and >40 respirations/min for children 1–5 years).
- Retractions or stridor are a key indication of severe pneumonia.
- First-line therapy for typical pneumonia is amoxicillin, at least 40 mg/kg/d divided in 2 doses for 3 days.
- First-line therapy for severe pneumonia is amoxicillin, at least 40 mg/kg/d divided in 2 doses for 5 days. Erythromycin, 50 mg/kg/d divided into 4 doses for 5 to 7 days, may be added if an atypical bacterial pathogen is suspected.
- First-line therapy for very severe pneumonia is parenteral ampicillin, 50 mg/kg every 6 hours for 5 days, plus gentamicin, 7.5 mg/kg IM/IV once daily for 5 days.
- Pulse oximetry and oxygen therapy are standards of care and adaptable to low-resource settings for detecting, treating, and monitoring hypoxemia.

- Children who die from respiratory infections are often malnourished.
- Improved preventive efforts (ie, vaccinations and timely access to medical care) could potentially reduce many deaths from respiratory illness.
- Differential diagnosis of respiratory symptoms should include atypical infections as well as noninfectious etiologies.
- Health care professionals on the front line are essential to reducing deaths from respiratory illness by recognizing the importance of respiratory symptoms and following a systematic approach to management.

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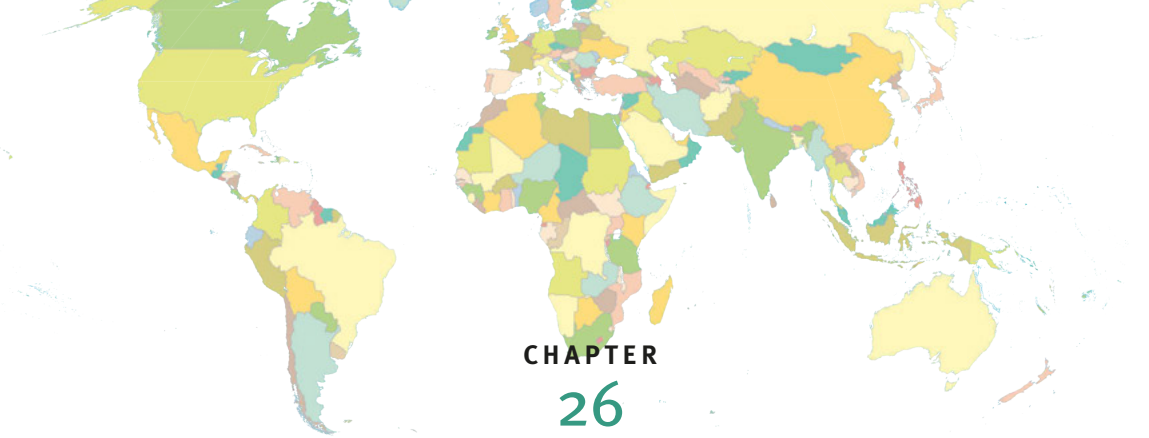

CHAPTER
26

Dermatology

Gregory Juckett, MD, MPH

INTRODUCTION TO DERMATOLOGIC DIAGNOSIS

Skin Anatomy

The skin is composed of the *epidermis* and the *dermis*. The epidermis, or upper layer, protects the body by producing *keratin,* a fibrous structural protein that creates a waterproof surface barrier, and *melanin,* a protective pigment that shields against ultraviolet (UV) light. Epidermal disorders are superficial in nature, including erosions, skin scaling, and pigmentary conditions. The dermis consists of supportive connective tissue that contains collagen, hair follicles, blood vessels, sebaceous and sweat glands, and nerves. Dermal disease, because of its depth, typically alters the elevation of the skin (atrophy, ulcers, and nodules). The condition of a patient's skin reflects his age and general health and may even provide clues about the presence of internal disease.

Rash Classification

Dermatologic diagnosis is largely a process of complex pattern recognition, similar to that employed by a naturalist using a field guide. The landmarks in question differ, but recognizing the major types of *primary skin lesions* and mastering a differential diagnosis for each lesion type facilitates quick rash identification. In this chapter, the term *primary lesion* refers to 5 pairs of descriptive terms. Each pair is distinguished by relative size, with the smaller lesion listed first: macules/patches, papules/plaques, nodules/tumors, vesicles/bullae, and petechiae/purpura. While this diagnostic approach must be mastered in stages, the process

soon becomes fairly intuitive. Once a final diagnosis is established, any standard dermatologic reference provides treatment guidelines.

Using correct terminology to describe the primary lesion is essential, not just for better communication but also for better comprehension. The 5 key pairs of useful descriptive terms are defined by their relative size (5–10 mm, depending on reference). *Macules* or spots are flat, discolored lesions up to 10 mm in size, whereas *patches* are flat, discolored lesions measuring more than 10 mm. Likewise, elevated lesions (*papules* and *plaques*) and deeper solid lesions (*nodules* and *tumors*) may also be distinguished by being less or greater than 10 mm. On the other hand, blisters (*vesicles* and *bullae*) and subcutaneous blood deposits (*petechiae* and *purpura*) are usually differentiated by whether they measure less or greater than 5 mm (Table 26-1). Many rashes present with various combinations of features, necessitating multiple terms to adequately describe what is seen (eg, *maculopapular, papulovesicular,* and *papulosquamous*). A much longer list of secondary descriptive terms (eg, *scaling, crusting,* and *lichenification*) is employed to further characterize the primary lesion (Table 26-2).

Exanthem, from the Greek exanthema, "breaking out," describes a typical external skin rash, such as seen in the typical infectious rashes of childhood (eg, red spots of measles). *Enanthema* refers to a rash of the mucous membranes such as Koplik spots in measles. Enanthemas

Table 26-1. Dermatologic Terminology for Primary Lesions

DESCRIPTION	SMALLER SIZE	EXAMPLES	LARGER SIZE	EXAMPLES
Flat, circumscribed spot	Macule <10 mm	Freckle (lentigo)	Patch >10 mm	Vitiligo
Raised lesion, circumscribed, superficial	Papule <5 mm	Wart, nevus, acne, insect bite	Plaque >5 mm	Psoriasis patch Mycosis fungoides
Solid lesion with depth below surface	Nodule <5 mm	Dermatofibroma	Tumor >5 mm	Lipoma
Raised blister(s) with serous fluid	Vesicle <5 mm	Chickenpox, contact dermatitis, HSV	Bulla >5 mm	Second-degree burn, blister
Blood deposit	Petechia <5 mm	Insect bite	Purpura >5 mm	Ecchymosis

Abbreviation: HSV, herpes simplex virus.

Table 26-2. Secondary and Descriptive Dermatologic Terminology	
Alopecia	Loss of hair or baldness. Pediatric causes include alopecia areata (autoimmune), traction alopecia, tinea capitis, telogen effluvium (stress shedding), and trichotillomania (self-induced from twisting or pulling).
Atopy	Allergy-mediated eczematous reactions causing dry, rough skin patches and itching (may be associated with asthma or hay fever)
Atrophy/Striae	Thinning of susceptible skin, often caused by prolonged steroid therapy; striae are stretch marks, a characteristic hallmark of atrophic skin.
Crust	Scab or dried exudate over damaged skin
Cyst	Enclosed cavity with a lining containing a liquid or semisolid
Erosion	Superficially denuded epidermis that usually heals without scarring
Exanthem Versus Enanthema	Exanthems describe a generalized skin eruption; erythematous (macular), vesicular, and papular subtypes are recognized. Enanthemas are mucous membrane eruptions.
Excoriation Versus Abrasion	Traumatic skin loss due to scratching versus scraping
Fissure	Skin split extending into dermis
Hypopigmentation/ Hyperpigmentation	Loss of skin pigmentation (eg, pityriasis alba, vitiligo, tinea versicolor) versus increased skin pigmentation (café au lait spots)
Keloid Versus Hypertrophic Scar	Exaggerated scarring. Hypertrophic scars appear earlier (within 1 min), remain confined to original scar, and regress with time. They are also less associated with skin pigmentation than keloids.
Lichenification	Leatherlike thickening of skin with accentuated skin markings because of chronic rubbing or scratching (eg, atopic eczema, lichen simplex chronicus)
Pustule	Papule containing pus (acne pustule)
Scale	Accumulation of desquamated stratum corneum (eg, seborrhea, psoriasis)
Telangiectasias	Dilated superficial blood vessels, often associated with skin atrophy
Ulcers	An area of destroyed dermis, resulting in a sunken sore. Deeper than an erosion and may result in scarring. Decubitus ulcers or bedsores are secondary to pressure-induced skin necrosis.
Wheal	Edematous smooth pink to red migratory papule, usually with pruritus (hives or urticaria)

often occur in conjunction with exanthems but are easily missed if not looked for.

Taking a Dermatologic History

History of the rash is important. Ask about primary symptoms and rash duration, progression, location, treatment, and evolution. Asking about *primary symptoms* helps with etiology. Does the rash itch or is it tender? *Pruritic* lesions suggest an *allergic* reaction. *Tender* lesions or rashes associated with fever are more likely to be *infectious* in origin.

Duration: When did the rash start? Acute rashes are easier to diagnose and treat, while chronic ones are much more challenging. The season during which the rash started may also be important. Outside the tropics, incidence of skin disease changes with the seasons—eczematous conditions worsen in winter and fungal infections and contact allergies increase in summer. Acne tends to flare in spring and fall. Within the tropics, the wet season is more likely to be associated with fungal and insect-borne diseases, such as dengue. Obviously, a travel and occupational history should also be performed, as many parasitic infections are travel related.

Progression of the rash is important: Where did it start and how did it spread? *Centrifugal* rashes start centrally and spread to the periphery (eg, varicella, rubella), while the reverse is true for *centripetal* rashes (eg, dengue, Rocky Mountain spotted fever [RMSF]). Asking about *prior treatment* and *rash evolution* also provides very useful information. Certain therapies may mask the original etiology (eg, inappropriate use of steroids on a fungal infection results in tinea incognito) or even provoke a secondary allergic response (eg, sensitizing products ending in -caine or -dryl, topical antibiotics such as Neosporin). The appearance of many rashes evolves over time. Pityriasis rosea starts as a herald patch mimicking ringworm (tinea) followed by the sudden appearance of multiple lesions. Dyshidrotic eczema starts with tapioca-like lesions between the fingers and then evolves into a scaly, itchy rash.

When confronted by a new rash, ask the following questions: What is the primary lesion (eg, macule, papule)? What are its secondary characteristics (eg, scaly, blanching if red)? Where on the body is it located (central or peripheral distribution)? What are the associated symptoms (eg, itching, fever, tenderness)? The answers will usually point in the right direction. Also, remember that uncommon presentations of common conditions (eg, contact dermatitis, eczema) are much more likely than common presentations of uncommon conditions; hence, this chapter will focus on the most common allergic and infectious pediatric conditions found in the tropics.

Skin Allergies

Several noninfectious skin conditions deserve special mention because they mimic many other rashes. *Allergic contact dermatitis,* perhaps the most common pediatric diagnosis, is a delayed cell-mediated hypersensitivity response to various allergens. Itching and erythema appear within 24 hours to several days post–allergen exposure, and the rash often becomes papular or vesicular. Poison ivy (*Toxicodendron*) is the best known example, but there are many tropical plant allergens—mango rind, cashew sap, poisonwood (*Toxicodendron*), and carrot weed (*Parthenium*). *Photodermatitis* causes rash only in areas exposed to sunlight; it is triggered by certain drugs (eg, tetracycline, thiazides) and plants (eg, fig, citrus juices, rue). *Polymorphous light eruption* (sun allergy) presents as pruritic papules or plaques after an unaccustomed exposure to UV-A light. Lastly, there are numerous *drug eruptions,* including generalized maculopapular rashes, urticarial reactions (hives), lichenoid reactions (flat-topped, itchy, red papules), and fixed drug eruption (local plaques). *Erythema multiforme* (target lesions evolving into bullae) may be caused by drugs or recent infection (eg, herpes simplex). Erythema multiforme reactions are part of a spectrum, including Stevens-Johnson syndrome or erythema multiforme major (with mucous membrane involvement), and life-threatening toxic epidermal necrolysis (TEN).

Urticaria (Hives)

Urticaria or hives are itchy red edematous plaques of varying shapes lasting for less than 24 hours. They usually signify an allergic response and are provoked by histamine release. Patients can be tested for their susceptibility to hives by lightly scratching the underside of their forearm; this test is called *dermographism* or skin writing.

Acute hives last fewer than 6 weeks and can often be linked with a specific allergen or environmental trigger. *Chronic hives* are present for longer than 6 weeks and pose a much greater clinical challenge because their etiology is often unclear. *Angioedema* describes a deep urticarial reaction in the skin that produces significant, possibly life-threatening, swelling, especially when affecting the larynx. There are acquired and hereditary forms. *Hereditary angioedema* (HAE) is a genetic condition caused by a deficiency of C1 esterase inhibitor and is often resistant to antihistamines and epinephrine. Consequently, HAE must be treated with plasma-derived C1 esterase inhibitor concentrate (C1-INH) or fresh frozen plasma if C1-INH is unavailable.

Hives have many potential triggers. These include environmental allergens, drugs, foods, infections, temperature changes (heat and

cold exposure), skin pressure, exercise or sweating (cholinergic urticaria), UV light exposure, emotional stress, and systemic diseases (eg, immunoglobinopathies).

Treatment usually starts with antihistamines (H_1-blockers); sedating antihistamines like diphenhydramine are often more effective than nonsedating ones. High-dose antihistamines may be necessary to control chronic urticaria, and H_2-blockers, such as ranitidine, can also be added when necessary. The next step, if antihistamines alone are unable to control symptoms, would be short courses of oral steroids. Severe urticaria and angioedema warrant epinephrine injection (EpiPen or EpiPen Jr). The pediatric dose of epinephrine is 0.01 mg/kg up to a maximum (adult) dose of 0.3 mg subcutaneous or intramuscular (IM). Chronic urticaria is often a frustrating condition for the patient and physician. New research suggests that vitamin D_3 supplementation (4,000 IU/d for adults) may reduce chronic urticaria by 40%.[1]

Physical Examination

The examination should be conducted with most of the patient's clothing off to avoid missing lesions of which she may be unaware. Scalp, genital, foot, and mouth lesions are the most easily missed. Oral examination for enanthemas is especially useful and may confirm conditions such as lichen planus. Nevi of concern and any congenital lesions should be measured, and diagrammed if possible, so they can be followed over time. Photography provides the best documentation because photos can be dated and placed in the chart.

Examination of Darkly Pigmented Skin

Skin pigmentation can be classified by its reaction to sun exposure. The Fitzpatrick skin pigmentation in Table 26-3 ranks skin from type I (always burns, never tans) to type VI (black, seldom burns). Physical examination of dark-skinned individuals poses additional challenges, especially for physicians new to the tropics who are accustomed to caring for those with lighter skin. Although darkly pigmented skin has the same number of melanocytes as white skin, dark skin melanocytes are far more efficient at producing pigment, which provides much better protection from UV radiation and reduces the risk of sunburn and skin malignancies (excepting more vulnerable areas such as fingernails, lips, and palms and soles). Post-inflammatory hyperpigmentation (post-acne) and hypopigmentation (post-cryotherapy) are less-desirable consequences. *Pityriasis alba,* which describes diffusely hypopigmented macules on the cheeks or arms subsequent to dry skin or eczema, is very common with darker skin. *Vitiligo,* well-demarcated immune-mediated

Table 26-3. Fitzpatrick Skin Pigmentation Types (Skin Reaction to Sun Exposure)	
Type I	Always burns, never tans
Type II	Always burns, sometimes tans
Type III	Sometimes burns, but always tans
Type IV	Seldom burns, always tans
Type V	Moderately pigmented (brown) skin
Type VI	Darkly pigmented (black) skin

pigment loss, is present in all skin types but is much more conspicuous with dark skin. *Erythema* is masked by skin pigment, although it can still be detected with experience. Palpation of the skin assists in detecting warmth and induration. *Cyanosis* can be identified by viewing lips and oral mucosa, while *jaundice* is apparent in the sclera, palms, and soles. Severe anemia causes an ashen appearance in black patients and a yellowish-brown shade in brown-skinned individuals.

Birthmarks are more prevalent (up to a 20% incidence) in blacks compared with whites (2%–3%). *Mongolian spots* are blue-gray macules present in up to 90% of blacks at birth and in a majority of Latino (70%) and Asian (80%) children.[2] Almost 10% of white infants are also affected. Mongolian spots are often located on the sacrum but may occur in other locations. The spots usually resolve by age 4 years but may last longer; their resemblance to bruises may lead to false suspicions of child abuse, as can real but benign bruises from the Asian folk practices of coining and cupping.

Keloids are the consequence of more efficient collagen production following trauma in darkly pigmented skin, resulting in exuberant scar formation (figures 26-1 and 26-2). Sternal areas, upper arms, shoulders, and earlobes are the most vulnerable areas. Many keloids are entirely preventable if unnecessary procedures, such as ear piercing, are avoided in high-risk individuals.

Dermatosis papulosa nigra is a common condition in black adults (10%–30%). *Dermatosis papulosa nigra* is characterized by small (1–5 mm), dark, dome-shaped seborrheic keratoses on both cheeks. They are benign and require no treatment. *Pseudofolliculitis barbae* ("shaving bumps") are also common in blacks because thick, curly beard

Figure 26-1. Extensive Keloids (Africa)

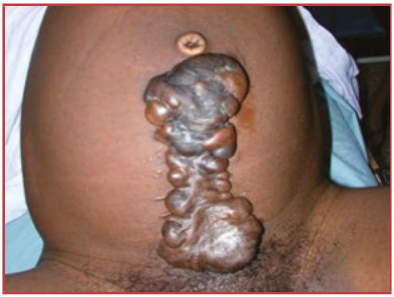

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Figure 26-2. Extensive Keloids (Africa)

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hair often becomes ingrown when shaved too closely. The inflammatory reaction mimics folliculitis. A common condition in young black women and girls is *traction alopecia* from excessively tight braids or cornrows, which can cause permanent hair loss if not corrected in time.

Basic Laboratory Assessment

Laboratory facilities are often quite limited in developing countries; however, scalpel blades, glass slides, a Wood lamp, and a microscope are helpful diagnostic tools. *Diascopy,* pressing a glass slide over an erythematous lesion, checks for blanching; inflamed capillaries transiently disappear with pressure, whereas petechiae do not. Scraping scaly lesions with a number 15 scalpel and adding a drop of 20% potassium hydroxide (KOH) to the resulting specimen will permit microscopic examination for fungal hyphae. Florescence with a Wood (UV) lamp can help distinguish *erythrasma,* a bacterial infection (fluorescing coral red) from *Microsporum* tinea infections (green). *Dermatoscopes,* when available, provide polarized light to view skin lesions under magnification without surface reflections; this process is called *epiluminescence microscopy.* With training, this permits a more accurate assessment of a lesion's potential for malignancy and helps guide the decision to biopsy. Finally, shave or ellipse biopsies of unusual lesions provide a definitive diagnosis as well as therapeutic guidance (or even cure) for skin malignancies. Web-based pathologic services have vastly improved the availability and reliability of these services in recent years.

Treatment Principles

Treatment involves knowing proper indications for topical preparations as well as standard oral therapies. The choice of which topical vehicle to use should be based on the condition's moisture content, location, and susceptibility to therapy. *Tapes and patches* provide optimal occlusion and coverage for small lesions. Occlusion with tape increases the penetration and potency of a topical steroid treatment. *Ointments* provide moisture to dry lesions and excellent occlusion but may be messy to apply. *Water-based creams* are the most popular for typical use because of their ease of application and lack of staining. *Lotions and sprays* are more practical to apply to extensive or hair-covered areas. *Alcohol-based gels* may be the most suitable for wet lesions because of their drying effect. It makes sense to dry wet lesions and moisten dry ones.

The potency of steroid preparations may be rated from 1 (most potent) to 7 (least potent) or, perhaps more usefully, as *strong* (high potency: classes 1–2), *moderate* (intermediate potency: 3–5), and *weak* (low potency: 6–7), as shown in Box 26-1. Areas of thin delicate skin, such as the face, genitalia, axillary and inguinal areas, and young children's skin in general, are subject to permanent atrophy and stretch marks (striae) if excessively potent steroids are prescribed for too long. Therefore, the lowest effective strength should be used, and even this should be modified as the condition improves.

Mild steroids should be used on the face or genital areas and more potent ones on the palms and plantar surfaces. More refractory skin conditions, such as contact dermatitis and psoriasis, mandate potent therapy to be effective. It is helpful to become familiar with an affordable generic option in each of the 3 categories: hydrocortisone 1% (mild), triamcinolone 0.1% (moderate), and betamethasone dipropionate 0.05% (potent). For most given agents, potency may be adjusted up or down with choice of vehicle (in order of potency): tape, ointment, cream, lotion, and gel. The amount of steroid is also critical. A *fingertip unit,* the amount of cream from the tip of the index finger to the first (distal) crease, will be enough to treat an area the size of an adult's palm. Without parental instruction, it is likely that far too much medicine will be applied. Duration of therapy should also be discussed to prevent indefinite use. High-potency steroids should be limited to fewer than 2 weeks of use.

Use of oral steroids is a double-edged sword; they dramatically improve symptoms for conditions such as contact dermatitis, but rebound occurs if the treatment is terminated too quickly, as happens with many dose packs. Rebounding psoriasis often ends up far worse than it was at the beginning—a good reason to avoid any systemic

Box 26-1. Topical Steroid Potency Ratings

LOW POTENCY (eg, FACE, GENITALS)
Alclometasone dipropionate 0.05% (Aclovate)
Fluocinolone acetonide 0.01% (Synalar Solution)
Hydrocortisone acetate 0.5%, 1%, 2.5% (Cortisporin, Hytone, Vytone)
Triamcinolone acetonide 0.025% (Kenalog, Aristocort)

INTERMEDIATE POTENCY (MOST USES, eg, ECZEMA)
Desonide cream 0.05% (DesOwen)
Desoximetasone 0.05% (Topicort)
Fluocinolone acetonide 0.025% (Synalar)
Flurandrenolide 0.025%, 0.05% (Cordran SP)
Fluticasone propionate 0.005%, 0.05% (Cutivate)
Hydrocortisone butyrate 0.1% (Locoid)
Hydrocortisone probutate 0.1% (Pandel)
Hydrocortisone valerate 0.2% (Westcort)
Mometasone furoate 0.1% (Elocon)
Prednicarbate 0.1% (Dermatop E)
Triamcinolone acetonide 0.1% (Kenalog, Aristocort)

HIGH POTENCY (eg, PSORIASIS, LICHEN, CONTACT DERMATITIS)
Amcinonide 0.1% (Cyclocort)
Betamethasone dipropionate 0.05% (Diprolene)
Clobetasol propionate 0.05% (Temovate, Temovate E)
Desoximetasone 0.05% (Topicort Gel)
Desoximetasone 0.25% (Topicort Cream, Topicort Ointment)
Diflorasone diacetate 0.05% (Psorcon E cream, Psorcon Ointment)
Fluocinonide 0.05% (Lidex, Lidex-E)
Flurandrenolide 4 mcg/cm^2 (Cordran Tape)
Halcinonide 0.1% (Halog, Halog-E)
Halobetasol propionate 0.05% (Ultravate)
Triamcinolone acetonide 0.5% (Kenalog, Aristocort)

steroid use for this condition. Steroid injections in the wrong areas (arms) may induce permanent tissue atrophy. Psychiatric symptoms, such as insomnia, anxiety, and even psychosis, may be provoked at higher doses (>40 mg) in susceptible patients. Chronic use results in steroid dependency, glucose intolerance, cataracts, ulcers, osteoporosis, and immune deficiency. In the developing world, prolonged use may unwittingly activate latent tuberculosis (TB) in malnourished, infected patients.

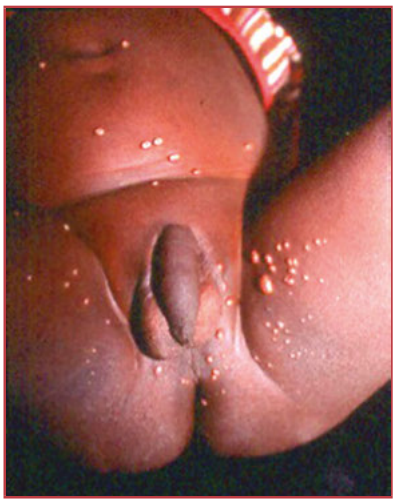
VIRAL SKIN INFECTIONS

Papular Presentations of Viral Infections

Molluscum Contagiosum

Molluscum contagiosum presents as characteristic 2- to 8-mm, often umbilicate, shiny papules, sometimes with surrounding erythema (Figure 26-3). This harmless poxvirus is easily spread by skin-to-skin contact in children between the ages of 2 and 12 years; lesions may appear 2 weeks to as long as 6 months postexposure.[3] The infection usually resolves within 4 to 6 months unless there is immune compromise, in which case unusually numerous or large (giant molluscum) or difficult-to-treat lesions occur. Molluscum usually appears on the trunk, face, or extremities in children. A genital presentation is more common in sexually active teens, although this same area can also be infected by scratching. Treatment involves destruction of lesions through curettage, application of trichloroacetic acid, or cryotherapy (freezing). Cryotherapy may produce areas of persistent hypopigmentation in dark-skinned patients. Lesions too numerous to treat individually respond to imiquimod 5% cream, although this indication is not yet approved by the US Food and Drug Administration (FDA).[4]

Figure 26-3. Molluscum Contagiousum



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Human Papillomavirus

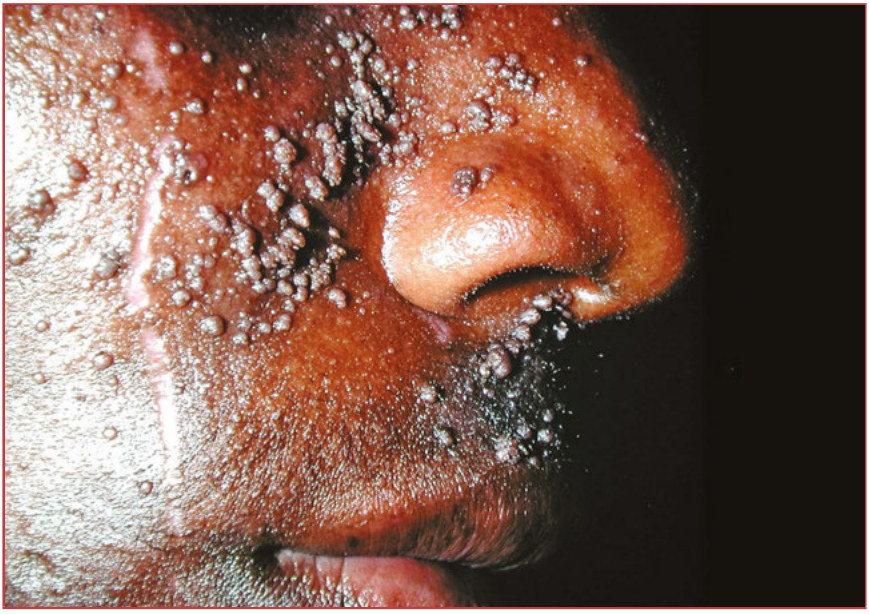
Human papillomavirus (HPV) consists of more than 70 genotypes clinically presenting as common, flat, plantar, and genital warts. They are ubiquitous, with an estimated 10% incidence in childhood, but two-thirds spontaneously resolve within 2 years.[5] *Verrucae vulgaris* or common warts (types 1, 2, 4, and 7) are flesh-colored, rough dome-shaped, or filiform papules that commonly affect the dorsum of the hands and periungual areas of fingers. Oral mucosal involvement is rare. *Verrucae plana* or flat warts (types 5, 8, and 17) are tiny, 2- to 5-mm flat papules occurring in colonies and easily spread though skin trauma or shaving

(Figure 26-4). *Plantar warts* (type 1) are ingrown, often painful lesions, sometimes forming colonies or mosaics, on the soles of the feet. *Genital warts* or *condyloma acuminata* occur on genital or perianal areas as multiple soft, verrucous papules. Human papillomavirus types 6 and 11 commonly cause genital warts, but other types (most notably 16 and 18) pose an increased risk of cervical cancer. In children, genital warts raise the additional possibility of sexual abuse; however, vertical (maternal) transmission may also occur.[6] An effective quadrivalent HPV vaccination (Gardasil, protecting against HPV types 6, 11, 16, and 18) is now approved for females and males 9 to 26 years of age. A bivalent HPV vaccine, Cervarix, protects against HPV types 16 and 18, which cause cervical dysplasia and cancer.

Warts are diagnosed by appearance; they are usually flesh-colored, verrucous papules. Plantar warts often require paring with a number 15 scalpel to distinguish them from calluses or black heel secondary to trauma. Dark specks or seeds (thrombosed capillaries) and interrupted skin lines distinguish warts from other lesions.

Treatment may be with cryotherapy (difficult and painful for children), salicylic acid liquids and plasters, topical cantharidin, or imiquimod 5% cream. For recalcitrant common or plantar warts,

Figure 26-4. Verrucae Plana or Flat Warts (Human Papillomavirus)



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injection with *Candida* antigen (0.1 mL of a 1:1,000 solution, same as used for dermal immune testing) with added lidocaine 1% is a non–FDA-approved option that is effective 74% of the time, often with concomitant disappearance of non-injected warts.[7] Cimetidine oral therapy, thought to stimulate T cells, has produced mixed results and may be no more effective than placebo.[8] Duct tape occlusion may also be ineffective. Surgical therapy or electrocautery should be avoided because it can result in permanent scarring and it is usually better to wait for natural resolution. Tretinoin cream, imiquimod 5% creams, or gentle cryotherapy are effective options for flat warts. Genital warts may be treated with cryotherapy, podofilox gel, or imiquimod 5% cream, although the latter 2 therapies are unapproved in children. Application of 5% acetic acid to genital warts for 1 to 2 minutes (the *acetowhite test*) turns them white and makes areas infected with HPV easier to visualize and treat.

Vesicular Presentations of Viral Disease

Human Herpesvirus

Human herpesvirus types 1 (oral) and 2 (genital) are a common cause of recurrent oral and genital vesicles. Human herpesvirus is capable of persisting in nerve ganglia in a dormant state where it cannot be reached by therapy. *Primary herpes gingivostomatitis,* usually from human herpesvirus 1, causes oral and perioral lesions with stomatitis, sore throat, and cervical lymphadenopathy, most commonly in children younger than 5 years. While many primary infections are asymptomatic, severe cases can last 2 weeks and result in dehydration. The recurrent vesicles of herpes labialis, known as *cold sores* or *fever blisters,* appear in clusters on the vermilion border of the lip following a brief prodrome of tingling. They often become secondarily infected (impetiginized) and are precipitated by stress, illness, or excess sun exposure. Herpetic whitlow occurs when a finger (the patient's or a caregiver's) is inoculated with the virus, causing a painful fingertip swelling for several weeks. *Herpes keratoconjunctivitis* may cause recurrent conjunctivitis (red eye) with corneal opacification, leading to permanent vision loss. Steroid eyedrops are notorious for exacerbating this condition, and ocular human herpesvirus should be excluded by slit lamp examination prior to their use. *Herpes gladiatorum* describes clustered vesicles on the trunk or extremities in wrestlers or athletes exposed to infected secretions. In patients with atopic dermatitis, *eczema herpeticum* (Kaposi varicelliform eruption) may produce a generalized vesicular outbreak due to the loss of a normal skin barrier. Erythema multiforme, with target lesions, is a secondary immune response often following an outbreak of labial herpes.

Genital herpes (usually human herpesvirus 2) also cause primary and secondary infections. Primary outbreaks occur 2 to 8 days after sexual exposure with painful genital vesicles and inguinal adenopathy. Scrapings from the base of fresh ulcers, as in human herpesvirus 1, are positive for multinucleated giant cells on *Tzanck preparations*. Secondary outbreaks are milder and more frequent in the first years following infection. Those with frequent episodes also have a higher risk for asymptomatic viral shedding, which renders them contagious between symptomatic outbreaks.[9] Treatment for either type of human herpesvirus is oral acyclovir, famciclovir, or valacyclovir started within 24 hours, although it is beneficial even 2 to 3 days later. Antiviral therapy can also be used to reduce genital recurrences and suppress human herpesvirus shedding indefinitely. Topical antiviral creams for cold sores are much less effective, although they may reduce symptoms and shedding by a day or 2 if started promptly.

Recurrent aphthous stomatitis (RAS) is sometimes confused with oral herpes. These "canker sores" are painful, shallow, gray ulcerations of the oral mucosa, not involving the vermilion border, that last for 1 to 2 weeks. Their etiology is poorly understood and they are thought to be related to stress, minor trauma, or an autoimmune response. Minor RAS (few small lesions) is very common, but occasionally, major RAS (with larger lesions) is noted. Treatment is symptomatic, often with topical lidocaine, amlexanox, or steroids in denture paste.

Varicella Zoster (Shingles)

Varicella zoster or *shingles* is a vesicular eruption caused by reactivation of latent varicella (chickenpox) virus in the sensory ganglia. Vesicles are clinically similar to those of herpes simplex (positive Tzanck preparation) but are characteristically unilateral and limited to a specific dermatome. Rash is preceded by hyperesthesia or discomfort in the involved area. Vesicles erupt over a period of 1 week, then take another week to crust over and heal.

Varicella zoster is usually associated with advanced age or immune compromise (frequently a presenting condition in AIDS), but it also occurs in children and teens, including healthy children immunized with attenuated varicella vaccine.[10] Common dermatomes infected include C2-L2 and the trigeminal (fifth) and facial (seventh) cranial nerves. *Hutchinson sign* is vesicular involvement of the tip of the nose, which indicates ophthalmic branch involvement of cranial nerve V (signaling impending keratitis) and should prompt an immediate ophthalmology referral. *Ramsay Hunt syndrome* describes Bell palsy, auditory canal shingles, and disturbed hearing and balance. Abdominal shingles

presents with severe abdominal pain, which sometimes leads to surgery, prior to any appearance of rash.

Treatment is with high-dose antiviral therapy, such as acyclovir, ideally started within 72 hours of rash onset. Postherpetic neuralgia, characterized by burning, persistent nerve pain, is uncommon in children but increases with age and delayed treatment. A live zoster vaccine (Zostrix) is available but is FDA-approved only for adults older than 50 years.

Viral Exanthems of Childhood With Fever

At the start of the 20th century, Filatov described 6 rashes of childhood, including rubeola (measles), scarlet fever or scarlatina (nonviral, due to group A beta-hemolytic streptococci [GABHS]), rubella (German measles), Duke disease (fourth disease, now obsolete but believed to be related to staphylococcal infection), erythema infectiosum (fifth disease), and exanthema subitum or roseola (sixth disease). Other childhood rashes include chickenpox (varicella), mumps, coxsackievirus, mononucleosis, Kawasaki disease, and assorted nonspecific viral exanthems. Dengue is a major cause of rash and fever in the tropics and the leading cause of fever with rash in returning travelers. Fortunately, the ancient scourge of smallpox (variola) is now extinct outside the laboratory, but a similar-appearing, albeit milder rash, monkeypox, occasionally occurs as a zoonotic infection in Africa.

Rubeola

Rubeola (measles) is a well-known contagious viral childhood illness that is now rare in the United States because of vaccination but is still common worldwide. Its prodrome consists of fever and the 3 Cs—cough, coryza, and conjunctivitis—along with characteristic *Koplik spots* (whitish papules on the buccal mucosa). The classic morbilliform or measles-like (red, maculopapular) exanthem starts on the face about 4 days after the beginning of the prodrome and spreads to the body and extremities. Atypical measles can cause a petechial rash mimicking RMSF or meningococcemia. Measles is infectious from 1 day prior to the start of the prodrome to 4 days after the rash appears. The incubation period is about 10 days. Diagnosis is clinical, but initial laboratory findings include leukopenia and the detection of measles IgM antibody within 4 days of illness.[11]

A live measles vaccine (now administered as part of the measles, mumps, rubella [MMR] vaccine) was introduced in the United States in 1963 for children 12 to 15 months of age. After a US measles outbreak in 1989 and 1990, a second dose of vaccine was recommended at 4 to 6 years of age (with revaccination at 11 to 12 years or older for children

who needed it). Americans born before 1956 usually have had wild measles, while those born after 1956 need 2 doses of MMR for lasting immunity. Measles complications include pneumonia, encephalitis, and the rare (1 in 100,000) delayed neurologic disease, subacute sclerosing panencephalitis.[11] Malnutrition, particularly vitamin A deficiency, significantly increases measles mortality; thus, vitamin A supplementation (200,000 IU orally) is critical if deficiency is suspected or if the region's measles mortality rate is greater than 1%.[12] Prompt vaccination efforts in overseas refugee populations can prevent devastating measles epidemics. Measles therapy is mostly supportive, although measles immunoglobulin can prevent or modify symptoms if given within 6 days of exposure.[13]

Rubella

Rubella (German or 3-day measles) is a much milder measles-like illness characterized by a pink macular eruption starting on the face and spreading onto the trunk and later to the extremities. The rash fades within 48 hours and is indistinguishable from many other viral exanthems. An estimated half of all cases are subclinical. The child usually appears well despite mild fever and posterior cervical lymph nodes that precede the rash. Infectivity begins a week prior to rash onset and lasts for 4 days afterward (although infants with congenital rubella syndrome can shed the virus for months). Incubation period is 14 to 21 days. Laboratory confirmation involves finding rubella IgM antibody within 28 days of rash.[11] A monarthric arthritis may also occur (more likely in females), outlasting the rash by weeks. This complex presentation—sore throat, arthritis, rash (STAR)—may be seen in rubella and parvovirus infections, among others. Rubella is notorious for causing *congenital rubella syndrome* in neonates born to mothers infected in the first trimester (microcephaly, deafness, mental retardation, and hepatomegaly). The best protection is through live, attenuated rubella vaccination prior to pregnancy.

Erythema Infectiosum

Erythema infectiosum (fifth disease) is a mild childhood illness caused by parvovirus B19. Rash begins with redness of one or both cheeks (75% of cases)—the classic *slapped-cheek* presentation—followed by a lacy reticular macular rash for 3 to 5 days, although this rash may transiently reappear with heat or exercise for up to 4 months. Palmar rash is common. Some patients may develop purple hands and feet (gloves-and-socks syndrome). Fever is present only in 20% of cases. The rash's appearance usually signals the end of infectivity, so these children may attend school and no treatment is necessary. However, like rubella, erythema infectiosum can present as the STAR complex (albeit with

symmetrical arthritis) and even cause fetal death if women in the first half of pregnancy are infected. The precaution of avoiding contact with pregnant women for 2 weeks may be overkill, as the diagnostic rash coincides with loss of infectivity. Exceptions would be rubella aplastic crisis cases (seen in sickle cell disease), in which the patient may be contagious for a week after symptoms, and immunocompromised patients, who may shed the virus for months.[11]

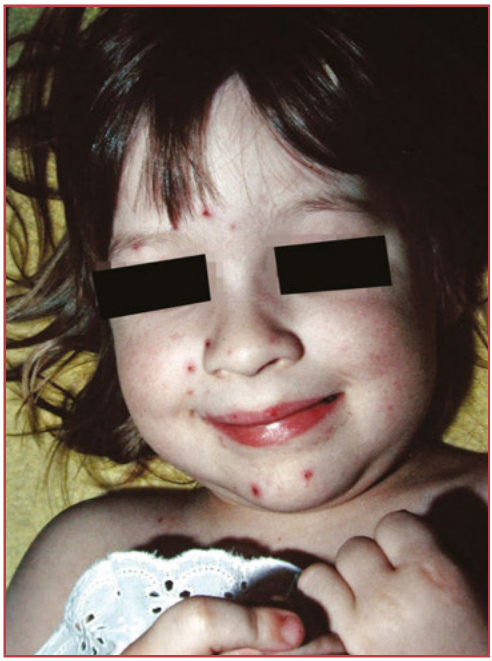
Roseola Infantum

Roseola infantum (erythema subitum) is a human herpesvirus 6 (or 7) infection in children younger than 2 years. Classically, there are 3 days of sustained high fever followed by the appearance of an erythematous macular rash that fades in 24 hours. Febrile seizures may occur, but the condition is otherwise benign. Echovirus 16 (Boston exanthem) may mimic roseola in preschool-aged children, although it can also cause petechial eruptions on the extremities and the fever may overlap with the rash.

Varicella

Varicella (chickenpox) is a common contagious childhood illness, peaking in late winter, with a prodrome of fever, chills, and myalgia followed within 48 hours by crops of vesicles on an erythematous base ("dewdrops on rose petals"). The centrifugal rash first appears on the trunk, face, and scalp (Figure 26-5) and then spreads to the extremities. New crops of vesicular lesions continue appearing and crusting over for 3 to 4 days, so it is usually possible to find lesions in all stages of development. Residual scarring often occurs, but infection results in lifelong immunity. The patient is infectious for 1 to 2 days before the prodrome

Figure 26-5. Varicella (Chickenpox) Rash



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starts until the last crusts form at about 5 days. Incubation period is about 14 to 21 days.[11] Most childhood chickenpox cases are uneventful, but adolescents older than 12 years and adults are prone to more severe illness and should be treated with antivirals such as acyclovir. Aspirin exposure in chickenpox and influenza must be avoided because of the risk of Reye syndrome, acute encephalopathy, and fatty degeneration of the liver.

Live, attenuated varicella vaccine (Varivax) has been recommended for children aged 12 to 18 months since 1996. A second dose is now recommended 1 month after the first for children and susceptible adults. Many young adults missed their second dose and are now susceptible to chickenpox.

Once infected (or vaccinated), the varicella-zoster virus remains dormant in sensory ganglia, from which it can later emerge to cause varicella zoster (shingles).

Dengue

Dengue (breakbone fever) is a mosquito-borne illness of the tropics and subtropics characterized by high (often biphasic) fever for 5 to 7 days, headache, retro-orbital pain, myalgia, arthralgia, and rash in 50% of cases. Four dengue flavivirus serotypes (dengue 1–4) cause the condition with very little cross-protection among the 4 serotypes. The generalized maculopapular rash, often with islands of spared paler skin, usually appears when the fever subsides, but this is often difficult to appreciate in dark-skinned patients. In light-skinned patients, the characteristic sunburn-like rash is often described as a "sea of red" with islands of white skin. Complications include dengue hemorrhagic fever (DHF), which is characterized by increased vascular permeability, thrombocytopenia, fever, and hemorrhage. The related dengue shock syndrome (DSS) describes DHF complicated by shock and carries a 12% mortality rate even with good care.[14] Secondary infection by another dengue serotype is considered the likely cause of DHF and DSS.

Dengue is usually diagnosed clinically, but reverse-transcriptase polymerase chain reaction (PCR) testing for viremia can confirm the diagnosis within the first 5 days of infection. An IgM antibody capture enzyme-linked immunosorbent assay test (eg, DENV Detect IgM Capture ELISA), turning positive 1 week postinfection, may help distinguish dengue from other tropical febrile illnesses, such as leptospirosis, malaria, typhoid, and the very similar chikungunya fever.[15] A 4-fold increase in hemagglutination inhibition antibody titer between acute and convalescent serum specimens is also diagnostic. In the United States, dengue testing is performed by the Centers for Disease Control and Prevention

(CDC) Dengue Branch. Leukopenia and thrombocytopenia are common findings. A positive result from a *tourniquet test* (>20 petechiae per square inch of skin) after 5 minutes of blood pressure cuff inflation, midway between diastolic and systolic pressures, indicates hemorrhagic risk. Abdominal pain and vomiting in children with a sudden drop in temperature also presages DSS.

Dengue often occurs in epidemics owing to high numbers of infected *Aedes* mosquitoes, which bite for several hours after dawn and before dusk. The illness usually starts 4 to 7 days after being bitten. The best protection is insect repellent, as there is no effective vaccine or medical prophylaxis. Treatment is supportive with hydration to prevent shock. Corticosteroids are ineffective.

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease is a common viral illness of young children (often <5 years) that causes deep vesicles on the palms and soles with painful oral vesicles. Malaise and fever may also be present. The disease is usually caused by coxsackieviruses A or B and is self-limited. However, enterovirus 71 epidemics may produce more severe hand-foot-and-mouth disease with death. Coxsackieviruses may also cause *herpangina* in somewhat older children with painful throat vesicles and fever. Hydration and pain relief is important. Herpangina resolves in 1 week without specific treatment.

Infectious Mononucleosis

Infectious mononucleosis is a several week syndrome of fatigue, sore throat (75%), fever, and anterior and posterior cervical adenitis in children and adolescents that is usually followed by extreme fatigue. Posterior lymphadenitis is a classic hallmark of infection. Childhood infections are much milder than those of college-aged students. Most children in developing countries are infected by 5 years of age, but those in higher-income countries are infected later in life. Epstein-Barr virus causes 85% of mononucleosis-like presentations; the remainder are caused by cytomegalovirus, human herpesvirus 6, toxoplasmosis, and others. Acute retroviral syndrome, the initial infection of HIV, may also mimic mononucleosis symptoms before entering the latent phase of infection.

About 5% to 15% of mononucleosis patients develop a transient macular skin eruption. Prescribing amoxicillin (and occasionally other antibiotics) for sore throat causes a delayed red morbilliform rash in most of these patients that lasts for at least 1 week. This is thought to be caused by an amoxicillin-antibody immune complex rather

than a true amoxicillin allergy. Jaundice from mononucleosis hepatitis occurs in 4% of young adults, although a majority may have mild liver enzyme elevation.[11]

Mononucleosis is spread through saliva (eg, kissing, sharing beverages); saliva continues to be infectious for 6 to 18 months. Incubation period is 2 to 7 weeks. A *heterophile IgM antibody test* (monospot) confirms the diagnosis, but 15% of patients may have negative test results until the second or third week of illness. Atypical lymphocytes are also common. Leukocytosis is common at first, but neutropenia and thrombocytopenia often develop later in the illness. Upper airway obstruction (preventable with oral steroids), mild hepatitis, and splenic rupture are other potential complications. Contact sports and jogging should be avoided for several weeks after diagnosis. Treatment is mostly supportive.

Nonspecific Viral Exanthems

Nonspecific viral exanthems may be described by their primary lesion as vesicular, papular (or maculopapular), petechial, or urticarial. They may also be described by the rash they resemble—*morbilliform* (measles-like), *scarlatiniform* (scarlatina-like), or *rubelliform* (rubella-like). These rashes are usually erythematous macular or maculopapular rashes without distinguishing features but are usually associated with respiratory or gastrointestinal illness. Most resolve in 1 week without treatment. Enteroviruses are common causes of exanthems in summer months, whereas respiratory viruses (eg, adenovirus, respiratory syncytial virus) are more common in the winter.

Variola Major (Smallpox) and Monkeypox

Smallpox was eradicated in 1980, with the last case occurring in Somalia in 1977. However, the virus is still maintained in high-security laboratories in the United States and Russia, and there is some concern that it might be used in future bioterrorism. The characteristic centrifugal rash is pustular, starting on the face and spreading to the rest of the body, with the extremities becoming extensively involved. Rash is preceded a few days prior by high fever, myalgia, and red oral macules. Mortality used to be around 30% and survivors were often scarred for life. No specific treatment exists. Malignant (vesicular) and hemorrhagic variants were usually fatal.

A much milder form of smallpox, *variola minor,* was also recognized. Vaccination against smallpox with cowpox (Dryvax live vaccinia vaccine, now obsolete) was sometimes complicated by eczema vaccinatum in atopic children, with vaccinia immunoglobulin being the treatment of choice. Myocarditis also occurred. The FDA licensed a new live

vaccine for smallpox (ACAM2000) in 2007, which the CDC now distributes as a replacement for Dryvax.[16] However, routine vaccination of first responders is now discouraged because of risk of vaccine-related myocarditis and pericarditis. Although routine smallpox vaccination in the United States ended in 1972, ACAM2000 vaccine is still being stockpiled out of concern for bioterrorism.

Monkeypox is a zoonotic infection that resembles smallpox and is occasionally reported from West and Central Africa. It is spread to humans from rodents (or from eating monkeys infected by rodents). It made headlines in 2003 when a brief US outbreak was triggered by pet prairie dogs that were infected by an imported Gambian rat. Fortunately, it is milder and less contagious than smallpox.

Hemorrhagic Fevers

Fever and hemorrhage (including skin manifestations) are principal symptoms of various Old and New World hemorrhagic fever viruses. *Arenavirus* includes multiple types, including lymphocytic choriomeningitis virus and Lassa virus (West Africa), which are zoonotic infections from rodents. *Filovirus* includes the rare but dreaded *Ebola* and *Marburg hemorrhagic fevers* of Africa that infect nonhuman primates and humans. Fruit bats have now been identified as the likely animal vector for Ebola virus, and primates may be infected after consuming bat-contaminated fruit. Humans are often infected after consuming infected bush meat. *Orthobunyavirus* includes *Rift Valley fever* (*Aedes* mosquito bites) and *Congo-Crimean hemorrhagic fever* (tick bites). There are multiple *Hantavirus* associated with rodents (worldwide), of which the Sin Nombre virus, described after a 1993 US outbreak, is representative. *Flaviviruses* include yellow fever and DHF, which are arthropod-borne viral infections with hemorrhagic manifestations. Bacterial infections, notably meningococcal meningitis, may also cause rash and hemorrhage.

Jaundice and Fever

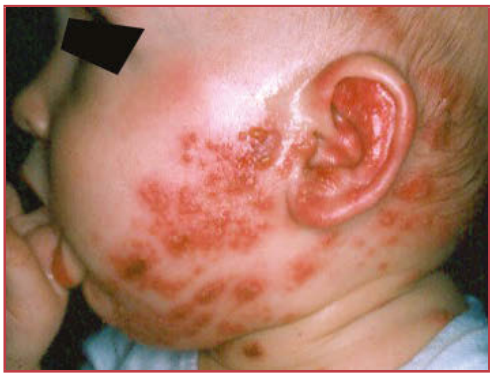
Yellow fever, malaria, infectious hepatitis, and leptospirosis are potential causes of febrile jaundice and can have clinically similar presentations. Scleral icterus, nausea, and dark urine are classic symptoms. Hepatitis A is usually less symptomatic in children and unlikely to cause jaundice in the very young. Yellow fever, spread by *Aedes* mosquitoes, is characterized by fever, myalgia, and vomiting, with 15% of cases progressing to a toxic, often fatal, phase with jaundice, abdominal pain, hemorrhage, and hematemesis (black vomit).[17] Nonviral causes of febrile jaundice include leptospirosis (secondary to the *Leptospira* spirochete) and malaria. Malaria may cause hemolysis with resultant unconjugated

hyperbilirubinemia and jaundice. Leptospirosis may present with fever, jaundice, renal failure, and hemorrhagic lesions (Weil disease) or as an anicteric illness with fever, headache, conjunctival hyperemia, hepatosplenomegaly, and an erythematous maculopapular or urticarial rash. The face and extensor surfaces are often spared.[18]

HIV and AIDS-Related Skin Disease

HIV is associated with a great many different skin manifestations. Acute retroviral syndrome occurs 2 to 4 weeks after infection and often resembles clinical mononucleosis with a nonspecific erythematous maculopapular rash and lymphadenopathy. A high viral load is present, but antibody testing results are negative at this stage of the disease. Later, AIDS-related rashes include herpes zoster (a prime indicator of AIDS in high-incidence areas [Figure 26-6]), intractable seborrheic dermatitis (scaly red rash of the scalp and face), oral candidiasis (thrush), severe tinea infections, cutaneous histoplasmosis, oral hairy leukoplakia (white lesions on the lateral tongue borders secondary to Epstein-Barr virus), eosinophilic folliculitis, cutaneous TB, and scrofula (TB adenitis). Bacillary angiomatosis (*Bartonella*) and Kaposi sarcoma (human herpesvirus 8) manifest as purple-red skin papules. Giant molluscum, cryptococcosis, and coccidioidomycosis may all present as papules that may be difficult to distinguish clinically. Penicilliosis (*Penicillium marneffei*) is the third most common AIDS-related opportunistic infection in Southeast Asia. It also presents with umbilicate papules closely resembling those of molluscum contagiosum.[19] AIDS-related hair changes include loss of normal curliness, alopecia, elongated eyelashes, and premature graying. Drug eruptions, especially those from sulfa, also occur more frequently.

Figure 26-6. Herpes Zoster in 8-Month-Old Following Varicella at 4 Months of Age



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Pityriasis Rosea

Pityriasis rosea is a common childhood and adolescent rash of probable viral origin (human herpesvirus 6 and 7 were found in some studies),

although there may well be other causative agents.[20] Most cases start with an oval, scaly herald patch that closely resembles tinea corporis (but is KOH negative). The herald patch is followed by a secondary outbreak of multiple smaller, scaly oval papules (often with a collarette of scale) that follow the lines of skin cleavage. Itching may occur during the outbreak but is usually minimal. Classically, a Christmas tree pattern may appear on the back when the rash is fully developed. Most of the rash is on the trunk and proximal extremities, usually sparing the face. Sometimes there is an inverse distribution affecting the arms, inguinal area, and lower extremities (sparing much of the trunk). Black children have a higher incidence of this variant and sometimes have more atypical-appearing (rounder, more papular) lesions. Any atypical case or the presence of distal lesions should prompt syphilis serology testing. Fortunately, this rash is self-limited and requires no treatment.[21] Sunlight exposure appears to hasten resolution of the rash, as may erythromycin.[22]

Kawasaki Disease

Etiology is still unknown for this acute febrile mucocutaneous lymph node syndrome. This childhood disease should be considered whenever there is sustained fever (>5 days), red eyes (non-exudative conjunctivitis), and a maculopapular erythematous rash (especially pronounced at the skin folds). Most cases occur in children younger than 5 years; Asian children are at increased risk. Red, crusted lips and a strawberry tongue are common. Hands and feet become swollen and develop red palms and soles that later desquamate. More than half of affected children have cervical lymphadenopathy. Diagnosis is basically clinical and there are no confirmatory laboratory tests. Other conditions possibly resembling Kawasaki disease include scarlet fever, toxic shock syndrome, drug reactions, and RMSF. Serious vasculitic complications may occur, particularly occlusion of the coronary arteries, which can cause sudden death even months after apparent recovery. Treatment is with aspirin (ideally started within 10 days of illness onset and continued for 2 months) along with intravenous (IV) immunoglobulin.[11]

BACTERIAL, TREPONEMAL, AND RICKETTSIAL SKIN INFECTIONS

Bacterial Skin Infections

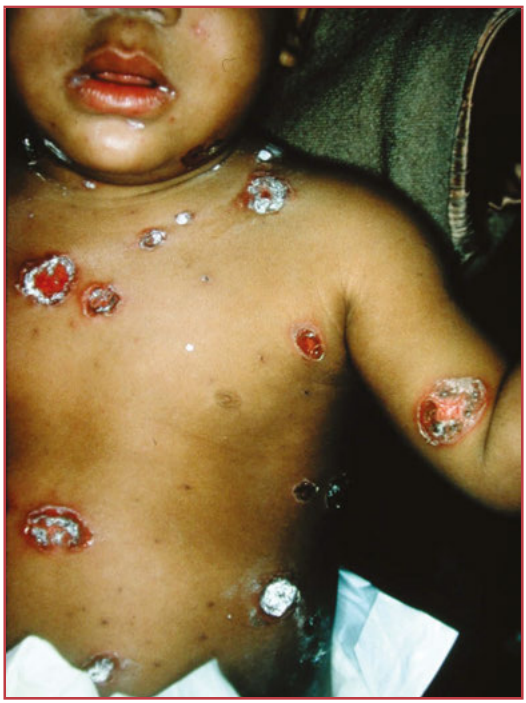
Pyodermas

Pyodermas are ubiquitous in the tropics. *Impetigo* (summer sores) is a common, contagious, superficial skin infection of children presenting

in non-bullous (crusted) and bullous forms. The hallmark of the more common non-bullous impetigo is a honey-colored crust that develops on an erythematous base. *Staphylococcus aureus* and GABHS are the principal causes. Bullous impetigo is characterized by small blisters due to *S aureus*. These bacteria often colonize the nasal mucosa (or genitalia) and are spread by scratching insect bites or traumatized skin with dirty hands. Mupirocin cream or ointment is an effective topical treatment for staphylococcal impetigo (including that caused by methicillin-resistant *S aureus* [MRSA]) and may also be used to reduce nasal carriage, albeit with less than permanent results.[23] Oral therapy for more extensive impetigo is accomplished with erythromycin, azithromycin, dicloxacillin, amoxicillin-clavulanate, or cephalexin. Methicillin-resistant *S aureus* infections respond to sulfamethoxazole-trimethoprim, doxycycline, vancomycin, or clindamycin. Although most impetigo is now staphylococcal related, nephritogenic streptococcal skin infections may still occasionally result in outbreaks of post-streptococcal nephritis and scarlet fever, despite appropriate antibiotics.

Ecthyma is a deeper form of GABHS impetigo (Figure 26-7), penetrating the epidermis to form deep, punched-out ulcers that heal slowly with scarring. A hemorrhagic ulceration, ecthyma gangrenosum, is caused by *Pseudomonas* infection in immunocompromised children. Superficial folliculitis, or staphylococcal hair follicle infection, typically appears as small pustules with central hairs (*Bockhart impetigo*) and usually responds to topical antibiotic treatment. Hot tub or *Pseudomonas folliculitis* occurs 1 to 2 days after exposure to a hot tub or pool with inadequate chlorination. Lesions are often on the trunk in areas covered by the swimsuit. They usually resolve in a week without any

Figure 26-7. Ecthyma



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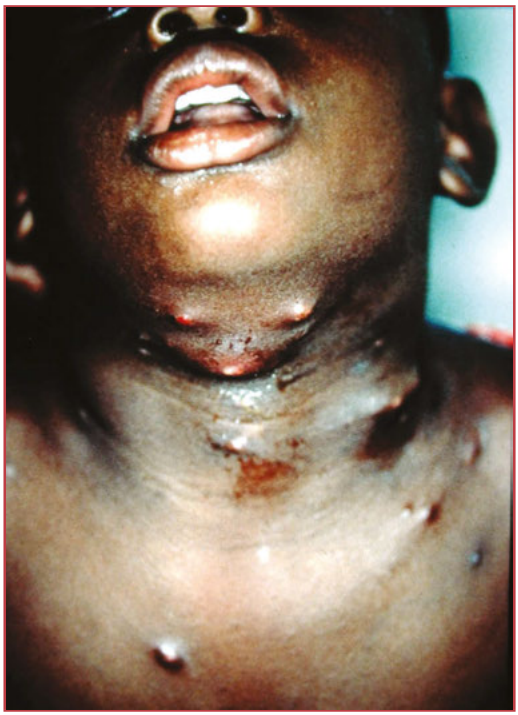
antibiotic treatment. *Pseudofolliculitis* (razor bumps) is an inflammatory condition caused by ingrown curly hairs, which is managed by growing the hair out or avoiding close shaves.

Deeper, more painful lesions include *furuncles* (boils or abscesses [Figure 26-8]) and the larger aggregates of furuncles called *carbuncles*. Both are caused by *S aureus* and may be misdiagnosed as spider bites in early stages. These lesions present as red, tender nodules that soon become fluctuant and filled with pus. Adequate incision and drainage is optimal treatment, and often incision and drainage alone is sufficient to resolve the problem; although in practice, systemic antistaphylococcal antibiotics are often added. In recent years, culture and sensitivity testing has become much more important because of the increasing incidence of MRSA infection.

Figure 26-8. Staphylococcal Furuncles



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Cellulitis is an acute infection of the subcutaneous tissue with tender erythema and swelling that often follows skin trauma. It is usually caused by *S aureus* or GABHS but occasionally may be caused by streptococcal pneumonia or *Haemophilus influenzae* type b. Systemic antistaphylococcal drugs are effective for most cases. *Erysipelas* is a cellulitis variant, usually caused by GABHS, characterized by shiny red plaques with sharply demarcated margins on the head or hands. Penicillin is the drug of choice. *Necrotizing fasciitis* (flesh-eating bacteria) is a life-threatening GABHS or polymicrobial infection that rapidly destroys tissue and requires immediate surgical debridement and multiple systemic antibiotics (including clindamycin).

Staphylococcal scalded skin syndrome is caused by an epidermolytic toxin-producing strain of *S aureus* that causes diffuse skin erythema and blistering in young children. Hospital outbreaks are common. The blisters are caused by the toxin, not the bacteria, and are followed by skin exfoliation. A first-generation cephalosporin or clindamycin may be used for treatment. Staphylococcal scalded skin syndrome is distinguishable from the similar TEN because the latter involves mucous membranes and is usually drug induced. *Toxic shock syndrome* is caused by toxin-producing *S aureus* strains that cause fever, rash, and hypotensive shock. A scarlatiniform erythroderma develops with a strawberry tongue followed by skin desquamation. While first associated with superabsorbent tampons, toxic shock syndrome may occur with nasal packing or, indeed, any toxin-producing staphylococcal infection. A streptococcal shock syndrome has also been identified.

Corynebacterial Kytococcus *Skin Infections*

Erythrasma (*Corynebacterium minutissimum*) is a superficial gram-positive bacterial skin infection closely resembling tinea cruris but distinguishable by a coral-red fluorescence on Wood lamp examination. It usually appears as an asymptomatic scaly red-brown patch, often in the groin or axilla. Topical antibiotics, such as erythromycin and clindamycin, are effective, as are oral antibiotics. Another corynebacterial infection is *trichomycosis axillaris* (*C tenuis*), which causes yellowish axillary or pubic hair nodules and reddish perspiration. Treatment involves shaving the infected hair. *Pitted keratolysis* was formerly considered a corynebacterial infection but is now reclassified as *Kytococcus* (*Micrococcus*) *sedentarius*. Topical antibiotics (ie, erythromycin, clindamycin, or mupirocin) are curative, but the condition can also be controlled with aluminum chloride antiperspirants.

Bartonella *Skin Infections*

Bartonella species are gram-negative bacteria that may cause cat-scratch disease, bacillary angiomatosis, trench fever, and Carrión disease (including Oroya fever and verruga peruana). *Bartonella henselae* causes cat-scratch disease. A small papule soon develops at the scratch site (usually from a kitten) and is followed by enlargement of regional lymph nodes, which occasionally become fluctuant. *Cat-scratch disease* is self-limited in immunocompetent children and lymph nodes usually start to subside after several months. Azithromycin or ciprofloxacin are recommended for at least 1 month in immunocompromised patients.[11]

In immunocompromised patients, usually with AIDS, *B henselae* (from cat fleas) and *B quintana* (from lice) may cause *bacillary angiomatosis,*

which presents as purplish, 1- to 2-cm skin papules. Biopsy distinguishes these from Kaposi sarcoma and pyogenic granulomas. The lesions resolve with prolonged erythromycin or doxycycline treatment.

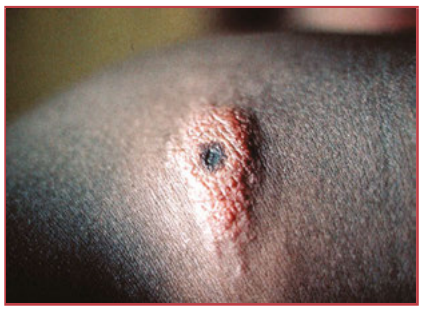
Trench or *shinbone fever* is caused by *B quintana* and is spread by lice. It is currently associated with homelessness but was also common in wartime. High fever recurring about every 5 days (fifth day = quintana) is associated with leg shin pain and a central maculopapular rash (80%). Tetracycline or chloramphenicol are quickly curative.[11]

Bartonellosis may manifest as a severe, often fatal hematogenous infection, termed *Oroya fever,* or as a milder cutaneous eruption known as *verruga peruana* (Peruvian wart). Both of the hematogenous and cutaneous manifestations of infection are now recognized as different manifestations of the same disease, Carrión disease. It is named after Peruvian medical student Daniel Carrión, who died from Oroya fever after a friend inoculated him with material from a wart, thereby proving these 2 conditions were linked. The disease is spread by *Lutzomyia* sandfly bites, which take several months to become symptomatic. Oroya fever is characterized by fever, headache, arthralgia, and hemolytic anemia, which persist for 2 to 4 weeks and are often fatal without treatment. Peripheral blood smears show the bacteria inside red blood cells. Verruga peruana is an angiomatous eruption on the extremities of children and may take 3 forms: *miliar* (multiple small, reddish papules), *nodular* (larger, skin-covered nodules), and *mular* (larger but open nodules). It is best diagnosed by biopsy with Warthin-Starry staining. Both manifestations of Carrión disease can be treated with ciprofloxacin.[24]

Cutaneous Anthrax

Cutaneous anthrax is a gram-positive, spore-forming infection of herbivores that incidentally infects humans. Contact with spores on infected hides or meat is the usual source of infection, although bioterrorism has become an additional concern. Most cases are the cutaneous form starting as a malignant pustule that turns into a black eschar surrounded by non-pitting edema (Figure 26-9). The lesion usually heals in 2 to 6 weeks with scarring; however, 20% of treated lesions may turn into a systemic fatal bacteremia.[25] The oropharyngeal and inhalation forms of anthrax

Figure 26-9. Anthrax (Malignant Pustule with Eschar)



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are usually fatal without prompt therapy. A Gram stain from the ulcer documents anthrax bacteria, which can also be readily cultured. Ciprofloxacin is the usual therapy if bioterrorism is suspected, but penicillin or doxycycline is effective for usual cases. A military vaccination is available, although it is not licensed for commercial use.

Meningococcemia

Meningococcemia is a flu-like, frequently fatal illness with headache, fever, nausea, and a grayish or purpuric petechial rash; the rash occurs in half to two-thirds of patients. The neck may be stiff in only half of patients at the time of initial presentation. A transient nonspecific maculopapular exanthem, very different from the petechial rash, may also appear for 1 or 2 days.

Meningitis is spread via droplet contact by *Neisseria meningitidis,* a gram-negative diplococcus with 5 different serogroups: A, B, C, Y, and W-135. Outbreaks in the African meningitis belt occur in the dry season (December–June) and are mostly due to serogroup A (or sometimes C). Outbreaks in Asia are usually serogroup A, and recent outbreaks related to the hajj religious pilgrimage were W-135. Serogroup B tends to be more common in higher-income nations because it is not amenable to prevention through vaccination. Two conjugate quadrivalent meningitis vaccines (Menactra and Menveo) are now available and recommended for travelers to areas of risk, military recruits, and freshman college students.

Ceftriaxone treatment should be started even while arranging for lumbar puncture because deterioration with fatal shock may occur extremely rapidly. Intravenous penicillin G is the standard treatment once diagnosis is confirmed. Cultures will likely be positive if cerebrospinal fluid (CSF) is obtained within an hour of antibiotic administration.[26] Prophylaxis for close contacts is usually with ciprofloxacin or rifampin.

Melioidosis

Melioidosis (*Burkholderia pseudomallei*) is a Southeast Asian gram-negative infection that is usually acquired from soil or water. It is especially common in rice paddy workers but is often subclinical in healthy patients. Diabetics and immunocompromised patients are likely to become very ill with fever, anemia, and jaundice. Subcutaneous abscesses or pustules develop in 10% to 20%, and children are likely to develop a parotid abscess. Treatment is with amoxicillin-clavulanate or ceftazidime.[27]

Erysipeloid

Erysipeloid (*Erysipelothrix rhusiopathiae*) is a gram-positive bacterial infection that closely resembles erysipelas, a streptococcal infection. Within a week of handling infected meat or shellfish, a painful, violet-red, well-demarcated hand rash develops. Occasionally, erysipeloid is complicated by systemic infection with endocarditis. Treatment is with systemic antibiotics such as penicillin, erythromycin, or doxycycline. Untreated cases usually resolve spontaneously.

Tropical Ulcer

Tropical ulcer (phagedenic ulcer) is a bacterial ulceration of the lower extremity caused by poor hygiene and malnutrition in moist tropical areas. In the initial stages the ulcer is quite painful and foul smelling, with 2 organisms usually found: *Fusobacterium nucleatum* and *Treponema vincentii*. The round or oval ulcer passes through acute, subacute, and chronic stages; in the chronic stage, it may be painless with a mixed bacterial flora. The edges are not undermined as they are in Buruli ulcer. Although healing eventually occurs with proper care with antibiotics and nutrition, many of these ulcers require skin grafting and some develop osteomyelitis or malignancies (Marjolin ulcer).

Noma

Noma (cancrum oris) is a rare gangrenous anaerobic infection of the mouth and cheek that is associated with *Fusobacterium* and *Borrelia*. Like the phagedenic ulcer, this disease only occurs with malnutrition and starts with a painful lesion that soon ulcerates. Periodontal disease, poor hygiene, and malnutrition (often exacerbated by a recent infection) appear to be necessary prerequisites. Antibiotics, surgical debridement, nutritional support, and reconstructive surgery are essential if the patient is to survive.

Noma neonatorum is a gangrenous *Pseudomonas aeruginosa* infection of the face or anogenital area of low birth weight infants. It may be a form of ecthyma gangrenosum.

Treponemal Infections (Spirochetes)

Syphilis

Syphilis, the best-known treponemal infection, is a sexually transmitted infection with primary (chancre), secondary (latent), and tertiary stages. The syphilis rash is polymorphic with multiple presentations that can mimic many other conditions. Children become infected through

maternal-fetal transmission. Other tropical treponemal infections, such as pinta and yaws, are non-venereal.

Congenital Syphilis

Congenital syphilis (*Treponema pallidum*) is maternal syphilis transmitted via placenta to the fetus. Although many babies with this condition are stillborn, two-thirds of surviving newborns appear normal at delivery but become ill several months later. The syphilitic umbilical cord may be streaked with red, white, and blue colors (a barber pole cord). Early congenital syphilis (up to 2 years of age) is characterized by hepatosplenomegaly, fever, rhinitis ("snuffles"), and rash. The infectious rash is similar to secondary syphilis in adults with a papulosquamous pink eruption often involving the palms (Figure 26-10) and soles (which are often red and shiny [Figure 26-11]) and later fading to a more coppery brown color. The plantar spots may blister (syphilitic pemphigus). Other lesions include genital *condyloma lata* (syphilitic warts), mucous patches around the lips (later forming scar-like fissures termed rhagades or Parrot lines), skin desquamation, and severe diaper rash. Late congenital syphilis (after 2 years of age) is characterized by various stigmata such as *Hutchinson incisors* (notched, peg-like front teeth), *mulberry molars* (malformed lower first molars), and *paroxysmal cold hemoglobinuria* (dark urine and

Figure 26-10. Syphilitic Macules of Palm

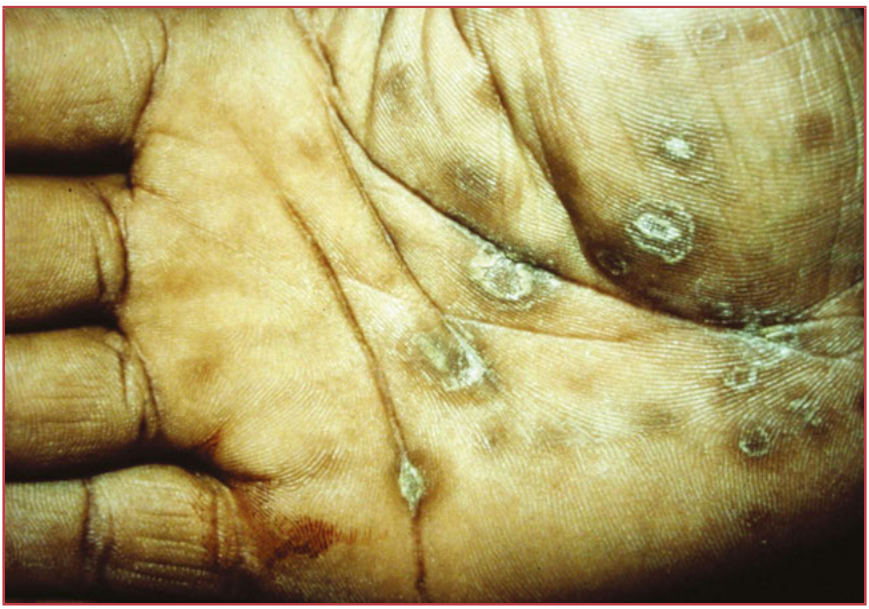

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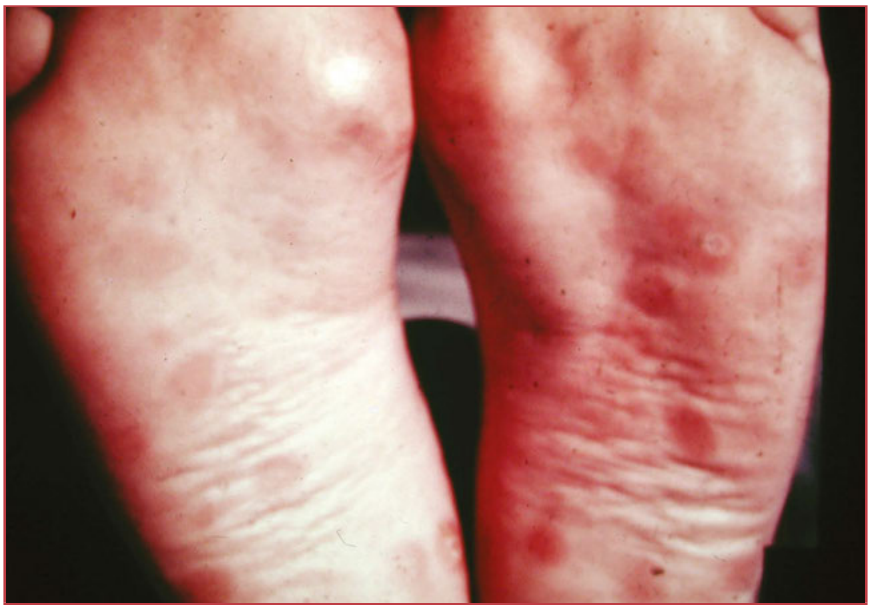
Figure 26-11. Syphilitic Macules of Soles



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chills after cold exposure). The classic but uncommon *Hutchinson triad* is Hutchinson incisors, interstitial keratitis, and eighth nerve deafness. Saber shins, saddle nose, frontal skull bossing, *Higoumenakis sign* (thickened inner third of clavicles), gummas (syphilitic fibromas), and mental retardation are other signs of late congenital disease.[28] Maternal screening and treatment for syphilis should be routine. Suspected newborns should be screened with serum and CSF-Venereal Disease Research Laboratory tests. Parenteral penicillin G is the treatment of choice.

Pinta

Pinta (*Treponema carateum*) is a rare non-venereal treponemal infection found in isolated indigenous peoples in Central and South America. The disease is spread by skin contact. In primary pinta, red papules at inoculation sites develop into erythematous, scaly plaques that may resemble psoriasis. *Pintids* (multiple scaly reddish papules later enlarging into multicolored scaly plaques) develop in the secondary stage. In tertiary pinta (2–5 years postinfection), abnormal skin pigmentation develops over bony prominences with spotty areas of hypopigmentation. The painted appearance is responsible for the Spanish name. Syphilis serology is positive in pinta cases. Penicillin is the treatment of choice.

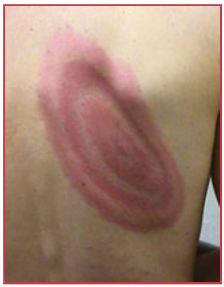
Yaws

Yaws (*Treponema pertenue*) is a more widespread non-venereal infection spread by skin contact. It usually starts in childhood and, like other treponemal infections, has primary, secondary, and tertiary stages. A papular *mother yaw* occurs at the inoculation site and develops satellite lesions before ulcerating and healing months later. The secondary stage (framboesiform yaws) begins with multiple smaller daughter yaws or frambesia (from their resemblance to raspberries). A rash on the palms and soles develops into painful fissures and a crab-like gait (crab yaws). Destructive skin and bone lesions (gummas) develop in the uncommon tertiary stage. Diagnosis and treatment is the same as for syphilis.

Lyme Disease

Lyme disease (*Borrelia burgdorferi*) is a spirochetal infection spread through the bite of tiny *Ixodes* (deer or black-legged) ticks, although the tick bite is often not recalled. Ticks must be attached for 24 hours to transmit the disease, and routine antibiotic prophylaxis for tick bites is not recommended. Lyme disease is common in the United States, Europe, and North Asia. The characteristic erythema migrans bull's-eye rash starts with a red papule at the site of the bite that enlarges into a red, round patch (Figure 26-12). As the patch continues to expand, it often develops central clearing before gradually fading. The classic bull's-eye appearance is often not evident initially. Multiple patches can be present in this early localized Lyme disease, but serologic testing results at this stage may still be negative.

Figure 26-12. Erythema Migrans Rash in Lyme Disease



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In early disseminated disease, headache, myalgia, arthralgia, lymphadenopathy, and Bell palsy (seventh cranial nerve paralysis) may develop. Arthritis, meningitis, and myocarditis with heart block are more serious Lyme sequelae. Late disease is characterized by arthritis (often knees), encephalitis, or neuropathy. Lyme antibody testing results are positive in disseminated disease. Treatment of Lyme disease is with doxycycline for 14 to 21 days in children older than 8 years. Younger children are treated with amoxicillin, erythromycin, or clarithromycin. Late disease with arthritis or encephalitis should be treated with ceftriaxone for 21 days.[11]

Rickettsial Diseases

Rickettsiae are obligate, intracellular gram-negative bacteria. Rickettsial infections are traditionally divided into spotted and typhus fevers.

Spotted Fevers

Rocky Mountain Spotted or Brazilian Spotted Fever

Rocky Mountain spotted fever or Brazilian spotted fever is caused by *Rickettsia rickettsii*. Despite its name, RMSF is most common in the southeastern United States in spring and summer when it is spread by dog ticks (*Dermacentor*). The same disease occurs in Central and South America and is known in Brazil as Brazilian spotted fever. A classic RMSF triad of fever, headache, and rash occurs within 1 to 2 weeks of tick bite but may not be evident early in the infection. Unfortunately, many patients fail to recall a tick bite, which makes diagnosis even more difficult. The centripetal rash (red, blanching macules or papules) begins on the extremities 2 to 3 days after the start of symptoms and spreads centrally before turning into petechial macules. About 10% of cases lack any rash. An indirect fluorescent antibody (IFA) test is positive 10 to 14 days postinfection, but empirical treatment with doxycycline for 7 to 10 days (or until afebrile for 3 days) is usually necessary while awaiting confirmation. Rocky Mountain spotted fever is an exception to the rule that doxycycline be avoided in children younger than 8 years because risk of this potentially fatal disease far outweighs the small risk of dental staining.

Mediterranean Spotted or Boutonneuse Fever

Mediterranean spotted or boutonneuse fever (*Rickettsia conorii*) is spread by the brown dog tick (*Rhipicephalus sanguineus*) in Mediterranean countries, North Africa, the Middle East, and India. The site of the bite develops a small, 1-cm black eschar or *tache noire*. Fever, headache, and an eventual centripetal spotted rash occur in most patients. Thrombocytopenia is common. As in RMSF, IFA serology confirms the diagnosis and doxycycline is the best treatment.

North Asian Tick Typhus, Queensland Tick Typhus, and Oriental Spotted Fever

North Asian tick typhus (*R sibirica*), Queensland tick typhus (*R australis*), and oriental spotted fever (*R japonica*) are similar tick-borne rickettsial infections with headache, myalgia, fever, eschar(s), and centripetal spotted rash best treated with doxycycline.

Rickettsialpox

Rickettsialpox (*R akari*) is spread by biting mites that normally feed off house mice. A papule, soon to be an eschar, develops at the site of the bite, followed a week later by fever and generalized papulovesicular rash (papules with central vesicles) for 1 to 2 weeks. Rickettsialpox may resemble chickenpox, but bite eschars and the lack of giant cells distinguish this infection. The infection is self-limited but may be treated with doxycycline for 2 to 5 days (brief 2-day courses in children). Rodent control prevents outbreaks.

Epidemic, Murine, and Scrub Typhus

Epidemic Typhus

Epidemic typhus (*R prowazekii*) is spread by body lice infestations, commonly in crowded refugee populations or wartime. The organism multiplies in the louse gut (eventually killing it) and is excreted in its feces. Scratching introduces typhus into the bites. Contact with southern flying squirrels, an animal reservoir, may also cause sporadic cases of typhus. Headache, fever, and an erythematous macular or petechial rash (developing around the fifth day) are key symptoms. Unlike spotted fevers, the centrifugal rash of typhus develops on the trunk and spreads to the extremities, sparing the palms and soles. Most cases resolve in 2 weeks, but vasculitis and gangrene are potential complications. *Brill-Zinsser disease* is a milder form of recurrent typhus, sometimes occurring many years later. Polymerase chain reaction testing is now the preferred method of diagnosis, replacing the older, less-specific Weil-Felix agglutination reaction.[29] Treatment for typhus is doxycycline 200 mg once daily for 5 days. Doxycycline can also be used as prophylaxis in an outbreak until delousing removes the source of infection.

Murine or Endemic Typhus

Murine or endemic typhus (*R typhi*) is a milder, worldwide form of typhus spread by fleas. In the United States, cases occur in southern California and Texas. Infected flea droppings are inoculated into bites by scratching. Fever, headache, nausea, and a maculopapular, usually truncal, rash (<50%) develop 1 to 2 weeks after flea contact. Treatment is similar to that of typhus.

Scrub Typhus

Scrub typhus (*Orientia tsutsugamushi*) is an Asian typhus that is spread by infected trombiculid mites (chiggers). A papule develops at the chigger bite evolving into an eschar with regional lymphadenopathy.

Fever, headache, and a maculopapular truncal (centripetal) rash follow. Neurologic symptoms (eg, obtunded mental state, deafness), meningitis, and vasculitis may occur. Untreated cases may have a mortality rate of 50%.[30] Travelers returning from endemic areas with headache, fever, and rash therefore warrant empiric treatment with doxycycline 200 mg per day for 14 days.

Q Fever

Q fever (*Coxiella burnetii*) is a widespread zoonotic infection from farm animals that is spread by inhaled aerosols. It recently received attention as a possible bioterrorism agent. Flu-like illness with fever and persisting malaise are the usual symptoms. While often undiagnosed and self-limited, Q fever may cause serious myocarditis or central nervous system involvement. A nonspecific variable rash may occur in 20% of cases. Diagnosis is by serology or PCR. Doxycycline or quinolone therapy is recommended.

Ehrlichiosis

Ehrlichiosis describes 2 different diseases with very similar symptoms: *human monocytic ehrlichiosis* (caused by *Ehrlichia chaffeensis*) and *human granulocytic ehrlichiosis,* now known as *anaplasmosis* (caused by *Anaplasma phagocytophilum*). Human monocytic ehrlichiosis is spread by the bite of the lone star tick in southeastern United States. Anaplasmosis or human granulocytic ehrlichiosis is spread by deer or dog ticks in much of the United States. Both diseases produce the usual rickettsial symptoms of fever, headache, fatigue, and nausea. Lymphocytopenia and thrombocytopenia are common. Human monocytic ehrlichiosis may be associated with hepatosplenomegaly and elevated liver tests. Rash is less common than in other rickettsial infections and is variable in appearance. Diagnosis, if accomplished, is often through paired serology (initial and recovery). Doxycycline is the usual therapy, although rifampin has been proposed for children.[31]

MYCOBACTERIAL INFECTIONS

Leprosy or Hansen Disease

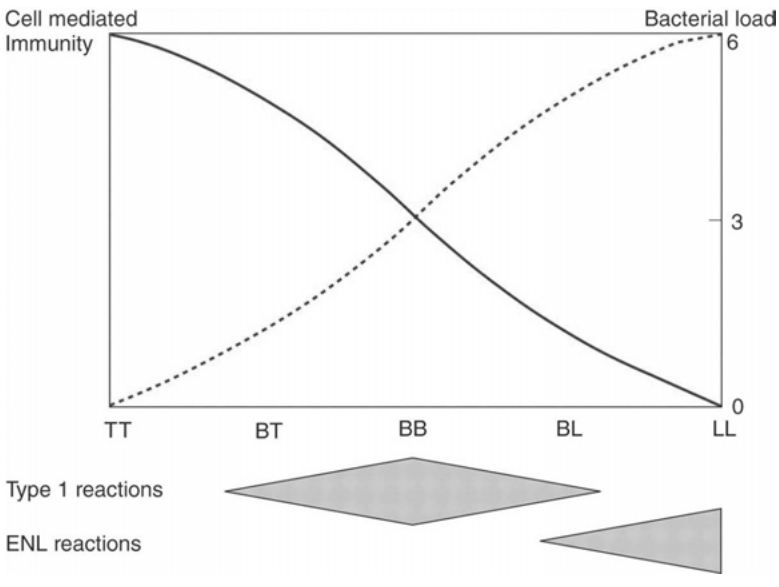
Leprosy or Hansen disease (*Mycobacterium leprae*) is becoming rare, with more than 80% of cases occurring in just 6 countries: India (highest incidence), Brazil, Madagascar, Mozambique, Nepal, and Tanzania.[32] Much of the world's population (95%) appears to be naturally immune, with less than 1% truly susceptible.[33] Deficient cell-mediated immunity is associated with the development of illness. Cases are most common

between 10 and 15 and 30 and 60 years of age. Spread is through airborne droplets or contact with skin lesions, but the incubation period may last many years. In addition to infected humans and primates, the 9-banded armadillo may host leprosy.

The Ridley-Joplin classification divides leprosy into 5 subtypes depending on host immune response; from greater to lesser response, these include *tuberculoid* (TT), *borderline tuberculoid* (BT), *borderline* (BB), *borderline lepromatous* (BL), and *lepromatous* (LL) (Figure 26-13). Yet another category, *indeterminate leprosy,* presents with only a few hypopigmented lesions but no sensory loss or nerve hypertrophy. The World Health Organization (WHO) considers tuberculoid leprosy as *paucibacillary* (TT, BT) and borderline to lepromatous leprosy (BB, BL, LL) as *multibacillary.*

Tuberculoid leprosy has a high cell-mediated immunity and consequently few bacteria (hence paucibacillary). It presents with fewer than 5 well-demarcated anesthetic hypopigmented or red plaques. Peripheral nerve enlargement is common. Borderline leprosy has more but less well-defined lesions with punched-out centers. Lepromatous leprosy, the leprosy of popular imagination, is associated with low cell-mediated

Figure 26-13. Ridley-Joplin Spectrum of Leprosy

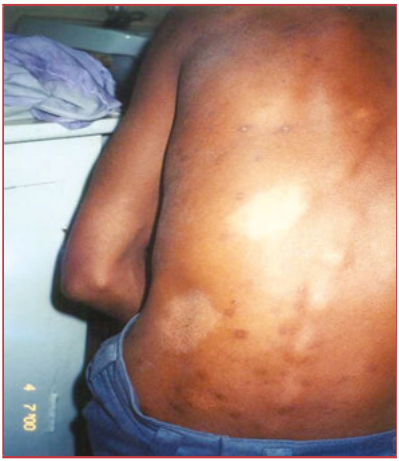


From Lockwood D. Leprosy. In: Warrell DA, Cox TM, Firth JD, Benz EJ, eds. *Oxford Textbook of Medicine.* 5th ed. Oxford, United Kingdom: Oxford University Press; 2010, with permission.

immunity and high number of bacteria (multibacillary). Bilateral infiltration of the earlobes and facial skin create the so-called leonine (lionlike) facies. Nasal destruction (saddle nose), neuropathy, inability to close the eyes (lagophthalmos), and multiorgan system involvement occur. Nosebleeds and nasal congestion are common. Motor and sensory neuropathy develop in all subtypes of untreated leprosy, resulting in a loss of sensation and repeated injury and infection, which cause the dreaded digit loss and deformities associated with the disease.

The WHO definition of *leprosy* is a patient with one of the following conditions: an anesthetic skin lesion (Figure 26-14), a hypertrophic peripheral nerve, and positive skin slit smears (usually obtained from the earlobe). Punch biopsies of the lesion border are also helpful.

Figure 26-14. Anesthetic Hypopigmented Patches in Leprosy



Courtesy of Gregory Juckett, MD, MPH.

Four reactions in leprosy may occur before, during, or after treatment. Type 1, *reversal* or *upgrading reaction,* occurs in borderline (BT, BB, BL) leprosy when there is an increase in cell-mediated immune response. It usually occurs 6 to 12 months after starting therapy and presents with a hypersensitivity reaction (lesion redness and swelling or hand/foot edema, sometimes with nerve damage). Type 2 reaction, *erythema nodosum leprosum,* is caused by antigen antibody immune complexes in BL and LL. It produces multiple red papules or nodules, fever, myalgia, and hand/foot edema. Type 3 is a *downgrading reaction* caused by a loss in cell-mediated immunity marked by new lesions in untreated or nonadherent patients. Type 4, usually found in Mexico and Central America, is termed *Lucio vasculitic reaction* in untreated Lucio leprosy (diffuse lepromatous skin infiltration), which manifests as tender purpura (later ulcerating) on the extremities.

Leprosy treatment is with dapsone and rifampin per WHO recommendations. Paucibacillary disease is treated with dapsone 100 mg daily for 6 months and supervised monthly rifampin 600 mg for 6 months. Multibacillary disease is treated with daily dapsone 100 mg and clofazimine 50 mg and supervised monthly rifampin 600 mg and clofazimine

300 mg for 12 months. National Hansen's Disease (Leprosy) Program recommendations are available for US cases.[33] Bacille Calmette-Guérin (BCG) vaccine appears to be partially protective against leprosy.

Tuberculosis Skin Manifestations

Cutaneous Tuberculosis Infection

Lupus vulgaris, describing TB infection of the skin, appears as soft red-brown papules that have a characteristic apple-jelly appearance when compressed by a glass slide (diascopy). It is slow growing, but papules can develop into plaques with time. *Mycobacterium tuberculosis* can also cause *scrofuloderma,* a painless cervical lymphadenopathy that drains through the skin. Treatment is the same as for uncomplicated pulmonary TB—isoniazid, rifampin, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months.

Tuberculid Hypersensitivity Reactions

Tuberculid hypersensitivity reactions include papulonecrotic tuberculid, erythema induratum of Bazin, and lichen scrofulosorum. All are characterized as inflammatory hypersensitivity reactions from the dissemination of TB to the skin. *Tuberculids* appear as red papules or nodules on elbows, knees, or buttocks that often ulcerate. *Erythema induratum* is a recurring reddish-purple panniculitis affecting posterior calves, which later heal as atrophic scars. *Lichen scrofulosorum* describes flattop, shiny, red-brown papules, usually on the trunk, associated with TB lymph node infection.

Mycobacterium marinum *(Fish Tank Granuloma)*

Mycobacterium marinum, an atypical TB organism usually affecting saltwater or freshwater fish, is frequently inoculated into minor wounds or abrasions. It is often acquired from fish tanks or ponds, hence the term *fish tank granuloma.* It starts as a firm red area that develops into a slow-growing reddish-brown nodule that may later develop satellites or ulcerate. Hands, feet, and extensor surfaces are commonly affected. Diagnosis is usually through biopsy. Treatment is with prolonged doxycycline or rifampin (with or without ethambutol). Without treatment, the granuloma may take several years to resolve. Many other atypical mycobacteria can cause similar skin lesions (ie, *M kansasii, M szulgai, M fortuitum-chelonae*) or cervical adenopathy (ie, *M avium-intracellulare, M scrofulaceum*).

Buruli Ulcer

Buruli ulcer (*M ulcerans*) is another atypical mycobacterium. It is a common cause of pediatric skin ulcers in West Africa and other humid tropical areas. A skin nodule often starts at a traumatized site and evolves into a painless ulcer with characteristically undermined borders. The ulcer enlarges and causes extensive scarring and deformity. Purified protein derivative skin testing results are often negative until the ulcer is healed. Although rifampin can help small lesions, most ulcers require surgical removal with skin grafting. Hyperthermic water baths or hyperbaric oxygen are experimental therapies.

Bacille Calmette-Guérin Reactions

In many countries, BCG, an attenuated strain of *M bovis*, is used in infants to prevent TB. As BCG is a live vaccine with variable regional strains, it may create larger than usual local ulcerations that may later be complicated by keloid formation. *Erythema nodosum,* a hypersensitivity reaction with red, tender nodules on the anterior legs, may occur after BCG, although streptococcal infections, drug reactions, and sarcoidosis are classically associated. Bacille Calmette-Guérin may occasionally spread to cause axillary lymphadenitis in an infant. Dactylitis (finger inflammation) is a rare complication.

FUNGAL SKIN INFECTIONS

Superficial

Tinea Infections (Ringworm)

Dermatophytic fungi can be classified as anthropophilic, geophilic, and zoophilic depending on whether they are acquired from people, soil, or animals. Anthropophilic species include *Trichophyton tonsurans* (by far the most common agent) and *Microsporum audouinii* (now rare due to treatment). Zoophilic species include *M canis* from pets and *T verrucosum* from cattle. These "alien" species provoke a more intense immune response. Classic scaly patches with central clearing and raised annular borders suggest the diagnosis, although it is occasionally confused with the herald patch of pityriasis rosea. Diagnosis is confirmed by seeing hyphae on microscopic examination of skin scrapings (best from the lesion border) with a drop of 20% KOH.

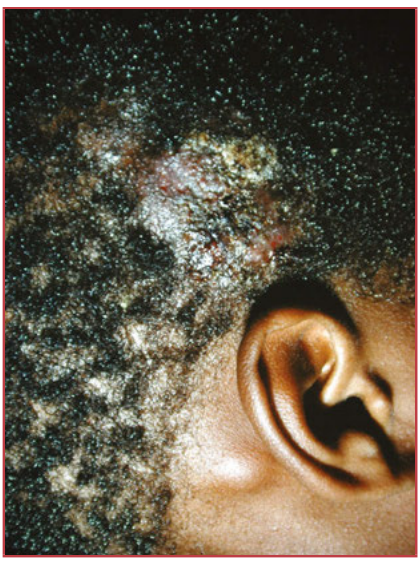
Tinea Capitis

Tinea capitis (*scalp ringworm*) (Figure 26-15) is common in children. It forms scaly scalp patches with hair loss and may also involve the eyebrows and lashes. *Black dot ringworm,* wherein hairs break off at the surface, is caused by *T tonsurans* and *T violaceum*. Gray patch ringworm is caused by *M canis*. A Wood lamp causes *Microsporum* to fluoresce green, whereas *Trichosporon* does not. Potassium hydroxide examination can also help speciate the fungus by identifying hair shaft involvement—*ectothrix* (outside the shaft, as in *Microsporum*) or *endothrix* (inside, as in *T tonsurans*). *Favic hair invasion* causes air bubbles in the hair shaft. *Kerion* (inflamed boggy scalp) is usually due to zoophilic infection. Dandruff in young children is highly unusual, so scalp ringworm should be suspected. Treatment is with an extended course of systemic antifungals, such as griseofulvin, fluconazole, or itraconazole.[34]

Tinea Corporis

Tinea corporis (*body ringworm*) (figures 26-16 and 26-17) affects the body and is most commonly caused by *T rubrum* and *T mentagrophytes*. Steroid therapy alters the classic appearance (tinea incognito). The ring-shaped lesions gradually expand outward. Treatment is with topical antifungal creams for several weeks. A tropical species, *T concentricum,* causes *tinea imbricata,* which produces annular concentric rings. Oral treatment with griseofulvin or terbinafine is necessary.

Figure 26-15. Tinea Capitis (Scalp Ringworm) With Kerion and Enlarged Lymph Node



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Tinea Cruris

Tinea cruris (*jock itch*) is tinea of the groin, usually in young men. Itching is a common symptom. It is occasionally confused with *Candida* (*Monilia*) infection, but unlike *Candida,* it never involves the scrotum. Treatment is with topical antifungals.

Tinea Pedis

Tinea pedis (*athlete's foot*) is a common cause of foot itching and odor by the same organisms that cause tinea corporis. Interdigital, moccasin-type, and vesiculobullous

Figure 26-16. Tinea Corporis (Body Ringworm) on Chin

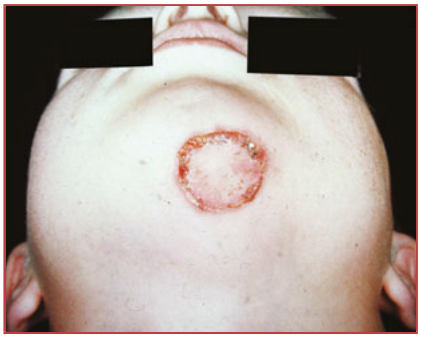

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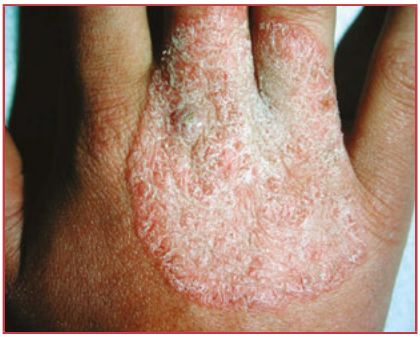
Figure 26-17. Tinea Manus (Body Ringworm)



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presentations are known. Treatment is with topical antifungal creams and antiperspirants. Tinea pedis can be mimicked by *pompholyx* (*dyshidrotic eczema*) of the feet.

Onychomycosis

Onychomycosis (tinea unguium or nail fungus) causes unsightly thickened yellow or white nails, often due to *T rubrum,* although non-dermatophytes like *Candida* may also be involved. Distal nail involvement is much more common than the proximal subungual type. Proximal white superficial onychomycosis is often associated with immune deficiency. Psoriatic nail involvement can look similar to fungal infection except for characteristic pitting. Nail trauma can cause similar nail deformities. Fungal culture or 20% KOH nail scrapings confirm diagnosis of onychomycosis. Daily oral terbinafine for 6 weeks (fingernails) or 12 weeks (toenails) is first-line therapy to clear this infection, although itraconazole and fluconazole are also effective.[35] Topical therapy usually fails to penetrate the nail matrix, but ciclopirox topical solution for 1 year may be considered if systemic therapy is not an option.

Candida (Monilia) *Infections*

Candida albicans and other *Candida* species are ubiquitous yeasts that cause a variety of skin infections. Scrapings of the lesions show pseudohypha or budding yeast. Oral candidiasis (thrush) is mucous membrane involvement in infants or immunocompromised adults that appears as adherent white oral plaques. *Candida* diaper dermatitis is characterized by a red base (involving skin folds) and erythematous satellite papules that differentiate it from more common irritant diaper dermatitis, which

lacks these features (figures 26-18 and 26-19). *Intertrigo* describes weeping erythematous yeast infections of moist skin folds. *Candida vulvovaginitis* is a curd-like white discharge with vaginal itching frequently following antibiotic therapy. Diabetics are particularly prone to recurrent infections. *Candida balanitis* describes tender red papules of the (usually) uncircumcised glans penis. Nail involvement (*onychomycosis* and *paronychia*) and *perlèche* (infections of the corners of the mouth where moisture accumulates) are other candidal syndromes. Treatment for *Candida* infections is with miconazole, ketoconazole, clotrimazole, or econazole creams, usually for 10 days. Terbinafine may be ineffective for yeast.[36] Fluconazole single-dose therapy is especially convenient for vaginal yeast infections.

Figure 26-18. Candidiasis With Erythematous Satellite Papules

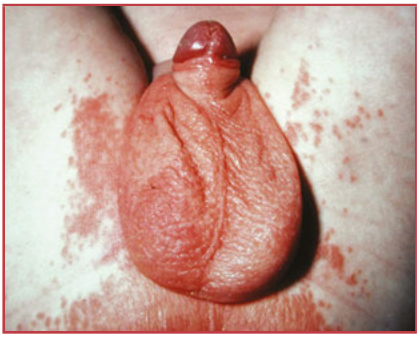

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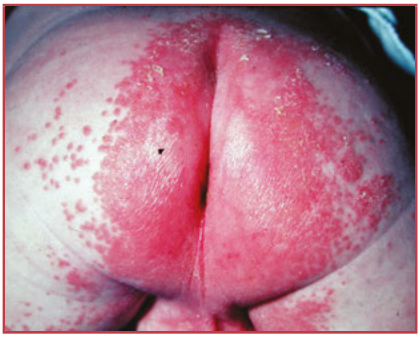
Figure 26-19. Candidiasis With Erythematous Satellite Papules



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Miscellaneous Fungal Infections

Tinea Versicolor

Tinea versicolor (*Malassezia furfur*) is a lipophilic yeast that colonizes the stratum corneum, producing scaly hypopigmented or hyperpigmented macules that often coalesce. *M pachydermatis* of animals can also infect humans. This unsightly fungal condition is widespread in young people, especially in humid, warm climates. The fungus is more conspicuous in summer months because it inhibits tanning. Skin scrapings (with added KOH) show characteristic clumps of spores and hyphae, the classic spaghetti-and-meatball pattern. Treatment is with antifungal creams (ie, terbinafine 1%, ketoconazole 2%, or fluconazole 2%) or selenium sulfide lotion. Unfortunately, this yeast appears to survive in the pores and

eventually recurs. Oral ketoconazole 200 mg as a 2-tablet single dose (or fluconazole 300 mg with a repeated dose in 2 weeks) is therefore even more effective.[37]

Piedra

Piedra is a tropical fungal hair infection that comes in black and white varieties. *Black piedra* (*Piedraia hortae*) produces black, firmly adherent nodules on the hair shaft. *White piedra* (*Trichosporon beigelii*) produces white lesions, somewhat similar to lice nits, which are easy to remove. Cutting the hair is usually curative and no medication is required.

Tinea Nigra Palmaris

Tinea nigra palmaris (*Hortaea werneckii*) is another tropical or subtropical fungus presenting as a brown, stain-like macule affecting the palms or soles and occasionally on the neck or trunk. It also has been reported in the southeast United States. It is easily treated with one of the azole antifungal creams or Whitfield ointment (6% salicylic acid, 12% benzoic acid).

Subcutaneous Fungal Infections

Sporotrichosis

Sporotrichosis (*Sporothrix schenckii*) is a saprophytic fungus that can be inoculated into wounds by minor trauma. Rose thorn injuries and working with sphagnum moss are classically associated. A nodular inoculation chancre develops at the site, which is sometimes followed by a line of other nodules that develop along superficial lymphatics (lymphocutaneous sporotrichosis). Biopsy identifies the fungus. Treatment is with a saturated solution of KOH given orally for 2 to 3 months. Children use half the adult dose.

Mycetoma or Madura Foot

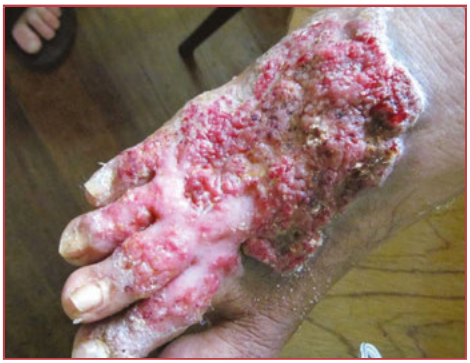
Mycetoma or *Madura foot* is a chronic tropical infection from actinomycetes (filamentous bacteria, including *Nocardia* and others) or various fungi (*Madurella* and others) that are introduced into tissue by traumatic inoculation. Rural farmers are commonly affected. Nodules and draining fistulae appear in the extremity, followed by a tumorlike swelling (mycetoma). Drainage granules enable identification of the specific actinomycete, and culture may identify the fungus. Treatment depends on the organism involved and is lengthy and complex. *Nocardia* is treated with sulfamethoxazole-trimethoprim for 2 to 3 years. Fungal Madura foot (eumycotic mycetoma) is even more difficult to treat with current

protocols, including itraconazole (or ketoconazole) for 1 to 2 years, surgery, and topical negative-pressure therapy.[38]

Chromoblastomycosis

Chromoblastomycosis is a third fungal infection introduced by skin trauma, usually to the legs. Dematiaceous (black mold) saprophytic fungi produce a plaque at the inoculation site that later enlarges into a warty growth (Figure 26-20). Diagnosis is by biopsy or microscopic examination of the exudate, which shows classic thick-walled (muriform) fungal cells. Treatment is difficult and early lesions should be excised. Prolonged azole or terbinafine antifungal therapy yields unpredictable results.

Figure 26-20. Chromoblastomycosis



Courtesy of Gregory Juckett, MD, MPH.

Lacaziosis

Lacaziosis (*Lacazia loboi*) is a very rare Amazonian fungal disease presenting with impressive keloid-like nodules. Diagnosis is confirmed by biopsy, but there is no effective treatment besides excision. It has also been found in dolphins and nonhuman primates.[39]

Systemic Fungal Infections

Systemic fungal infections include histoplasmosis, North American blastomycosis, South American blastomycosis (paracoccidioidomycosis), coccidioidomycosis, and penicilliosis marneffei, an opportunistic infection of AIDS patients in Southeast Asia. Most produce various granulomatous skin lesions in addition to systemic disease but are beyond the scope of this chapter.

PARASITIC INFECTIONS

Endoparasites

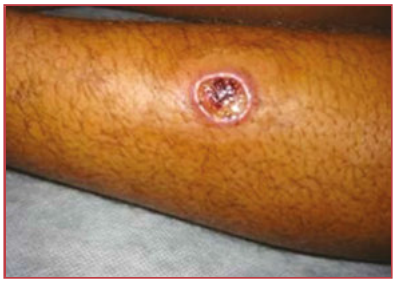
Leishmaniasis

The term *leishmaniasis* (*Leishmania*) describes cutaneous, mucocutaneous, and visceral diseases caused by obligate intracellular protozoan parasites. There exists a confusing array of Old and New World

Leishmania species. The vector is sandflies—*Phlebotomus* in the Old World or *Lutzomyia* in the New World.

Cutaneous leishmaniasis (CL) is known by multiple names depending on geographic location—*uta,* bay sore, oriental sore, Baghdad boil, and chiclero ulcer. A papule develops at the site of the sandfly bite, followed by a persistent, shallow, pizzalike ulcer with raised margins (figures 26-21 and 26-22). In Asia, CL may present as wet ulcers (the oriental sore of *L major*) or crusted dry ulcers (*L tropica*). *Chiclero ulcer* develops on the ears of rubber tappers working in New World jungles. Occasionally these ulcers may develop an atypical (eg, lichenoid, nodular, impetiginous) appearance, making diagnosis more difficult. Untreated lesions usually heal with scarring, but this takes many months, and certain species may recur to involve the mucous membranes.

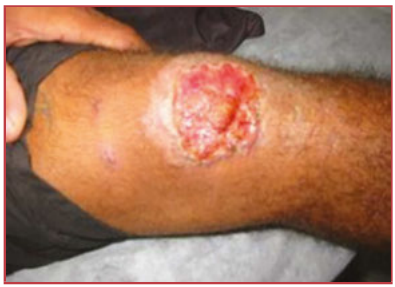
Figure 26-21. Cutaneous Leishmaniasis



Courtesy of Gregory Juckett, MD, MPH.

Mucocutaneous leishmaniasis (MCL), sometimes known as *espundia,* is a much more invasive infection that causes facial ulcerations and deformities (tapir nose). New World species such as *L (Viannia) braziliensis* are most often associated with espundia, sometimes many years after the initial cutaneous infection resolves, with presenting symptoms usually being nasal congestion and bleeding.[40] Diagnosis of CL and MCL is usually from biopsy of the ulcer margin.

Figure 26-22. Cutaneous Leishmaniasis (Brazilian Amazon)



Courtesy of Gregory Juckett, MD, MPH.

Visceral leishmaniasis (*kala-azar* or "black disease" in Hindi) is less important for this chapter, as it often lacks dermatologic features. Only some patients develop the darkened skin on the abdomen and extremities that gives this disease its name. It is usually treated with miltefosine in south Asia due to widespread antimonial resistance there.

Treatment of CL and MCL depends on the extent of lesions and the causative organism. Many ulcers eventually heal without therapy. Multiple or persistent lesions warrant pentavalent antimony

compounds, eg, sodium stibogluconate (IV or IM) for 20 days. Treatment is also indicated for *L braziliensis* and related New World forms associated with mucocutaneous disease. Intralesional pentavalent antimony, heat, pentamidine, and paromomycin sulfate ointment (available in Israel for *L major*) are alternative regimens.[41] Leishmaniasis is amenable to prevention through vaccination, but no commercial vaccine is currently available.

Filarial Infections

Filarial infections are blood and tissue nematode infections that have specific skin manifestations. Insect vectors spread the disease. Adult filarial worms inhabit the host lymphatics or subcutaneous tissue. Their progeny, termed microfilaria, are transmitted to other people via insect bites or, in the case of *Dracunculus,* by ingesting infected water fleas.

Onchocerciasis

Onchocerciasis is popularly known as *African river blindness, craw-craw,* or *sowda*. It is prevalent in West Africa and a few localized areas of Latin America, where it is known to produce eye inflammation leading to blindness and skin disease. The vector is the blackfly *Simulium,* which breeds near streams. Adult worms inhabit subcutaneous nodules called *onchocercoma*. Interestingly, blindness is more common in African savannahs, while the pruritic skin manifestations (*sowda, craw-craw*) predominate in forested regions. The microfilaria are found in subcutaneous tissue, where they produce chronic itching and atrophic skin changes (eg, depigmentation of the shins, hanging groin), and in the anterior chamber of the eye, where they are visible with slit lamp examination. Skin snips from the iliac crest area are incubated in warm saline to examine for characteristic microfilariae. Ivermectin kills the microfilariae but not the adults, requiring periodic re-treatment to control or prevent symptoms.[42] There is risk of encephalitis from ivermectin if coinfected with *Loa loa*. Adjunctive therapy with doxycycline 100 mg daily for 6 weeks kills *Wolbachia* bacteria required for *Onchocerca* fertility.

Loa loa (African Eye Worm)

Loa loa is a West African filarial nematode that migrates through the subcutaneous tissue. It is known as the African eye worm because it occasionally appears beneath the conjunctiva of the eye, causing temporary eye irritation and conjunctivitis. The vector is the *Chrysops* deer or antelope fly. *Loa loa* microfilariae are active in the blood stream by day (when the vector is biting) but retreat into the lymphatics at night. Identification of *Loa* microfilaria on a blood smear confirms diagnosis.

Eosinophilia, an allergic response, is often present in *Loa* and other migratory nematode infections, at least in immunocompetent hosts. Eosinophilia is usually absent in protozoal infections and worm infections restricted to the gut. Skin manifestations of *Loa* are *Calabar* or *fugitive swellings* that appear to be localized allergic reactions to the migrating worm. Treatment is with diethylcarbamazine (DEC) with escalating doses and steroids to prevent encephalopathy from dying microfilariae.[43] However, because of the rarity of this condition in the United States, DEC is only available from the CDC. Excision of adult worms, when visible, is also an option, although there may be 4 to 6 adult worms in the average patient.

Elephantiasis

Elephantiasis (lymphatic filariasis) describes lymphatic obstruction produced by *Wuchereria bancrofti* or *Brugia malayi* filarial worms. Both are transmitted by several species of night-feeding mosquitoes, so the microfilariae are present in the blood only at night. Adult worms residing in the lymphatics result in inflammation followed by obstruction and lymphedema of the scrotum or leg. The term *elephantiasis* refers to the elephant-like skin changes and swelling of the extremity. *Podoconiosis* (non-filarial elephantiasis) is a similar-appearing condition caused by lymphatic scarring from chronic silicate exposure in barefoot people. It is preventable by wearing shoes. Treatment of true filariasis is accomplished with cautious use of DEC for 3 weeks. Unfortunately, this treatment will not undo prior damage, so later procedures to improve lymphatic drainage and surgical reduction may be necessary.

Dracunculiasis

Dracunculiasis (guinea worm) is a tissue infection by *Dracunculus medinensis* found in Africa and (previously) South Asia. The adult worm resides in the subcutaneous tissues of an extremity. When female worms mature (after about 1 year), they protrude to form a painful subcutaneous nodule. Intense burning at this site causes the patient to immerse the lesion in water and this, in turn, stimulates the female to release her larvae. Copepods (water fleas) consume these and people inadvertently ingest the infected fleas in drinking water, thus completing the cycle. Fortunately, humans are the only host and the cycle is easily interrupted by filtering copepods out of drinking water with cheesecloth. Guinea worm is on the verge of eradication and only persists in remote African areas, particularly in Sudan and Nigeria. Treatment is manually extracting the worm by coiling it around a matchstick at the rate of 2 to 5 mm per day. No medical therapy appears to be effective.

Trypanosomiasis

African Trypanosomiasis

African trypanosomiasis (African sleeping sickness) is primarily a neurologic disease caused by *Trypanosoma brucei* and is transmitted by the tsetse fly (Glossina). There are 2 forms—*T brucei gambiense* of West Africa and the more virulent *T brucei rhodesiense* of East Africa. The bite of an infected tsetse fly produces a boil-like trypanosomal chancre within 48 hours, especially with the East African variety. Fever, headache, and transient papular rashes follow waves of parasitemia. Posterior cervical adenopathy (*Winterbottom sign*) develops in the West African variety. Psychiatric symptoms are also common. The final stages of the disease involve meningoencephalitis and coma. Treatment is complex, depending on the type (West or East African) and stage (early or late) of the infection.[43]

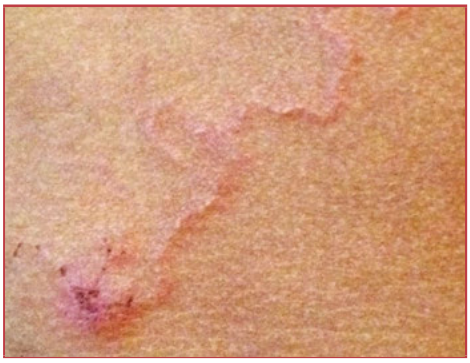
South American Trypanosomiasis

South American trypanosomiasis (*Chagas disease*) is found in rural Central and South America. *Trypanosoma cruzi* is transmitted by reduviid or kissing bugs (*Triatoma* or *Rhodnius*) that reside in the palm thatch or cracked walls of substandard housing. These bloodsucking insects defecate near their bite and the infection is inoculated into the wound by scratching. A few cases have been transmitted by drinking açaí (palm fruit) juice contaminated by these insects.[44] If the eye is the site of inoculation, unilateral periorbital swelling occurs (Romana sign). Other sites of infection result in chagomas, furuncle-like lesions at the inoculation site, usually with regional lymphadenopathy. After a latent period, cardiac, esophageal, and intestinal disease (megacolon) develop. Treatment is with benznidazole or nifurtimox for several months.[43]

Cutaneous Larva Migrans

Cutaneous larva migrans (CLM) (creeping eruption) (figures 26-23 and 26-24) is mostly caused by *Ancylostoma braziliense,* the dog or cat hookworm, although other parasites and migratory myiasis occasionally produce a similar picture. The infection is often acquired while walking barefoot on a beach where

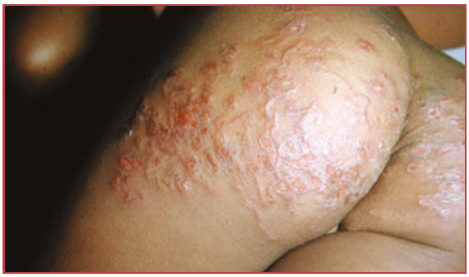
Figure 26-23. Cutaneous Larva Migrans



Courtesy of Gregory Juckett, MD, MPH.

dogs have defecated. The hookworm larva penetrates the skin, causing considerable itching, and then creates a serpiginous wandering track under the skin. Cutaneous larva migrans is self-limited in humans because the parasite cannot escape from the skin and eventually dies. Clinical appearance is diagnostic. Usual treatment is with oral mebendazole, albendazole, or ivermectin. Thiabendazole ointment is very effective if it can be locally compounded.[45] Single lesions can sometimes be cured with cryotherapy if this is directed ahead of the advancing margin. Other nematode parasites (*Strongyloides, Gnathostoma*) can mimic CLM but generally respond to oral ivermectin.

Figure 26-24. Severe Cutaneous Larva Migrans



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Ectoparasites and Insect Bites and Stings

Scabies or Itch Mite

Scabies or itch mite (*Sarcoptes scabiei*) is a common human infestation that causes intense itching, particularly at night. The female mite burrows into the stratum corneum, producing a hypersensitivity reaction with characteristic burrows, papules, and excoriations. Finger webs (Figure 26-25), the flexor aspect of wrists, axillae, breasts, belt line, buttocks, and genitals (where it often appears as a nodular variant [Figure 26-26]) are common areas of involvement. Infants often develop scabies papules on their palms and soles (Figure 26-27). The face is usually spared, except in infants. Scabies is easily spread through

Figure 26-25. Scabies of Finger Webs

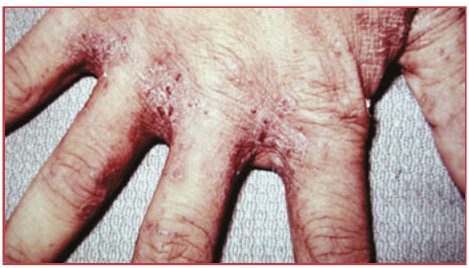

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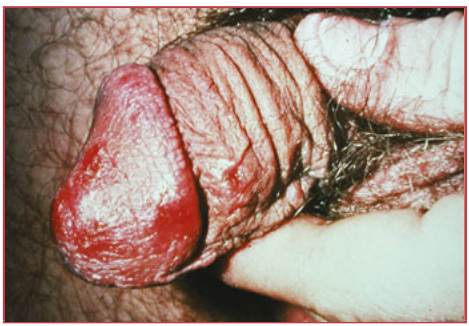
Figure 26-26. Nodular Scabies of Penis



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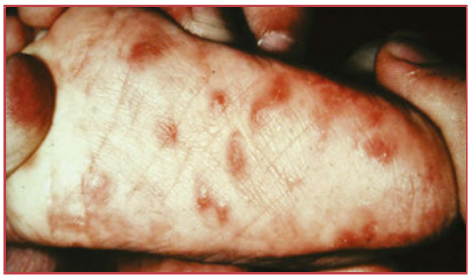
any skin contact, often as a sexually transmitted infection. Thus, it is important to treat sexual partners and any close contacts. Crusted scabies is a severe, highly infectious form often found in institutionalized or immunocompromised patients. Sarcoptic mites from dogs or other animals (the cause of mange) may cause itching but are unable to reproduce on human hosts.

Figure 26-27. Scabies of Soles (Infant)



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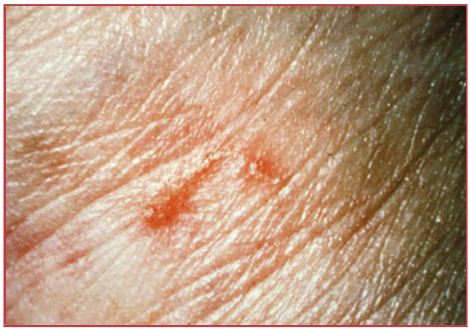
Careful skin inspection may reveal characteristic burrows (Figure 26-28), but these are often obscured by excoriation. A wash of diluted india ink painted over affected skin will help visualize burrows. Microscopic examination of scrapings obtained from the end of the burrow with a number 15 blade usually reveals mites or their eggs and feces.

Figure 26-28. Scabies Burrow



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Treatment is usually with permethrin 5% cream applied over the entire body from the neck down and left on overnight. The cream is showered off the next morning and all bedding and clothing must be washed. Treatment is ideally repeated in 7 to 14 days to ensure eradication.[46] A similar regimen with gamma-benzene hexachloride lotion (lindane) is more toxic and is being abandoned for safety and environmental reasons. It is contraindicated in infants and pregnancy. Under less unhygienic conditions, oral ivermectin 200 mcg/kg may be given as a single dose and, if possible, repeated in 2 weeks.[47] This off-label use of ivermectin for scabies is safe in patients without concomitant filarial infection. With any of these treatments, itching from the dead mites persists for 1 to 2 weeks posttreatment.

Pediculosis

Pediculosis (lice) describes an infestation of bloodsucking insects that include head or body lice (both subspecies of *Pediculus humanus*) or crab lice (*Phthirus pubis*). Itching is the primary symptom. Head lice are the most common and are usually diagnosed by nits (eggs), which are most

evident on hairs behind the ears or on the nape of the neck. African head lice are adapted to flat hair shafts, whereas their European cousins prefer round hair shafts. This explains why African American children are often spared head lice in the United States, where the European variety predominates. Nits hatch within 1 week and lice mature in 15 days. Nits further out on the hair shaft (>5 mm from scalp) are usually nonviable, and no-nit school policies are unnecessary.[48]

Crab lice are spread through sexual contact affecting pubic and body hair. In addition to nits, an associated skin finding is *maculae caeruleae* (blue spots), which probably represents hemosiderin deposits. Body lice are uncommon except in conditions of poverty. Nits are deposited on the clothing instead of body hair.

Topical treatment is with pyrethrin, synthetic pyrethroids (permethrin), gamma-benzene hexachloride (lindane), and 50% isopropyl myristate (Resultz). The latter treatment damages the louse exoskeleton, causing dehydration. Shaving the scalp is useful but nit combs, used after a vinegar rinse, are an alternative. Malathion 0.5% lotion application (Ovide) applied for 8 hours is a more toxic second-line therapy for resistant infections approved for children older than 6 years. Ivermectin also seems to work at the same dosage as for scabies. All family members and close contacts should be treated, even if asymptomatic.

Because of increasing resistance to pyrethrin, newer treatments, such as spinosad (Natroba), benzyl alcohol (Ulesfia), or heat (LouseBuster), are gaining popularity.

Other Insects

Fleas include the human flea (*Pulex irritans*) and dog and cat fleas (*Ctenocephalides canis, C felis*). Pruritic ankle papules from fleabites are the usual presentation. Fleas occasionally act as vectors for plague and endemic typhus. Flea traps and sprays, oral and systemic flea treatments for pets, and topical insect repellents are all effective.

The chigoe or jigger flea (*Tunga penetrans*) is a burrowing flea found in tropical South America, Africa, and south Asia. The female burrows between the toes or on the feet, producing an inflamed pea-sized nodule in which she produces eggs. Sometimes, small white eggs may be seen extruding from these lesions. The nodules frequently become secondarily infected. Treatment consists of removing the lesion and updating tetanus if necessary.[46]

Myiasis

Myiasis describes infection by human botfly larvae. Perhaps the best known species is *Dermatobia hominis,* the common botfly of Central and

South America. This fly captures biting insects, attaches its eggs to them, and releases the insects to find new animal or human hosts. When eggs reach their destination, the larvae hatch, penetrate the skin, and create small furuncles, each having a tiny central breathing pore. In Africa, the tumbu fly (*Cordylobia anthropophaga*) lays its eggs on clothing hung out to dry. The eggs hatch once the clothing is worn, after which they develop into numerous furuncles. Fortunately, ironing clothes will kill the eggs. This species produces multiple furuncles that mature in 2 to 3 weeks, whereas *Dermatobia* lesions are few but last 6 weeks. The African Lund fly (*C rodhaini*) places its eggs on the ground, where they infest the feet. The Congo floor maggot does not burrow but feeds on humans sleeping on dirt floors at night.

Patients often report a crawling sensation with furuncular myiasis. Surgical excision is an option, but this can be facilitated by first applying petroleum jelly over the furuncle. This occludes the larvae spiracle (breathing apparatus), forcing it to partially emerge. Applying raw bacon or fatback over the furuncle causes larva to migrate upward, facilitating easy removal with forceps a few hours later.[46]

Chigger Bites

Chigger bites are caused by larval trombiculid mites or red bugs (*Trombicula alfreddugèsi*) that inject an irritant when they bite. Contrary to popular opinion, chiggers do not burrow into the skin. Lesions are usually large, itchy papules with a central punctum that develop on areas where clothing is tight, such as sock and belt lines. A "summer penile syndrome" occurs from chigger bites on the penis. Straw itch mites and avian mites can produce similar lesions. Treatment is symptomatic with antihistamines and topical steroids, but applying nail polish to "smother the chigger" is ineffective.

Insect Bites

Insect bites (eg, bedbugs, mosquitoes, sandflies, gnats, blackflies, deerflies, horseflies) appear as erythematous itchy papules, often with a central punctum. Bedbugs (*Cimex lectularius*) are oval, 3- to 5-mm flat reddish-brown insects that feed at night, producing itchy papules. There are often several lesions in a row—the classic *breakfast, lunch, and dinner sign*. Tropical bedbugs (*Cimex rotundatus*) are longer insects but otherwise similar. Although there has been much speculation that these insects could act as disease vectors, clinical evidence for this is lacking, although some may be colonized with antibiotic-resistant bacteria. Lesion treatment is symptomatic, but eradication to prevent further bites is essential.[49]

Insect bites are treated with cool compresses, oral antihistamines, and stronger steroid creams. Severe mosquito bite allergy ("skeeter syndrome") may require short courses of oral prednisone. Bite prevention is with insect repellents ideally containing diethyltoluamide (DEET) 30% or picaridin 20%.[50] Both are applied to exposed skin, and DEET lotions appear safe in infants and children older than 2 months (avoiding the hands and lips). DEET concentrations greater than 50% are not recommended and may pose a greater risk of toxicity. Permethrin 0.5% spray (Permanone) may be applied to clothing to repel ticks and insects.

Insect Stings

Insect (*Hymenoptera*) stings from bees (*Apidae*), wasps, hornets and yellow jackets (*Vespidae*), and stinging ants (*Formicidae*) produce an immediate reaction with a painful papule that usually resolves within a few hours. Cold compresses, sometimes with baking soda or papain meat tenderizer, are used with variable success. Calamine lotion and oral antihistamines also help. Late-phase local hypersensitivity reactions closely resemble cellulitis with a red, warm area appearing around the sting site within 48 hours and lasting up to a week. Local hypersensitivity reactions are best treated with oral steroids or antihistamines rather than antibiotics. Anaphylactic reactions involve generalized urticaria (hives), hypotension, and possible airway obstruction and cardiovascular collapse. Subcutaneous or IM epinephrine (1:1,000) is immediate therapy, with diphenhydramine and systemic steroids preventing relapse. Anaphylaxis cases should be observed for a minimum of 6 hours because relapses are common.[51] An epinephrine injection device (EpiPen, EpiPen Jr) and insect sting desensitization should be recommended for those with a history of generalized hives or anaphylactic reaction to stings.

KEY POINTS

Diagnosis

- First try to identify the primary skin lesion (eg, macule versus patch, papule versus plaque, vesicle versus bullae).
- Are there any secondary characteristics present (eg, scaling, crusting, excoriations)?
- Pruritus suggests allergy, while tenderness suggests infection.
- Did the rash start on the trunk and spread to the extremities (centrifugal), or did it spread from the extremities to the trunk (centripetal)?
- Always ask what the patient has been using on the rash, as it may now be contributing to it.
- Always take a thorough drug and travel history.

- Uncommon presentations of common conditions are more likely than common presentations of uncommon ones.
- Have the patient disrobe for the examination and do not forget to examine the mouth.

Treatment

- Instruct the patient or parent on the correct amount of the topical agent (in fingertip units) to apply and how to apply it. Discuss duration and conclusion of therapy.
- Avoid high-potency steroids on the face, genitals, and axillary and inguinal areas.
- Avoid systemic steroid use in psoriasis because of the risk of a flare on discontinuation.

Viral Infections

- Removing a viral skin lesion with a number 15 scalpel to check its gross or microscopic appearance often aids diagnosis (eg, molluscum lesions, human herpesvirus vesicles).
- Cryotherapy frequently results in hypopigmentation in dark-skinned patients.
- Viral exanthems can be differentiated by age of onset, site of onset, rash progression, and appearance.

Bacterial Infections

- Honey-colored crusts and erosions are typical findings in impetigo. Topical mupirocin is usually effective.
- Skin pyodermas may initially resemble spider bites. Methicillin-resistant *S aureus* often presents this way.
- Abscesses should always be drained of pus, not just treated with antibiotics. Thorough drainage is usually sufficient treatment in immunocompetent patients.

Fungal Infections

- Classic tinea appears as a scaly pruritic patch with annular margins and central clearing.
- Diagnosis of fungal infection is confirmed by obtaining a skin scraping with a number 15 scalpel and examining it for hyphae under a drop of 20% KOH.
- Use of topical steroids on fungal skin lesions alters their appearance and may confuse diagnosis (tinea incognito).

- Most tinea infections do not fluoresce with Wood lamp illumination. *Microsporum* infections fluoresce green (but are now rare) and erythrasma, a bacterial infection resembling tinea, fluoresces coral red.

Rickettsial Infections

- Fever, headache, and (often) rash are characteristic of rickettsial infections. Doxycycline is the best therapy.

Parasitic Infections

- Eosinophilia is associated with helminthic tissue infection in immunocompetent hosts.
- Eosinophilia is usually absent in protozoal infections.
- A travel history is essential in determining differential diagnosis for parasitic infection.

Ectoparasitic Infestations

- Patients should be counseled that pruritus from scabies is slow to resolve after treatment and antihistamines may be helpful in the interim.
- Increasing pyrethrin resistance in head lice mandates newer treatments such as spinosad, benzyl alcohol, and heat treatments.

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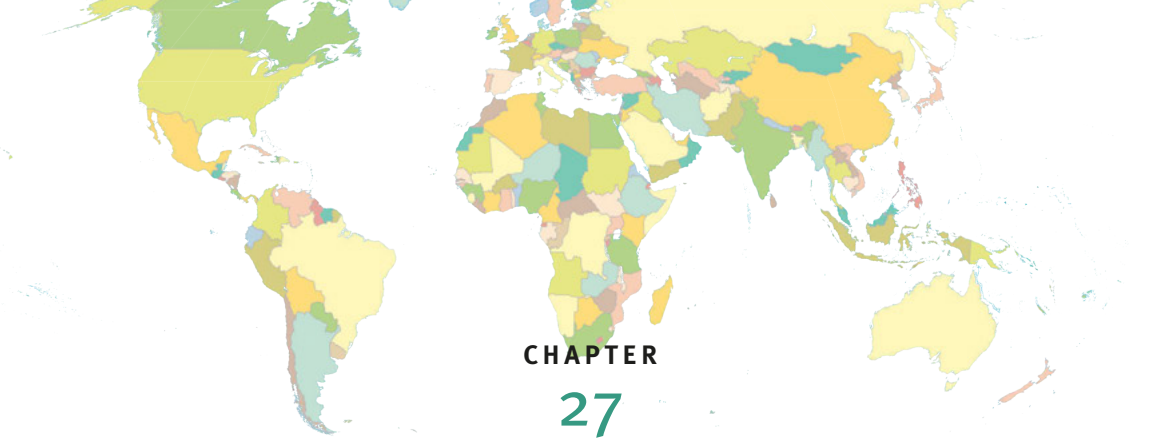

CHAPTER

27

Bites and Stings

Gregory Juckett, MD, MPH

INTRODUCTION

Travel to the tropics invariably raises concerns about deadly snakebites, voracious insects, and malign infestations. Fortunately, these fears are typically exaggerated. For travelers, snakebites are extremely rare events that can usually be avoided with a few simple precautions. While insect bites and stings are another matter, even in the tropics they usually are only a nuisance.

The major exception to this rule is anaphylaxis from bee and wasp stings. Anaphylaxis represents a true medical emergency that may occur anywhere. Because emergency care is far less available in lower-income countries, the most important medical item to bring along is epinephrine 1:1,000 in a self-injectable form (eg, EpiPen). Epinephrine remains the key intervention in anaphylaxis and will outperform all other medical options, such as steroids and diphenhydramine, for life-threatening allergic reactions.

In contrast with travelers, residents of the tropics are confronted by local fauna on a daily basis and lack many of the resources (eg, footwear, bed nets, insect sprays) insulating more affluent travelers from their environment. Snakebites usually affect agricultural workers, making it an occupational, rather than a recreational, disease in these settings. Once bitten, there may be far less access to immediate care, making morbidity and mortality rates for residents much higher.[1]

SPIDER BITES

Most spider bites are relatively harmless. Only widow (*Latrodectus*), recluse (*Loxosceles*), and South American bird spiders (*Phoneutria*) are causes for concern in the Americas. Worldwide, the Australian funnel web spiders (*Atrax*) rank as the most dangerous. However, other much-feared spiders, such as the tarantula, pose very little threat to human health, although they can certainly bite and are even known to flick urticating hairs if annoyed. Most tarantula bites hurt, but they rarely require any medical intervention.

In general, spider bites tend to be overly dreaded and overdiagnosed. Patients and physicians falsely attribute many unexplained skin lesions, usually pyoderma, to spiders. In fact, many of these lesions appear to be caused by methicillin-resistant *Staphylococcus aureus*.[2]

Widow spiders (*Latrodectus*) are distributed worldwide, but the best-known species is the black widow (*L mactans*), famous for its characteristic red hourglass mark on the ventral abdomen. It possesses a very potent neurotoxic venom known as alpha-latrotoxin. Black widow bites are usually felt as a mild pinprick (often presenting with a halo around the site) followed within an hour by severe pain and muscle cramping. Bites usually occur outdoors. Systemic symptoms such as nausea, vomiting, and sweating may also occur. Upper extremity bites produce chest pain, while those on the lower extremity may mimic an acute abdomen. Fatal respiratory arrest has occurred in children.

Widow bites are treated with local application of ice and intravenous (IV) diazepam to reduce muscle spasm. Traditionally, 10% calcium carbonate was used to treat muscle cramps, but benzodiazepines and narcotics have replaced this as standard therapy.[3] An equine *Latrodectus* antivenom* (1 vial diluted in 50 mL normal saline) is available but is usually reserved for pediatric envenomation. Black widow antivenom is also very effective at relieving pain.

Brown recluse (Figure 27-1) or fiddleback spiders (*Loxosceles reclusa*) of the south-central United States are the most important American cause of necrotic arachnidism, or skin necrosis caused by spider bites (figures 27-2 and 27-3). Brown recluse venom contains sphingomyelin phosphodiesterase D. These spiders are readily identifiable by an inverted violin-shaped marking on the dorsal thorax and by having only 6 eyes (most spiders have 8). Even more dangerous is the larger South American *Loxosceles* relative, the Chilean recluse (*L laeta*), which has established limited colonies in parts of the United States. Recluse spiders usually

*The World Health Organization recommends the term *antivenom* replace the older French equivalent *antivenin* in English usage.

live in homes where they seek out dry, dark locations such as inside clothing or behind picture frames. Bites may not be painful at first, but a painful blister with a multicolored halo (red, white, and blue sign) usually forms within 6 hours. The skin around the bite sloughs off after several days, leaving a very slow-healing ulcer.

Most recluse bites clear up with the initial application of ice, routine wound care, and antihistamines. Routinely cutting out the bite site is no longer recommended.[4] However, skin grafting may eventually be required in the rare severe case. Transdermal nitroglycerin has been tried on bites to prevent skin necrosis. Although dapsone (to limit neutrophil degranulation within the first 48–72 hours) is still sometimes recommended, there is little conclusive evidence confirming its effectiveness; as such, dapsone is no longer standard therapy.[5] Steroid use is also controversial. There is little evidence-based research with which to guide spider bite therapy.

The Brazilian wandering spider or banana spider (*Phoneutria nigriventer*) can cause severe pain requiring local anesthetic injection. Narcotics may increase the risk of respiratory arrest and should be avoided. The male funnel web spider (*Atrax robustus*) is probably the most dangerous spider in the world but is limited to eastern Australia. Its neurotoxic bites are treated with a compression and immobilization dressing, atropine, and *Atrax* antivenom.

Figure 27-1. Brown Recluse Spider

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Figure 27-2. Brown Recluse Spider Bite Showing Early Skin Necrosis

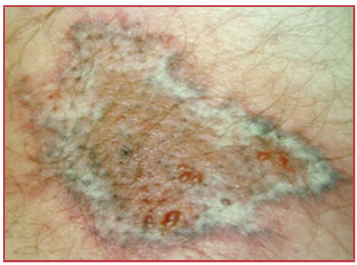

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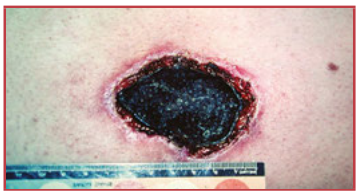
Figure 27-3. Brown Recluse Spider Bite Showing Late Skin Necrosis



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SCORPION STINGS

Scorpions are nocturnal arachnids that often enter homes in hot climates, where they can be easily spotted with a black (ultraviolet) light. Their habit of seeking refuge in shoes results in many stings. While

most scorpion stings are no more dangerous than bee stings, a few can be life threatening. Many small-clawed scorpions have a tendency to compensate with much more potent venom in their tail stinger (telson). The *Buthidae* family of scorpions, characterized by small claws and a triangular sternal plate, are notorious for severely neurotoxic stings that cause an autonomic storm (Box 27-1). A few non-buthid scorpions, such as *Hemiscorpius lepturus,* may also inflict serious stings; however, their venom results in local skin necrosis.[6]

The bark scorpion (*Centruroides exilicauda* [*sculpturatus*]) of Arizona and Mexico is the most dangerous US buthid. Its sting is painful and causes local paresthesia, violent neuromotor hyperactivity, cholinergic symptoms (eg, nausea, sweating, salivation), tachycardia, hypertension, and respiratory complications. Stings are treated with local ice, IV diazepam, atropine, and careful blood pressure control in an intensive care unit setting. Anascorp, a recently US Food and Drug Administration–approved but very expensive Fab antivenom (2011), appears quite effective in severe envenomations[7] and replaces a goat-derived scorpion antivenom that is no longer manufactured.

STINGING CATERPILLARS

Many caterpillars possess venomous spines or hairs for defense. The US saddleback caterpillar (*Acharia* [*Sibine*] *stimulea*) and the io moth (*Automeris io*) are typical species producing severe stings on contact. The puss moth, wooly slug, or asp caterpillar (*Megalopyge opercularis*) is also capable of producing long-lasting pain. Tape application may remove adherent spines, and ice compresses with local anesthetic injection help alleviate pain.

Box 27-1. Most Dangerous Scorpions

***BUTHIDAE* FAMILY: NEUROTOXIC VENOMS**

Tityus—Caribbean, South America
Androctonus australis (yellow scorpion)—North Africa
Buthus—North Africa
Leiurus quinquestriatus (5-keeled yellow scorpion)—North Africa and Middle East
Mesobuthus tumulus (red scorpion)—India
Centruroides exilicauda (bark scorpion)—southwest United States and Mexico (cholinergic toxicity)
Parabuthus—South Africa (cholinergic toxicity)

***SCORPIONIDA* FAMILY: CYTOTOXIC VENOM**

Hemiscorpion lepturus—Middle East (sting site necrosis)

Some tropical caterpillar bites are much more serious. *Lonomia* caterpillars from South America are probably the most dangerous, with venom that activates prothrombin, causing a persistent coagulopathy.

HYMENOPTERA STINGS

Hymenoptera stings (bees, wasps, and ants) are responsible for more fatalities than any other venomous animal. Anaphylaxis with shock is the usual cause of death. Bee venom appears to be the most allergenic; however, yellow jackets, a type of wasp, actually cause more fatalities because of their aggression. Wasps are also capable of stinging repeatedly, whereas bees, with barbed stingers, do so only once—their venom sacs and stingers remain in the victim as the bee flies off to die. Typical immediate sting reactions involve short-lived pain and swelling that is usually treated with ice, antihistamines, or compresses of baking soda or papain (meat tenderizer). Late phase reactions (48 hours to a week later) appear as local areas of redness, heat, and swelling that closely mimic cellulitis. A short course of antihistamines or prednisone is the most effective treatment. Antibiotics are frequently prescribed but are seldom needed. Prednisone is also very useful for the serum sickness–like reaction (fever, arthralgia, urticaria) that may sometimes follow a sting.

Honeybee (*Apis mellifera*) venom consists largely of melittin (50%) with highly allergenic phospholipase A, adolapin (an anti-inflammatory peptide), and hyaluronidase.[8] Africanized "killer" bee venom is no more toxic than the European variety, but the bees are far more aggressive. Swatting bees causes them to release pheromones that provoke an even more aggressive attack. Wasps or vespids include paper wasps (*Polistes*), bald-faced hornets (*Dolichovespula*), European hornets (*Vespa*), and yellow jackets (*Vespula*). The intense pain of wasp stings is caused by the serotonin in its venom.

Fire ants (*Solenopsis invicta*) are an imported Argentine species that are now widespread throughout the southern United States. Their nests are conspicuous mounds of dry earth that must be avoided at all costs. Attacking fire ants anchor themselves to their victim by biting and then stinging repeatedly around their attachment site. These painful stings soon develop into clusters of sterile white pustules.

The samsum ant (*Pachycondyla*) in Africa and the Middle East is the equivalent of the American fire ant. In tropical Latin America, the bullet or 24-hour ant (*Paraponera*) has the most dreaded sting, which often requires anesthetic injection at the sting site. The local name, 24-hour ant (hormiga veinticuatro), refers to the 24 hours of pain it causes. However, symptomatic therapy (eg, ice, antihistamines) suffices for most ant stings.

Anaphylaxis is a life-threatening emergency that usually occurs within 30 minutes (occasionally longer) after an allergenic exposure. Generalized urticaria, intense anxiety, shortness of breath, and weakness are usually evident. Death often occurs within 1 hour and is precipitated by airway obstruction or cardiovascular collapse. A biphasic pattern occurs in 20% of cases in which an apparent remission is followed by another episode 3 to 5 hours later. Therefore, it is imperative that every suspected case of anaphylaxis be observed for at least 6 hours before discharge.[9]

The cornerstone of anaphylaxis therapy is intramuscular or subcutaneous epinephrine (1:1,000) injection at a dosage of 0.01 mL/kg (0.3 mL maximum) repeated every 15 to 20 minutes until improvement. Diphenhydramine is also useful, but relapse with diphenhydramine alone is very common. Antihistamines alone should never be depended on to reverse anaphylaxis. Airway intubation, bronchodilators, IV steroids, and normal saline are all part of standard care. Patients on beta-blockers are notoriously refractory to epinephrine and require IV glucagon for effective treatment.[9]

Anaphylaxis is mimicked by many other conditions: anaphylactoid events (non-IgE mediated but managed the same way), certain drug reactions, panic attacks, and vasovagal episodes. Tryptase, released from mast cells, peaks within 1 hour of true anaphylaxis and remains elevated for at least 24 hours. Patients with systemic reactions should be prescribed an epinephrine injection device (eg, EpiPen, EpiPen Jr) and referred for insect sting desensitization. Venom immunotherapy should continue until repeat skin results are negative, usually at 3 to 5 years.[10]

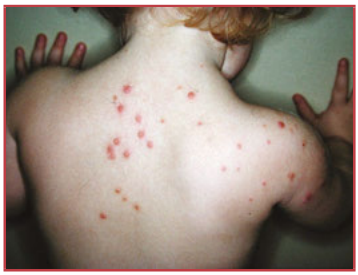
INSECT BITES

Dipteran insects, such as mosquitoes, blackflies, and gnats, commonly cause allergic reactions at the bite site. These itchy red papules typically have a minute central punctum, but their severity and duration depend on individual sensitivity. “Skeeter syndrome” describes an intense hypersensitivity reaction to mosquito bites. While insect bites respond well to antihistamine therapy, they are best prevented by the judicious use of insect repellents. Diethyltoluamide (DEET)-containing repellents up to 35% concentration are now considered safe in children older than 2 months.[11] Concentrations greater than 50% do not offer any significant advantage and may be associated with increased skin absorption. Sustained-release preparations such as Ultrathon (35% sustained-release DEET) may provide up to 12 hours of protection.

Similar itchy papules on the ankles suggest an allergic reaction to fleabites, which are usually from a cat or dog flea (*Ctenocephalides*

canis). This flea is especially prone to attack humans (Figure 27-4) if its preferred host is temporarily unavailable. Human fleas (*Pulex irritans*) occur in less hygienic situations. Bedbugs (*Cimex*) cause clusters or short lines of large pruritic papules on the trunk or extremities. These clustered 3 to 4 lesions are sometimes termed the *breakfast, lunch, and dinner sign*. Extermination is the only effective solution.

Figure 27-4. Flea Bites



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Chiggers or red bugs are harvest mite (*Trombicula*) larvae that live in dry grass and migrate up the body until clothing constriction stops them, which explains why their large, intensely itchy bites often occur at sock or belt lines. "Summer penile syndrome" in children describes a severe inflammation of the penis from chigger bites. Contrary to popular opinion, these itchy bites are allergic reactions to the mite's feeding, not to the mite itself—the red spot is just where the mite was feeding. Treatment is with calamine lotion, cold compresses, and antihistamines, but no treatment is really satisfactory. Unfortunately, applying nail polish does not work.

The tropical burrowing chigoe or jigger flea (*Tunga penetrans*) actually embeds itself in the tissues of the toes or feet where it provokes severe inflammation and sometimes secondary infections. These tiny 1-mm fleas are common in Africa, India, and Latin America (where they are called bicho de pies or "foot bugs"). Diagnosis is often confirmed by observing the discharge of tiny white eggs from the skin lesion. Proper footwear is critical in preventing infestation. The best therapy is surgical removal.

TICK BITES

Ticks are 8-legged arthropods that feed on mammals and humans. They are well-known vectors of Lyme disease (*Borrelia burgdorferi*) and various rickettsial diseases. The 2 major types of ticks include hard ticks of the family *Ixodidae* (head of tick is visible when viewed from above) and the less medically important soft *Argasidae* ticks (head cannot be seen from above). Hard ticks are the common dog or wood ticks that attach on hikes, whereas soft ticks are usually nest parasites. Most tick bites appear as transient red macules left after the engorged tick detaches or is removed. Gravid female tick bites can produce tick paralysis, a toxin-mediated ascending paralysis that resolves after tick removal but which occasionally proves fatal if the tick is not found and removed. Pajahuello

or straw-colored soft ticks of the Southwest United States (*Ornithodoros coriaceous*) produce intense local inflammatory reactions but are not known disease vectors. Tick-borne lymphadenopathy is a new rickettsial disease in Europe caused by *Dermacentor* hard ticks infected with *Rickettsia slovaca*.[12]

Deer or black-legged tick bites (*Ixodes scapularis*) are notorious for transmitting Lyme disease, especially in the Northeast and upper Midwest United States. Infected deer tick bites develop an erythematous patch that expands and often develops into a bull's-eye rash (erythema migrans), which may last for weeks before fading. Multiple patches may be present. *Ixodes* ticks also are capable of transmitting human granulocytic anaplasmosis and babesiosis, a malaria-like protozoal infection. Prophylactic treatment of *Ixodes* tick bites with a single dose of doxycycline 200 mg is reasonable if the tick is identifiable as *I scapularis,* it has likely been attached longer than 36 hours, doxycycline can be administered within 72 hours of removal, and Lyme disease is prevalent in the area (local vector infection rate >20%).[13]

Prompt removal of ticks is important because they do not usually transmit disease if removed before they are engorged. The tick should be grasped firmly behind the head with forceps and gently pulled out without twisting. The use of irritants, alcohol, nail polish remover, a recently lit match, or petroleum jelly should be avoided because it may cause the tick to regurgitate, thus increasing disease transmission. Spraying clothing with permethrin, a synthetic insecticide, is an excellent way to prevent bites. In one study, people wearing permethrin-treated socks and sneakers received almost 75% fewer bites than those wearing untreated items.[14] Exposure can also be reduced by tucking pants into socks, wearing hats, and performing a daily tick check after returning indoors.

Lone star ticks (*Amblyomma americanum*) of the Southeast United States have a central white "star" on their dorsal shield. These ticks are potential vectors of southern tick-associated rash illness (STARI), a southern Lyme-like disease that may produce a circular red rash (like erythema migrans), fever, and headache. Although the cause of STARI has not yet been identified, the condition responds to doxycycline.[9] Lone star tick bites have also been associated with a persistent allergy to red meat (and cetuximab) caused by IgE antibodies to galactose-alpha-1,3-galactose, also known as alpha-gal. Sensitized individuals develop hives or, in some cases, anaphylaxis after eating red meat (ie, beef, pork, or lamb).[15] Other diseases transmitted by this tick include human monocytic ehrlichiosis, tularemia, and Q fever, all of which respond to doxycycline. The other common US hard tick is the dog tick, *Dermacentor variabilis,* which is a

potential vector of Rocky Mountain spotted fever (known as Brazilian spotted fever in South America) and tularemia.

MYIASIS (HUMAN BOTFLY INFESTATION)

Several species of botflies attack humans in addition to animals. In Central and South America, the human botfly, *Dermatobia hominis,* captures mosquitoes or other biting insects on which to attach its eggs. When these released insects reach their victim, the eggs hatch and infest the host, producing a small furuncle. Over the next 6 weeks, the maggot develops within the skin to eventually emerge as an adult fly.

In Africa, the tumbu or putzi fly (*Cordylobia anthropophaga*) lays its eggs on damp or sweat-stained clothing, especially clothing that is hung up to dry. Unless these clothes are thoroughly ironed before being worn, eggs will hatch on contact with skin to produce multiple boils, which develop much faster than the prior species (often within several weeks). The patient's perception of motility within the lesion suggests the correct diagnosis. Lund fly (*Cordylobia rodhaini*) is a similar species that infests the feet. There is even a free-living Congo floor maggot (*Auchmeromyia*) that temporarily attaches to and feeds on people sleeping on the ground.

Fly larvae of many species can infest necrotic wound tissue. Less commonly, screwworm larvae may attack viable tissue of humans and animals; these can be paralyzed with topical 5% chloroform in olive oil and removed manually. *Hypoderma* fly larvae may tunnel through human skin to produce lesions closely resembling those of cutaneous larva migrans (creeping eruption); ivermectin clears this infection.[16]

Surgically excising or ejecting botfly larvae by injecting 2-mL local anesthetic into the lesion base is curative. Traditionally, applying fatback (raw bacon) or any occlusive material over the larval spiracle (breathing aperture) encourages the maggot to migrate upward, making removal much easier. Usually larvae can be removed with forceps several hours after bacon therapy.

VENOMOUS SNAKEBITES

There are 4 principal venomous snake families in the world: vipers, elapids (including *Hydrophis* and *Laticauda* sea snakes), colubrids (mostly nonvenomous but including some rear-fanged species such as the boomslang), and burrowing asps of Africa (Box 27-2). Most important are the vipers, usually fat, thick-bodied snakes with broad heads and cytotoxic or hemotoxic venom that digests tissue and breaks down blood. American pit vipers (ie, rattlesnakes, copperheads, and cottonmouths) are crotalid representatives of the viper family. Elapids

Box 27-2. Venomous Snake Families

Viperidae (vipers and pit vipers: mostly hemotoxic venom)
True vipers include the European adder, saw-scaled, or carpet viper (Africa and Asia); puff adder (Africa); Gaboon viper (Africa); and Russell viper (Asia). The crotalid or pit viper subfamily includes rattlesnakes (Americas), copperheads (North America), water moccasins or cottonmouths (North America), fer-de-lance (Central and South America), bushmaster (South America), Malayan pit viper (Asia), and Temple viper (Asia).

Elapidae (elapids: mostly neurotoxic venom)
Typical elapids include black and green mambas (Africa), cobras (Africa and Asia), spitting cobras (Africa and Asia), king cobra (Asia), kraits (Asia), coral snakes (Americas), taipans (Australia), and the misleadingly named death adder of Australia (all venomous Australian snakes are elapids).

The sea snake subfamily (*Hydrophis*) includes many aquatic species living in the Indian and Pacific oceans, such as the beaked sea snake and annulate sea snake. These seldom bite in the water but often do so when captured.

The *Laticauda* subfamily includes the yellow-lipped sea krait, which may be found on shore rocks or in the ocean.

Colubridae (colubrids: mostly nonvenomous snakes but includes venomous rear-fanged species as well)
Venomous colubrids include the boomslang (*Dispholidus*) and twig snakes (*Thelotornis*) of Africa and the Asian red-necked keelback (*Rhabdophis*).

Atractaspididae (African burrowing asps): uncommon causes of snakebite, but these are the only snakes unable to be held safely behind the head because they are capable of rotating their fangs sideways or backward to inflict bites.

(including mambas, cobras, kraits, coral snakes, and sea snakes) are slender tropical and subtropical species with mostly neurotoxic venom that paralyzes respiratory muscles. Thus, elapid snakes can kill within hours, whereas most vipers, with rare exceptions, take days to kill their victims. Sea snakes are mostly neurotoxic but frequently produce rhabdomyolysis.

Other exceptions to the "only viper venom is cytotoxic" rule include Russell viper venom (with neurotoxic effects) and cobra venom, which can attack tissue and the nervous system. Populations of Mojave rattlesnakes from the desert Southwest may have a neurotoxic (type A) venom, containing Mojave toxin, or more typical pit viper (type B) venom. Elapid snake envenomation in Australia may also give mixed neurotoxic/myotoxic syndromes.

First aid for snakebite depends on the snake type. Viper or pit viper bites (including nearly all US snakebites) are treated with a lymphatic

constriction band loose enough to allow a finger to slide beneath and rapid transport to a nearby hospital where antivenom can be administered. Tourniquets do more harm than good. Rings and jewelry should be removed before swelling starts. Ice packs, fang mark cutting, wound suction, and electric shock therapy should all be avoided. Stun guns and other forms of shock do not neutralize venom and may be harmful. Venom extraction devices are probably of no benefit, even if used within the necessary 3-minute window, because the high viscosity of snake venom makes removal difficult.[17]

Envenomated elapid bites are very different from those of vipers and often have little, if any, local reaction. Because there is less local destruction of tissue, the entire extremity should be immobilized and wrapped in a lymphatic constriction band; this effectively traps the neurotoxic venom in the limb lymphatics, keeping it from reaching the central nervous system. Antivenom must be given for some elapid bites (eg, coral snakes, kraits) even when there may be minimal signs of local envenomation. Elapid neurologic symptoms, once begun, are quite difficult to reverse. Respirations should be closely monitored and ventilator support should be available.

Pit viper bite envenomation usually produces a significant local reaction with immediate pain and swelling. Table 27-1 lists the common symptoms of envenomation. Classically, 2 fang marks are present; rarely, there may be 1 to 4 fang marks because of fang loss or the presence of replacement fangs. Many bites turn out to be dry with no appreciable venom. It is estimated that 20% to 30% of pit viper bites are dry

Table 27-1. Symptoms of Snakebite Envenomation

HEMOTOXIC SYMPTOMS	NEUROTOXIC SYMPTOMS
Intense pain	Minimal pain
Edema	Ptosis
Weakness	Weakness
Swelling	Paresthesia (often numb at bite site)
Numbness or tingling	Diplopia
Rapid pulse	Dysphagia
Ecchymoses	Sweating
Muscle fasciculation	Salivation
Paresthesia (oral)	Diaphoresis
Unusual metallic taste	Hyporeflexia
Vomiting	Respiratory depression
Confusion	Paralysis
Bleeding disorders	

From Juckett G, Hancox JG. Venomous snakebites in the United States: management review and update. *Am Fam Physician*. 2002;65(7):1367–1374, with permission.

compared with more than 50% of elapid and 75% of sea snake.[18] Any suspected dry pit viper bites should be observed a minimum of 8 hours before discharge versus 24 hours for elapids.[17] Basic laboratory tests should be performed as soon as possible, before venom effects interfere with typing and crossing blood, and repeated within 12 hours to monitor bleeding parameters and renal function (Table 27-2). Bites should also be graded at the time of admission and periodically thereafter because severity determines the starting dose of antivenom (Table 27-3).

Swelling of the bitten extremity is usually dramatic in pit viper or viper bites and is often quite persistent, notably so even in the otherwise less venomous American copperhead. Swelling frequently mimics a compartment syndrome, but unless measured compartment pressures are truly elevated, fasciotomy usually causes more harm than good. Most swelling proves to be superficial.[19]

Antivenom is the most effective therapy for a venomous snakebite and should ideally be administered within 4 to 6 hours but may be helpful for up to 72 hours if coagulopathy is evident. Specific monovalent antivenom (made for one particular species) is most effective, but polyvalent antivenom is often the most practical solution because it covers many related snakes. Children need the same antivenom dose as adults (or more) because the amount of venom to be neutralized may be the same with a much smaller body size. Common errors include giving too little antivenom too late or, in the case of viper bites, giving antivenom without any sign of envenomation. If death occurs from viper bites, it is usually delayed (taking several days) and occurs from bleeding disorders or delayed renal failure from myoglobinuria.

Table 27-2. Laboratory Evaluation in Snakebite

Complete blood cell count with platelets and differential[a]	Blood urea nitrogen
Prothrombin time[a]	Platelet count
Partial thromboplastin time[a]	Liver function tests
Fibrinogen[a]	Bilirubin
Fibrin degradation products[a]	Creatine phosphokinase
Blood type and cross match	Creatinine urinalysis[b]
Serum electrolytes	Stool Hemoccult
Glucose	Electrocardiography[c]
	Arterial or capillary blood gas[d]

[a] Should be performed as soon as possible and repeated within 12 hours.

[b] Including free protein, hemoglobin, and myoglobin.

[c] Suggested for patients older than 50 years and patients with a history of heart disease.

[d] Should be tested if any signs or symptoms of respiratory compromise are evident.

From Juckett G, Hancox JG. Venomous snakebites in the United States: management review and update. *Am Fam Physician.* 2002;65(7):1367–1374, with permission.

Table 27-3. Grading Scale for Severity of Pit Viper Bites and CroFab Antivenom Administration[a]

DEGREE OF ENVENOMATION	PRESENTATION	TREATMENT
0. None	Punctures or abrasions; some pain or tenderness at the bite	Local wound care, no antivenom[b]
1. Mild	Pain, tenderness, edema at the bite; perioral paresthesia may be present.	If antivenin is necessary, administer about 4 vials CroFab.
2. Moderate	Pain, tenderness, erythema, edema beyond the area adjacent to the bite; often, systemic manifestations and mild coagulopathy	Administer 4–6 vials of CroFab
3. Severe	Intense pain and swelling of entire extremity, often with severe systemic signs and symptoms; coagulopathy	Administer more than 6 vials of CroFab.

[a] Modified to include recommended CroFab dosages.

[b] Because of their less potent venom, grade I (mild) copperhead bites are often not treated with antivenom.

Adapted from Juckett G, Hancox JG. Venomous snakebites in the United States: management review and update. *Am Fam Physician.* 2002;65(7):1367–1374, with permission.

The choice of which antivenom to use is determined by knowing which species of snake is most likely responsible for the bite. Monovalent antivenoms are very effective against a single snake species, whereas polyvalent antivenoms are effective against many different species (those snakes whose venoms were used in its manufacture). In most of the United States, this decision is easy because CroFab antivenom is currently effective against all native pit viper bites. Overseas, where there may be many types of venomous snakes, the decision may be much more challenging. However, most regions have a polyvalent antivenom available that covers most local bites. The right antivenom must be chosen because rattlesnake antivenom will be ineffective for a coral snake (elapid) bite and vice versa. Most antivenoms are now available as a lyophilized freeze-dried ampule that requires reconstitution before being given intravenously. Snake antivenoms are often expensive and in short supply.

Most antivenom worldwide is made by injecting escalating doses of snake venom into horses and harvesting the antibody. Horse serum antivenom sometimes provokes anaphylactic or anaphylactoid reactions and should be given by a physician with epinephrine and antihistamines

available at bedside. Manufacturers recommend prior skin testing for horse serum allergy, but this is notoriously unreliable and some experts dispense with it. Even if a skin test result is positive, there may be no alternative except to premedicate the patient with IV steroids and diphenhydramine. Equine antivenom administration is complicated by serum sickness 1 to 4 weeks later in approximately 50% of cases and should be treated with oral prednisone therapy.

New, more expensive non-equine Fab antivenom is being developed because whole IgG equine antivenom is associated with allergic reactions. This new antivenom lacks the more antigenic antibody "tail" (Fc portion) and is consequently much safer. CroFab antivenom has now replaced antivenom (*Crotalidae*) polyvalent for the treatment of all US pit viper bites but at a higher cost (>$1,200/vial). CroFab is made from injecting sheep with the venom of western and eastern diamondback rattlesnakes, Mojave rattlesnakes (type B), and cottonmouths. Skin testing is not recommended due to a lower risk of anaphylactic reactions; however, papain allergy is a contraindication because papain is used to create Fab fragments. Reconstitution of a vial of freeze-dried CroFab is accomplished in less than 45 minutes compared with 60 minutes for the older *Crotalidae* antivenom.[20] Each CroFab vial should be diluted with 10-mL sterile water and then diluted in 250-mL normal saline for infusion over 60 minutes. The manufacturer recommends an initial infusion rate of 25 to 50 mL per hour for the first 10 minutes, all the while checking for signs of allergy. Infusion can be increased to 250 mL per hour until completion if allergy signs do not develop. Four to 6 vials are recommended for mild to moderate envenomation; more than 6 vials are recommended for severe envenomation.[21]

Antivenom binds to and neutralizes snake venom, but it does not reverse damage that has already occurred. Although recovery is now the rule with antivenom, many victims continue to experience long-term sequelae, including pain, paresthesia, skin discoloration, and weakness, for years afterward.[22]

Unfortunately, the current US equine coral snake antivenom has been discontinued due to being unprofitable (supplies finally expired October 31, 2013, after multiple extensions), but trials are underway to approve a Mexican Fab coral snake antivenom, Coralmyn, for use in the United States. The only alternative for coral snakebites in the interim (barring participation in the antivenom study) is prolonged ventilation to prevent respiratory failure.

Most fatal snakebites occur in lower-income countries where barefoot farmers labor in fields. Proper footwear would prevent many of these

bites. South Asia has the most fatalities, but southeast Asia, tropical Africa, and the Amazon are also considered moderate to high risk. Bites increase in the rainy season when flooding forces snakes onto higher ground. Although elapids are more dreaded because of their rapid-acting venom, the bulk of fatalities actually occur from rural viper bites, which result in coagulopathies or delayed renal failure. Bites of the irritable saw-scaled or carpet viper (*Echis carinatus*) of Africa, the Middle East, and South Asia cause severe coagulopathies with later renal failure, making that viper perhaps the snake responsible for the most fatalities, despite the fact that other species possess far more potent venom.[23] Although Australia is known for having many dangerous elapids, its mortality rate is remarkably low because of good footwear and prompt medical care.

Most snakebites can be prevented by wearing boots, avoiding tall grass and brush, and using a flashlight when on a path at night. Many so-called illegitimate snakebites occur while teasing or attempting to kill snakes; alcohol is often a contributing factor. Dead snakes are able to bite through reflex action for several hours even if decapitated. Children should thus be warned to leave even dead snakes alone. Bites from exotic snakes kept as pets are a growing concern in urban areas. Because crotalid antivenom is quite ineffective in such situations, the appropriate exotic antivenom must be located through poison control or regional zoos or aquariums.[24] Further information may be obtained through Poison Help at 800/222-1222 or the Rocky Mountain Poison & Drug Center at 303/389-1100 or www.rmpdc.org.

KEY POINTS

- Widow spider bites result in intense muscle spasms and are usually managed with benzodiazepines or narcotics.
- Brown recluse spider bites result in local skin necrosis, but most can be managed conservatively with antihistamines. Outside of this spider's native range (south-central United States), most spider bites may actually be early MRSA infections.
- *Buthidae* scorpions, such as *Centruroides,* are characterized by small claws, triangular breastplates, and severely neurotoxic stings. Most other scorpion stings can be managed conservatively.
- Hymenoptera (ie, ant, bee, and wasp) stings kill more people through anaphylaxis than any other type of envenomation.
- Epinephrine 1:1,000 injection is the drug of choice for anaphylaxis. Patients taking beta-blockers are resistant to epinephrine and may require IV glucagon.

- Observe all patients with anaphylaxis for at least 6 hours after treatment because 20% of cases may relapse in 3 to 5 hours.
- Vipers and pit vipers have mostly cytotoxic or hemotoxic venom, which causes severe local swelling and coagulopathy. Death usually takes days.
- Most elapids have rapidly acting neurotoxic venom that causes ptosis, respiratory paralysis, and death from respiratory failure. Cobra bites result in local swelling, but no swelling may occur even in serious coral snake and krait envenomation.
- Most traditional snakebite first aid does more harm than good. Immobilization and wrapping the affected extremity in a compression dressing are helpful in elapid bites. Tourniquets should be avoided, although a temporary compression band (restricting lymph but not blood flow) may be useful in viper bites.
- Avoid fasciotomy in snakebite unless critically elevated compartment pressures can be documented.
- Prompt antivenom administration is the key treatment for venomous snakebite. Dose is not reduced for children. Epinephrine should be available by the bedside in the event of an anaphylactic reaction.

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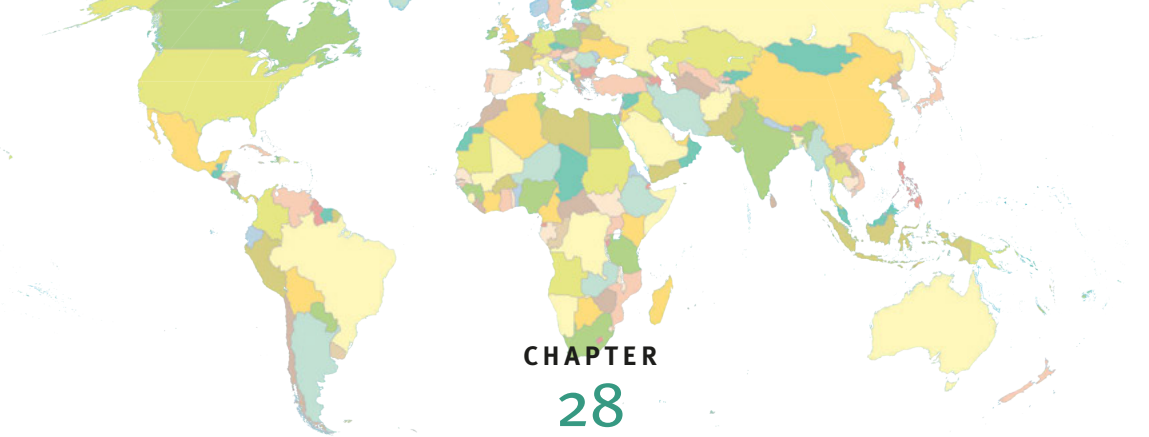


CHAPTER

28

HIV and AIDS

Michael A. Tolle, MD, MPH

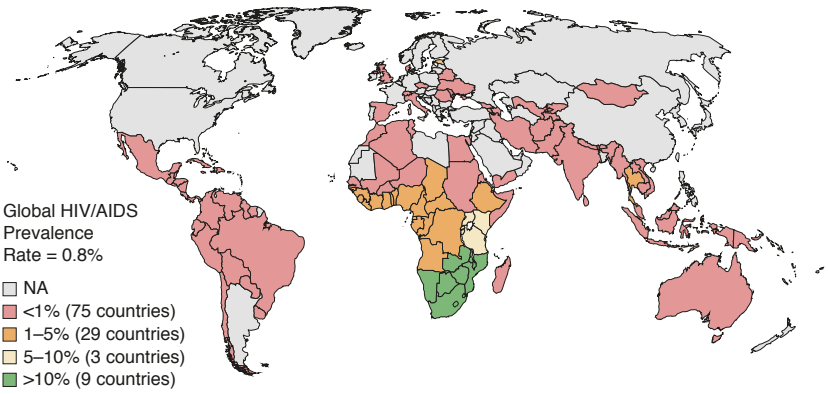
INTRODUCTION

The global HIV pandemic has had a devastating effect on children. HIV is a major cause of death where prevalence is high (Figure 28-1)—even with advances in recent years, more than one-third of child deaths are HIV related in some settings.[1] In addition, millions of children worldwide have been orphaned by HIV. HIV and its associated morbidities place a substantial strain on fragile health systems.

Pediatric HIV infections are rare in higher-income countries because of effective interventions to prevent mother-to-child transmission (MTCT); however, they remain common in many lower-income settings. Scaling up the prevention of MTCT and antiretroviral therapy (ART) programs for children is a global health priority, yet the uptake of several critical interventions remains low in many settings, particularly where health systems struggle to meet even basic maternal-child health needs and where stigma associated with HIV infection remains high.[2]

While tremendous strides have been made in the global response to pediatric HIV over the past few years, challenges persist and children remain underrepresented in care and treatment programs compared with adults.[2] In settings of high HIV prevalence, Millennium Development Goals (MDGs) related to child and maternal survival will not be met without further concerted efforts and progress toward making HIV prevention, care, and treatment universally available as part of community-level, primary health care.[1–3]

Figure 28-1. Adult HIV Prevalence Rate, 2013



Notes: Data are estimates. Prevalence rates include adults ages 15–49. The estimate for Sudan represents data for Sudan only. The estimate for South Sudan is 2.2%.

From Kaiser Family Foundation. Adult HIV Prevalence Rate, 2013. http://kff.org/global-health-policy/slide/adult-hiv-prevalence-rate. Accessed June 10, 2015. Based on Joint United Nations Programme on HIV/AIDS. *The Gap Report*. Geneva, Switzerland; Joint United Nations Programme on HIV/AIDS; 2014.

EPIDEMIOLOGY

While no country or region is spared the effects of HIV infection, its distribution is not uniform (see Figure 28-1). Sub-Saharan Africa bears the largest burden with more than 90% of the world's estimated 3.2 million HIV-infected children, as well as more than 90% of the approximately 220,000 children worldwide newly infected with HIV in 2013.[4] Nearly 85% of the 18 million children orphaned by HIV worldwide live in sub-Saharan Africa, and in some high-prevalence countries, such as Zambia and Botswana, more than 15% of all children and adolescents are orphans—most due to HIV.[5]

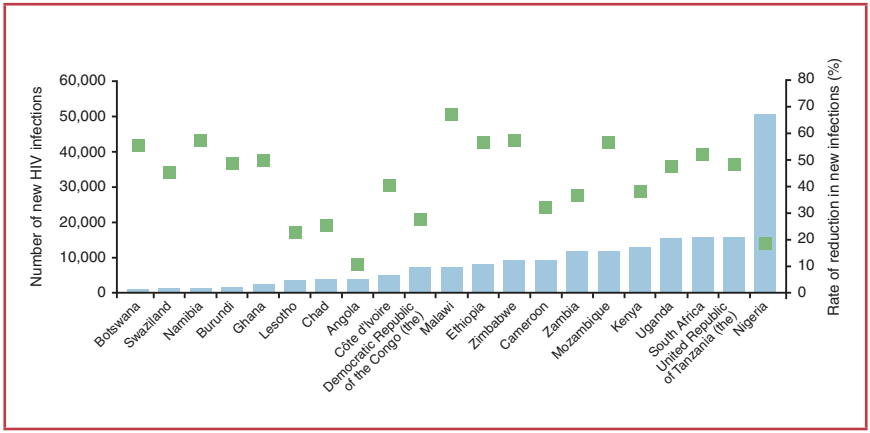
HIV accounts for a reasonably small proportion of global child deaths (<5% of deaths in children <5 years); however, child mortality attributable to HIV may exceed one-third in areas of high prevalence. Thus, HIV-specific interventions form the cornerstone of attempts to reach MDG 4—a two-thirds reduction in child mortality by 2015 (from 1990 levels).[1,2] In regions of high HIV prevalence, progress toward reaching MDG 4 lags behind other regions; generalized HIV epidemics were noted in nearly 80% of countries where child mortality worsened in the 1990s and first decade of the 2000s.[3,6]

Most pediatric HIV infections (>90%) are caused by MTCT (vertical transmission); accordingly, pediatric HIV infection is common where antenatal HIV prevalence is high.[2] The geographic focal effect of HIV is noted in a total of 21 countries in sub-Saharan Africa (prioritized in the Joint United Nations Programme on HIV/AIDS [UNAIDS] Global Plan to Eliminate HIV Infections in Children) accounting for more than 90% of the pregnant women needing antiretrovirals to prevent vertical transmission, as well as more than 90% of children younger than 15 years in need of ART (Figure 28-2).[2]

Historically, children have been neglected in national responses to HIV infection for a myriad of reasons.[7] This remains the case today: in the 21 highest burden settings, only 3 of 10 eligible children had been enrolled in HIV treatment, while more than 60% of adults who need ART have access to it in these settings.[5]

Health system approaches to pediatric HIV infection vary by particular prevalence within a given country. HIV services are, by necessity, delivered at the primary health care level where HIV is prevalent and affects a broad cross section of the population. Most countries with such a context place a high priority on making HIV services universally available via integration into national health services, particularly maternal and child health. The World Health Organization (WHO) produced detailed recommendations on prevention of MTCT and pediatric HIV

Figure 28-2. Number of New HIV Infections Among Children in 2013 and Rate of Reduction in New Infections Since 2009 in the 21 Global Plan Priority Countries



From Joint United Nations Programme on HIV/AIDS. *The Gap Report.* Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS; 2014. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf. Accessed June 10, 2015.

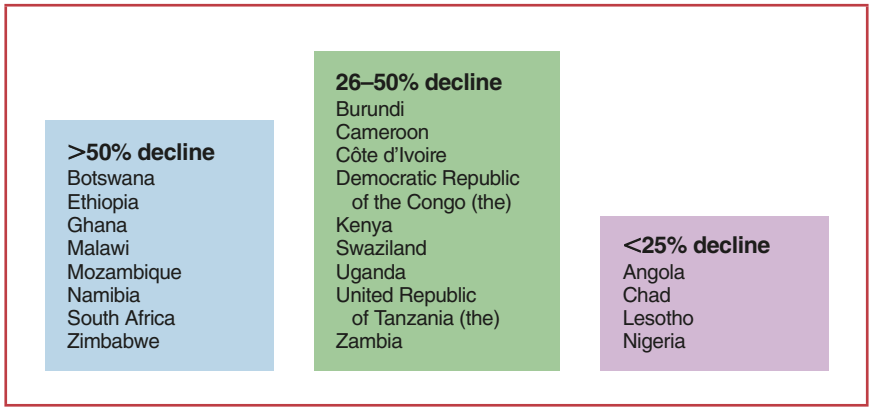
care and treatment that are aligned to this paradigm and widely used in developing countries around the globe.[8]

PREVENTION OF HIV INFECTION IN CHILDREN

While not neglecting other routes of HIV transmission in children (eg, contaminated blood transfusions and injections, early sexual debut, sexual abuse), HIV prevention efforts in pediatric health care focus on prevention of MTCT given the dominant role of MTCT in HIV infection. At the population level, scaling up effective prevention programs yields benefits beyond preventing new infections to improving child survival and is the most effective strategy for preventing HIV-attributable mortality in children.[2] Toward this end, UNAIDS set the goal of virtually eliminating MTCT by 2015.[2]

Indeed, since 2009, there has been a substantial decline (43%) in new HIV infections among children in the 21 Global Plan priority countries (see Figure 28-2). The number of new HIV infections among children in these countries was fewer than 200,000 in 2013, compared to an estimated 350,000 new infections in 2009. While declines were recorded in all Global Plan priority countries between 2009 and 2013, rates varied widely—from 67% decline in Malawi and more than 50% declines in Botswana, Ethiopia, Ghana, Mozambique, Namibia, South Africa, and Zimbabwe to a 19% decline of new pediatric HIV infections in Nigeria (Figure 28-3). Starkly, Nigeria now records one-fourth of all new HIV

Figure 28-3. Percentage Decline in New HIV Infections Among Children in the 21 Global Plan Priority Countries, 2009–2013



From Joint United Nations Programme on HIV/AIDS. *The Gap Report.* Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS; 2014. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf. Accessed June 10, 2015.

infections among children in the Global Plan priority countries—nearly 51,000 in 2013.[9]

HIV MTCT may occur during pregnancy, labor and delivery, and breastfeeding. Risk factors are well defined and include prenatal maternal factors such as high viral load (the level of HIV RNA in the blood), low CD4 cell count (indicative of immune suppression caused by HIV), and advanced clinical stage (the progressive clinical deterioration of an individual infected with HIV), as well as obstetric factors such as prolonged membrane rupture, invasive obstetric procedures, and whether the child breastfeeds.[10]

Without any intervention, the risk of MTCT in a non-breastfeeding population is 15% to 30%. Approximately 70% of transmission in a non-breastfeeding population occurs before delivery, with roughly 30% of transmission occurring during delivery.[11]

In a breastfeeding population, an additional 5% to 20% of infants are at risk for postnatal HIV transmission, such that the total risk increases to as much as 50%.[11] An individual patient could have a substantially higher or lower risk depending on individual risk factors, such as the mother's health, viral load, and duration of breastfeeding.

There are opportunities to prevent perinatal HIV transmission at each point when it can take place—pregnancy, labor and delivery, and breastfeeding. The effectiveness of strategies to reduce perinatal transmission differs by setting. The risk of MTCT can be decreased to less than 2% in a non-breastfeeding population in a developed country by administering antiretroviral drugs to women during pregnancy and labor, obstetric interventions including cesarean delivery (prior to membrane rupture), complete avoidance of breastfeeding, and administering antiretrovirals to the neonate after birth.[12]

In developing countries, several of these interventions may prove difficult. Cesarean delivery is often not safely available, and while WHO and the United Nations Children's Fund (UNICEF) have defined criteria that must be present for formula-feeding to be considered safe (see Infant Feeding on page 831), these criteria may be difficult for families to satisfy.

However, studies show that perinatal transmission rates comparable to higher-income settings can be achieved in lower-income countries, including high-prevalence, low-income settings in sub-Saharan Africa, without cesarean delivery and with breastfeeding.[13] For example, in a Mozambican cohort, only 0.8% of babies born to women who were given antiretrovirals (ie, zidovudine [AZT], lamivudine [3TC], and nevirapine [NVP]) from as early as the 25th week of pregnancy

through 6 months of breastfeeding were HIV infected at 6 months of age; similar results have been seen elsewhere.[13–16]

In response to the needs of developing countries, particularly where HIV prevalence is high, WHO issued comprehensive MTCT prevention guidelines organized around a comprehensive strategic approach that includes the following 4 components[13]:

- Primary prevention of HIV infection among women of childbearing age
- Preventing unintended pregnancies among women living with HIV
- Preventing HIV MTCT
- Providing appropriate treatment, care, and support to mothers living with HIV and their children and families

The first 2 components, while broad, are surmountable. The WHO notes that minimally reducing the prevalence of HIV infection and moderately reducing the number of unintended pregnancies among HIV-positive women of childbearing age can reduce infant HIV infection similarly to single-dose NVP-based prevention interventions.[17] This is a substantial effect given that such interventions (administering a single dose of NVP [a non-nucleoside reverse-transcriptase inhibitor] to a pregnant woman at the onset of labor and to the baby as close to birth as possible) can reduce perinatal transmission by approximately 40%.[18] Preventing HIV transmission from an HIV-infected woman to her newborn focuses on ensuring that she is able to access antiretrovirals early in her pregnancy. Paramount to this is awareness of one's HIV status, which is inextricably linked to the availability and uptake of HIV testing; the opportunity to access perinatal transmission prevention interventions will not be realized if HIV-infected status is not appreciated. Globally, HIV testing rates in pregnancy remain low—only 35% of pregnant women in developing countries received an HIV test in 2013. Rates also vary by location, ranging from 80% in Europe and Central Asia, to near 0% in the Middle East and North Africa, and near 50% in high-prevalence sub-Saharan Africa.

Rates of retesting during pregnancy are much lower.[2] This has implications for perinatal transmission because women whose test results are negative early in pregnancy (per standard recommendations) may become infected later in pregnancy. Acute HIV infection is associated with high viral load and thus an increased risk of perinatal transmission.[12] A substantial number of perinatal transmissions occur after HIV infection during pregnancy in high-prevalence settings; thus, retesting in late pregnancy (or during labor or as soon as possible after delivery) is recommended.[2,13] In any setting (including pediatric testing), rates of accepting HIV testing are higher when suggested by health care

professionals rather than relying on patients or families to seek testing on their own.[19] Instituting provider-initiated testing and counseling into standard maternal-child health packages (including antenatal care) is appreciated as a critical feature of programs in higher-income countries and resource-limited settings with high MTCT prevention coverage and pediatric HIV services.[2,19]

Revisions in 2013 to WHO guidelines for prevention of MTCT (Box 28-1) reflect evidence of the efficacy of various interventions, particularly antiretroviral use during pregnancy. Unlike in past guideline revisions, current advice from WHO recommends use of antiretrovirals in all pregnant women and continuing ART after pregnancy—so-called Option B-plus. This reflects an addition to the 2010 guidelines Options B, the use of ART in pregnancy regardless of clinical stage or CD4 criteria. (In the 2010 guidelines, Option A, AZT prophylaxis, could be used when mothers did not meet stage or CD4 treatment criteria.)

Evidence from Botswana shows that the choice of specific ART makes little difference in transmission outcomes. In a comparison of 3 different triple antiretroviral combinations (AZT + 3TC + abacavir [ABC], AZT + 3TC + lopinavir/ritonavir [LPV/r], and AZT + 3TC + NVP) administered during pregnancy through planned weaning after 6 months of breastfeeding, all 3 regimens resulted in high rates of virologic suppression and a cumulative perinatal transmission rate of 1.1%.[15]

Antiretroviral therapy recommendations for pregnant mothers and their infants are shown in Box 28-2.

Box 28-1. World Health Organization Prevention of HIV Mother-to-Child Transmission Guidelines, 2013

All pregnant and breastfeeding women with HIV should initiate triple antiretrovirals (ARVs) (antiretroviral therapy [ART]), which should be maintained at least for the duration of mother-to-child transmission (MTCT) risk. Women meeting treatment eligibility criteria should continue lifelong ART (*strong recommendation, moderate-quality evidence*).

For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (*conditional recommendation, low-quality evidence*).

In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of MTCT risk has ceased (*conditional recommendation, low-quality evidence*).

From World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva, Switzerland: WHO Press; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en. Accessed July 15, 2015.

Box 28-2. Antiretroviral Therapy Recommendations for Pregnant Mothers and Their Infants

A once-daily fixed-dose combination of tenofovir disoproxil fumarate (TDF) + 3TC (or emtricitabine [FTC]) + efavirenz (EFV) is recommended as first-line antiretroviral therapy (ART) in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies to lifelong treatment and ART initiated for prevention of mother-to-child transmission and then stopped (*strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants*).

Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily nevirapine (NVP). If infants are receiving replacement feeding, they should be given 4 to 6 weeks of infant prophylaxis with daily NVP (or twice-daily zidovudine [AZT]). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (*strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding*).

From World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva, Switzerland: WHO Press; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en. Accessed July 15, 2015.

Safety of Antiretrovirals

In developing countries, health care practitioners and families commonly express concerns about antiretroviral safety in the developing fetus and newborn. While certain antiretroviral combinations have been shown unsafe for pregnant women (eg, stavudine plus didanosine is associated with lactic acidosis), they are generally felt to be safe for the fetus and newborn.[20–22] The Antiretroviral Pregnancy Registry longitudinally assesses the risk of birth defects associated with antiretrovirals. Based on prospective reports to the registry as of January 31, 2014, the overall proportion of birth defects was not significantly higher than those reported in the registry's 2 population-based comparators. With the exception of didanosine and nelfinavir, an analysis of individual drugs with sufficient data to allow for separate analyses detects no increases of concern in risk. The registry notes modest but statistically significant elevations of overall defect rates with didanosine and nelfinavir compared with population-based comparators; however, no pattern of defects has been detected, and the clinical relevance of this finding is unclear.[23]

Zidovudine, as part of ART, may cause anemia in infants and children, but clinically significant anemia during newborn prophylaxis is rare.[24] In addition, NVP prophylaxis is well tolerated by babies; toxicity was uncommon in trials of extended NVP (through 14 weeks).[25,26] However,

efavirenz (EFV) caused teratogenic effects in monkeys[27] and case reports showed neural tube and other birth defects in human newborns who were exposed to EFV in utero,[28,29] which led to the recommendation that it not be used in the first trimester of pregnancy.[13] The WHO recommends that NVP be substituted for EFV if it is realized that a woman taking EFV is in the first trimester of pregnancy.[13] However, a recent meta-analysis found no overall increased risk of birth defects among women exposed to EFV during the first trimester of pregnancy compared with exposure to other antiretroviral drugs. In this study, overall prevalence of birth defects with first-trimester EFV exposure was similar to that of the general population, but sample size was limited, preventing definitive conclusions as to the risk of neural tube defects and other rare outcomes.[30]

Infant Feeding

Avoidance of breastfeeding has long been part of standard approaches to prevention of MTCT, given that as much as 40% of perinatal HIV transmission may be because of breastfeeding.[11] This approach has proven successful in developed countries where perinatal HIV transmission has become rare,[12] as well as in many low- and middle-income settings. Thailand incorporated replacement feeding into its national approach to MTCT prevention since the 1990s, as did Botswana. Rates of perinatal transmission in both countries are now less than 5%,[31,32] with the success credited in part to national formula programs. However, providing free formula to infants as a part of MTCT prevention is not economically or logistically feasible in many developing countries. In addition, breastfeeding is recognized as one of the most powerful child survival interventions and a cornerstone to reduce younger-than-5-years mortality worldwide.[33]

The issue of infant feeding is further complicated, particularly in lower-income countries, in that prevention of HIV infection in an infant does not necessarily increase an infant's likelihood of survival. Studies in developing countries show serious morbidity and mortality risks associated with formula-feeding. In the Botswana Mashi trial, cumulative mortality from all causes at 7 months of age was significantly higher (9.3% versus 4.9%) in infants who were randomly assigned to formula-feeding versus those who were assigned to breastfeeding plus AZT. HIV-free survival at 18 months of age was equivalent between the 2 groups, showing that the early mortality increase seen with formula-feeding negates the benefits of reduced HIV transmission.[34]

A Kenyan study showed that formula-fed infants have higher early mortality than breastfed infants (11% versus 9%).[35] A South African

study showed cumulative 3-month mortality of 15.1% in infants who were given replacement feedings, whereas the corresponding rate in exclusively breastfed infants was only 6.1%.[36] Additionally, more than 22,000 Botswanan infants experienced diarrhea (compared with a little more than 9,000 for the same period in 2005), and the number of deaths in children younger than 5 years increased 20-fold during an outbreak of diarrhea in early 2006.[37] Virtually all the deaths that occurred during the outbreak were in formula-fed infants, which suggests a lack of protective immunity in formula-fed versus breastfed infants. This finding is consistent with the long-appreciated immunologic benefits of breastfeeding. Malnutrition and growth failure are also more common in formula-fed versus breastfed HIV-exposed infants.[38]

Recognizing this, WHO guidelines on HIV and infant feeding focus on the prevention of perinatal HIV transmission, as well as what strategy—breastfeeding or its avoidance—is most likely to result in HIV-free survival of those infants who are exposed to HIV. National health authorities are advised to make their decisions based on national epidemiologic trends, the coverage of prevention of MTCT and ART services, and the main local causes of maternal and child undernutrition and mortality.

This decision will favor breastfeeding in most lower-income countries. The WHO has clarified the conditions required to formula-feed safely (Box 28-3); however, these conditions are difficult to satisfy in most developing countries. Even in relatively wealthy settings, such as South Africa, the unavailability of formula at clinics was common during the time the country used formula provision as a standard part of its national prevention of MTCT program[39]; this practice has now been abandoned and breastfeeding recommended. Studies show other factors

Box 28-3. Conditions Needed for an HIV-Positive Woman to Safely Use Formula-Feeding

1. Safe water and sanitation are ensured at the household level and in the community.
2. The mother or other caregiver can reliably provide sufficient infant formula to support normal growth and development of the infant.
3. The mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhea and malnutrition.
4. The mother or caregiver can, in the first 6 months, exclusively give infant formula.
5. The family is supportive of this practice.
6. The mother or caregiver can access health care that offers comprehensive child health services.

From World Health Organization. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Recommendations for a Public Health Approach: 2010 Version.* Geneva, Switzerland: WHO Press; 2010. http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf. Accessed January 13, 2015.

not specifically included in WHO criteria to be associated with safe formula-feeding, such as a mother's disclosure of her HIV status.[40]

Recent evidence shows that the likelihood of HIV transmission via breastfeeding is markedly reduced when a mother is receiving ART or infants receive extended courses of NVP while breastfeeding when ART is not available for this aspect of MTCT prevention. Indeed, as mentioned previously (see Box 28-2), WHO recommends that all HIV-exposed infants who are breastfeeding receive prophylaxis. Exclusive breastfeeding is recommended for the first 6 months, after which complimentary foods are introduced and infants continue to breastfeed up to 12 months. Weaning, a time when the risk of the infant developing malnutrition rises precipitously, should occur over approximately 1 month, and breastfeeding should cease only when a safe diet and adequate nutrition without human milk can be ensured.

FOLLOW-UP OF THE HIV-EXPOSED INFANT

Prevention of perinatal HIV transmission does not end when an infant completes postnatal antiretroviral prophylaxis or is successfully weaned. In concert with a longitudinal, family-centered approach to care, mothers must have postpartum care and ongoing management of HIV infection, while infants must receive an assessment of HIV status, clinical monitoring, co-trimoxazole preventive therapy (CPT), and general infant care.

Diagnosis of HIV infection in exposed infants is of particular importance, as mortality is high in untreated HIV-infected children—as much as 50% by 2 years of age and 80% by 5 years of age.[41] Antiretroviral therapy reduces pediatric mortality considerably. The South Africa Children with HIV Early Antiretroviral Therapy study demonstrated a 75% decline in mortality for infants initiated on ART immediately after diagnosis,[42] and WHO now recommends that all infants younger than 60 months, regardless of clinical stage or CD4 count, receive ART. While year-on-year gains in ART coverage in children have been impressive (now totaling approximately 700,000), there remains a gap of more than 1 million children in need of ART not yet receiving it.[41] Increasing HIV testing opportunities for children is a critical priority in the global response to pediatric HIV, particularly in high-prevalence developing countries.

Antibody tests such as HIV enzyme-linked immunosorbent assay and rapid HIV tests are not suitable for diagnosing HIV in infants because maternal antibodies to HIV cross the placenta and are detectable in infants up to 18 months of age. Therefore, a positive HIV antibody test result in an infant younger than 18 months only indicates that an infant was perinatally exposed to HIV and may or may not be infected.

A virologic polymerase chain reaction (PCR) test must be used instead. While HIV DNA PCR is the gold standard for infant diagnosis, HIV RNA PCR is also sensitive and specific.[12]

In most developing countries, the first HIV DNA PCR test is performed at 4 to 6 weeks postpartum via dried blood spot collected from the infant's heel; this initial visit is also used to initiate CPT as well as give first immunizations. While WHO guidelines allow for an infant who was never breastfed to be considered definitively HIV negative after a single negative HIV DNA PCR test result (sensitivity and specificity >99% at age 6 weeks), some developing country guidelines require 2 negative tests. Breastfeeding infants must have repeat HIV DNA PCR testing 6 weeks after breastfeeding cessation.

Because more than 90% of 9-month-olds who do not have HIV have lost their maternal antibodies,[43] many developing countries use rapid testing for infants 9 months or older, with HIV DNA PCR tests performed only on those who are still antibody positive. In children older than 18 months, rapid antibody tests can be used for definitive HIV diagnosis, and most developing countries use a confirmatory rapid test at 18 months of age, regardless of prior test results, to demonstrate seroreversion (definitively HIV uninfected) or definitive HIV-infected status.

As mentioned earlier, mortality is high for untreated HIV-infected infants. Rapid disease progression is not uncommon. *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii* pneumonia) is often the first manifestation, which may occur before HIV infection is realized. Accordingly, all HIV-exposed infants should be placed on co-trimoxazole prophylaxis against *Pneumocystis* pneumonia until HIV infection is excluded and the infant is no longer at risk of HIV acquisition through breastfeeding. Co-trimoxazole, which is safe, inexpensive, and widely available, has benefits for HIV-infected children beyond *Pneumocystis* prevention, including prevention of *Toxoplasma* encephalitis (also seen with advanced HIV disease, usually in older children and adults), as well as non–HIV-related diseases, including malaria, severe bacterial infections, and diarrhea, which are responsible for much child mortality in developing countries.[44]

Data from Zambia show a 50% mortality reduction and significant reduction in children's hospital admissions when on CPT,[45] while Zimbabwean data demonstrate reduced deaths due to acute respiratory infection in HIV-infected infants younger than 6 months.[46] Accordingly, WHO advises CPT for all HIV-exposed infants and all HIV-infected infants and children in settings with high HIV prevalence, high infant mortality from infectious diseases, or limited health infrastructure.[44]

Despite the evidence and recommendations for CPT use, only 25% of HIV-exposed infants globally received CPT in 2012, and fewer than 25% in high-prevalence Eastern and Southern Africa. A clear need exists for scaling up this critical survival intervention.

The first set of routine immunizations, all of which are given to HIV-exposed infants, takes place during the first visit at 6 weeks of age. Given the propensity for substantial reactions,[47,48] bacille Calmette-Guérin (BCG) immunization is withheld from ill-appearing, HIV-exposed infants and from all HIV-infected infants. There is concern that immunizations given to HIV-infected infants prior to ART initiation (and subsequent immune reconstitution) may not generate long-lasting immunity. While recent data indicate children on ART may benefit from revaccination, more data from regions of high HIV prevalence are needed to determine the ideal timing and number of vaccine doses for each vaccine-preventable disease.[49]

HIV-exposed infants should be seen monthly during the first year of life, with repeat HIV testing at any point should HIV be suspected on clinical grounds. The WHO defined clinical criteria for presumptive diagnosis of severe HIV disease when virologic testing is not available.[50] Such a diagnosis is made when an infant is HIV antibody positive and an AIDS-indicator condition is present or the infant is symptomatic with 2 or more of oral thrush, severe pneumonia, or severe sepsis. Other factors supporting presumptive HIV diagnosis in an HIV-exposed infant include recent HIV-related maternal death, advanced maternal HIV disease, or a CD4 count less than 20%.

IDENTIFYING THE HIV-INFECTED CHILD NOT IDENTIFIED IN INFANCY

As mentioned, fewer than half of women globally, including in high-prevalence sub-Saharan Africa, are tested for HIV in pregnancy. It is likely that even today, most HIV-infected babies are born to mothers who were never tested for HIV and thus did not receive MTCT prevention interventions.[41] Not placed into post-prevention follow-up, these infants are at great risk of remaining unidentified and succumbing to HIV-related conditions and complications at an early age. When these HIV-infected children are identified, substantial HIV-related conditions and complications are often present. Targeted HIV testing strategies for infants and children are of paramount importance, particularly in high-prevalence settings.

Provider-initiated testing and counseling have been shown in many developing countries to yield higher rates of pediatric testing than older approaches, such as relying on families to approach health care

professionals asking to be tested.[51] Efforts to make HIV testing part of health care routines are also gaining ground in many lower-income countries. Whatever the baseline HIV prevalence in a community, prevalence will be higher in settings where children are seeking health care and particularly where they are ill. Routine testing in health care settings, including pediatric wards, malnutrition units, and even immunization clinics, yields large numbers of HIV-infected patients,[52–54] particularly in high-prevalence settings. The willingness of health care workers to promote testing is a key factor influencing its utilization.[55] Therefore, training health care workers to increase their comfort level in discussing pediatric HIV with families is crucial.

Creative approaches toward increasing the identification of HIV-exposed and HIV-infected children may pay dividends. For example, in Malawi, the innovative strategy of incorporating volunteer parents of HIV-infected children to promoting routine testing on a busy pediatrics ward was shown to markedly increase the number of children tested, identified, and enrolled into care compared with a standard approach using counselors.[56] Another program in Malawi uses health care workers to improve identifying HIV-infected and HIV-exposed children and referring them earlier to community health centers. In this program, the approach of assigning a dedicated worker to HIV-infected pregnant women in the community has been particularly effective in improving outcomes for HIV-exposed infants.[57]

Health care workers should operate with a high index of suspicion for HIV infection when encountering ill children in developing countries, particularly where HIV is prevalent. Certain clinical findings suggest HIV infection, especially when children were orphaned or have mothers with known HIV infection. Integrated Management of Childhood Illness (IMCI) is a WHO/UNICEF strategy directed at reducing mortality in children younger than 5 years by improving health care at a primary level.[58] The IMCI algorithm for suspected symptomatic HIV infection focuses on whether the child has 1 or more of 4 conditions (pneumonia, persistent diarrhea, ear discharge, very low weight for age) or 3 findings (oral thrush [in children >3 months], parotid enlargement [typically bilateral], generalized lymphadenopathy).[59] Positive findings direct the clinician into the algorithm, where the likelihood of HIV infection is classified. It should be noted that in the absence of HIV testing, the IMCI algorithm is not a sensitive tool for diagnosing HIV infection in children[60] but is very useful as a prompt for clinicians to suggest testing. Table 28-1 lists several physical findings that suggest HIV infection in children.

Table 28-1. Association of Physical Findings With Likelihood of HIV Infection in a Child, Particularly in Settings of Moderate to High HIV Prevalence

HIV VERY LIKELY	SUGGESTIVE OF HIV INFECTION	SUSPICIOUS FOR HIV INFECTION BUT ALSO COMMONLY SEEN IN HIV-UNINFECTED CHILDREN
Kaposi sarcoma *Pneumocystis* pneumonia Severe retinitis Persistent, severe diarrhea Esophageal candidiasis Invasive salmonellosis Cryptococcal meningitis Herpes zoster (multidermatomal)	Generalized lymphadenopathy Hepatosplenomegaly[a] Parotid enlargement Persistent or recurrent fever Recurrent, severe bacterial infection Persistent or recurrent oral candidiasis Persistent, unexplained dermatitis Loss of milestones Neurologic dysfunction	Persistent or recurrent upper respiratory infections, including otitis media Failure to thrive Tuberculosis Recurrent diarrhea Severe pneumonia Unexplained sepsis

[a] Areas non-endemic for malaria.

Adapted from African Network for the Care of Children Affected by HIV/AIDS. In: Tindyebwa D, Kayita J, Musoke P, et al. *Handbook on Paediatric AIDS in Africa.* 3rd ed. Kampala, Uganda: African Network for the Care of Children Affected by HIV/AIDS – ANECCA; 2014; and Baylor International Pediatric AIDS Initiative. *HIV Curriculum for the Health Professional.* 4th ed. Houston, TX: Baylor College of Medicine; 2010.

STAGING, DETERMINING ELIGIBILITY FOR ANTIRETROVIRAL THERAPY, AND COMMON MANIFESTATIONS OF HIV INFECTION

Once a child is identified as HIV infected, the clinical approach focuses on determining the child's eligibility for ART. Current recommendations suggest that all children younger than 60 months be initiated on ART at the time of diagnosis regardless of clinical stage or CD4 count. Children older than 60 months must meet criteria based on clinical stage and CD4 count for ART initiation. Box 28-4 shows WHO recommendations for initiating ART in children.

Generally, clinical stages as determined by WHO (Box 28-5) reflect the natural history of HIV infection in an individual over time. Table 28-2 lists specific conditions included in each clinical stage. Accurate clinical staging depends on the clinician taking a careful, detailed history and performing a thorough physical examination.

HIV pathophysiology centers on its effect on $CD4^+$ T cells. HIV leads to CD4 reduction with concomitant immunosuppression through a variety of mechanisms. Stage 4 conditions are notable for the presence

Box 28-4. World Health Organization Recommendations for Initiating Antiretroviral Therapy in Children

Antiretroviral therapy (ART) should be initiated in all children younger than 5 years infected with HIV, regardless of World Health Organization (WHO) clinical stage or CD4 cell count.

- Infants diagnosed in the first year of life (*strong recommendation, moderate-quality evidence*)
- Children infected with HIV 1 year to younger than 5 years (*conditional recommendation,*[a] *very low-quality evidence*)

ART should be initiated in all HIV-infected children 5 years and older with CD4 cell count less than or equal to 500 cells/mm^3, regardless of WHO clinical stage.

- CD4 count less than or equal to 350 cells/mm^3 (*strong recommendation, moderate-quality evidence*)
- CD4 count between 350 and 500 cells/mm^3 (*conditional recommendation,*[b] *very low-quality evidence*)

ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count (*strong recommendation, moderate-quality evidence*).

ART should be initiated in any child younger than 18 months who has been given a presumptive clinical diagnosis of HIV infection (*strong recommendation, low-quality evidence*).

[a] This recommendation is conditional because of the lack of evidence supporting earlier initiation in this age group, but this approach is expected to provide significant programmatic advantages in settings with limited access to immunologic testing, high burden of pediatric HIV disease, and low ART coverage among children because simplifying eligibility criteria for initiating ART is likely to increase ART coverage in children infected with HIV and improve their health outcomes.

Priority for ART initiation should be given to children younger than 2 years, regardless of WHO clinical stage or CD4 cell count, because of higher mortality risk, and to children between 2 and 5 years of age with advanced disease (WHO HIV clinical stages 3 and 4) or with CD4 count less than or equal to 750 cells/mm^3 or less than 25%, whichever is lower, regardless of WHO clinical stage (*strong recommendation, very low-quality evidence*).

[b] This recommendation is conditional because of the lack of evidence in this population for individual benefit as a result of initiating ART earlier; however, this approach is expected to provide significant programmatic advantages in settings with high coverage of pediatric ART and a programmatic need to align with ARV drug recommendations for adults. If this recommendation is not adopted, ART should be initiated at WHO HIV clinical stages 3 and 4 or with CD4 count less than or equal to 350 cells/mm^3 regardless of WHO clinical stage (*strong recommendation, very-low-quality evidence*).

From World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva, Switzerland: WHO Press; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en. Accessed July 15, 2015.

Box 28-5. World Health Organization Clinical Staging of HIV Infection

1. Asymptomatic
2. Mild signs and symptoms of HIV infection
3. Substantial signs and symptoms of HIV infection
4. Severe illness due to HIV infection, including most opportunistic infections

From World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. Geneva, Switzerland: WHO Press; 2007. http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf. Accessed June 10, 2015.

Table 28-2. World Health Organization Clinical Staging of HIV/AIDS for Children With Confirmed HIV Infection

CLINICAL STAGE 1	CLINICAL STAGE 2	CLINICAL STAGE 3	CLINICAL STAGE 4
• Asymptomatic • Persistent generalized lymphadenopathy	• Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Extensive wart virus infection • Extensive molluscum contagiosum • Fungal nail infections • Recurrent oral ulcerations • Unexplained persistent parotid enlargement • Lineal gingival erythema • Herpes zoster • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, or tonsillitis)	• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhea (≥14 days) • Unexplained persistent fever (>37.5°C intermittent or constant, for >1 month) • Persistent oral candidiasis (after 6–8 weeks of life) • Oral hairy leukoplakia • Acute necrotizing ulcerative gingivitis or periodontitis • Lymph node tuberculosis • Pulmonary tuberculosis • Severe recurrent bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease, including bronchiectasis	• Unexplained severe wasting, stunting, or severe malnutrition not responding to standard therapy • *Pneumocystis* pneumonia • Recurrent severe bacterial infections (eg, empyema or pyomyositis bone or joint infection, meningitis [excluding pneumonia]) • Chronic herpes simplex infection (orolabial or cutaneous of >1 month's duration or visceral at any site) • Extrapulmonary tuberculosis • Kaposi sarcoma • Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) • Central nervous system toxoplasmosis (after 1 month of life) • HIV encephalopathy • Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at older than 1 month • Extrapulmonary cryptococcosis (including meningitis) • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) • Chronic cryptosporidiosis • Chronic isosporiasis

Table 28-2. World Health Organization Clinical Staging of HIV/AIDS for Children With Confirmed HIV Infection, continued

CLINICAL STAGE 1	CLINICAL STAGE 2	CLINICAL STAGE 3	CLINICAL STAGE 4
		• Unexplained anemia (8 g/dL), neutropenia (<0.5 × 10^9 per L), or chronic thrombocytopenia (<50 x 10^9 per L)	• Disseminated nontuberculous mycobacterial infection • Cerebral or B cell non-Hodgkin lymphoma • Progressive multifocal leukoencephalopathy • Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy • Additional specific conditions included in regional classifications (eg, reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in the WHO region of the Americas, penicilliosis in Asia, and HIV-associated rectovaginal fistula in Africa)

Abbreviation: WHO, World Health Organization.

Adapted from World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children.* Geneva, Switzerland: WHO Press; 2007. http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf. Accessed June 10, 2015.

of opportunistic infections not generally seen in immunocompetent individuals. Whereas the mean time from infection to immunosuppression in adults is several years, HIV typically causes a much swifter drop in CD4 counts in children. This drop varies by age, with infants being notable for very early immunosuppression after infection (months) to older children, where 1 to 3 years of age is more common. In all age groups, there are those who are slow in progressing who tolerate HIV infection for long periods without developing clinically advanced disease or immunosuppression; however, this is much less common in children than adults, and all of the factors influencing this phenomenon remain to be determined.

The WHO produced guidelines for managing common illnesses, including HIV-associated conditions, in hospitals with limited resources; an excellent resource for those practicing in developing countries is *Pocket Book of Hospital Care for Children,* 2nd Edition.[61] While details on the diagnosis and management of the many HIV-associated conditions listed in Table 28-3 are beyond the scope of this chapter, some particularly important conditions deserve mention.

Generalized lymphadenopathy, especially if persistent, suggests HIV infection and represents early HIV clinical manifestation in a child

Table 28-3. World Health Organization Recommendations for Co-trimoxazole Preventive Therapy for HIV-Exposed and HIV-Infected Infants and Children

GENERAL RECOMMENDATION FOR MOST SETTINGS	IN SETTINGS WITH HIGH HIV PREVALENCE, HIGH INFANT MORTALITY FROM INFECTIOUS DISEASES, OR LIMITED HEALTH INFRASTRUCTURE
All exposed infants <1 y regardless of clinical or immunologic staging, starting at 4–6 wk HIV-exposed breastfeeding children, regardless of clinical or immunologic staging All children 1–5 y for clinical stages 2, 3, 4, *or* CD4 percentage <25 All patients >5 y if ● Clinical stage 2, 3, 4 (if no CD4) ● CD4 <350 cells/μL ● Clinical stage 3 or 4 (regardless of CD4)	CPT for *all* children born to HIV-positive mothers CPT for *all* HIV-positive children <5 y, regardless of symptoms CPT for *all* symptomatic HIV-positive children ≥5 y

Abbreviation: CPT, co-trimoxazole preventive therapy.

Adapted from World Health Organization, United Nations Children's Fund. *Co-trimoxazole Prophylaxis for HIV-Exposed and HIV-Infected Infants and Children: Practical Approaches to Implementation and Scale Up.* Geneva, Switzerland: WHO Press; 2009. http://www.unicef.org/aids/files/CotrimoxazoleGuide_2009.pdf. Accessed June 10, 2015.

(stage 1). Stage 2 conditions are notable for being common and nonspecific and are certainly seen in non–HIV-infected children as well. However, their recurrence or persistence is notable with HIV infection. For example, it is not uncommon for an HIV-infected child's health record to note multiple outpatient visits for recurrent otitis media, sinusitis, or bronchitis prior to HIV infection ultimately being diagnosed. Persistent hepatosplenomegaly outside of malaria-endemic areas is also characteristic of HIV infection. Health care workers are taught to recognize such recurrent presentations as indicative of HIV infection and to offer testing accordingly in HIV-prevalent areas.

Several skin conditions are notable for the presence of HIV infection and are unusual in its absence. Papular pruritic eruptions, extensive plane warts, and angular cheilitis (in adolescents) are particularly characteristic; having 3 or more discrete skin conditions and a history of recurrent skin rashes or angular cheilitis have been associated with immunosuppression.[62]

Malnutrition is a very common and important feature of advancing HIV infection that is multifactorial in nature, including the additional metabolic demand HIV infection places on the child, malabsorption, and the synergistic effect of food insecurity all too common in HIV-prevalent areas. Clinicians should note that the presence of even just a moderate degree of otherwise unexplained malnutrition (ie, due to poor or inadequate feeding, food insecurity, or other infections and not responding to standard management) makes a child clinical stage 3 and qualified for ART, regardless of age or CD4 counts. Moderate malnutrition is defined by low weight-for-age *z* scores between 2 and 3, while severe malnutrition (stage 4) is defined by weight-for-height *z* scores (wasting) or height-for-age *z* scores (stunting) less than 3 or edema in the presence of malnutrition.

The effect of HIV on a child's developing nervous system can be profound. While cognitive delay and difficulty with school are common findings in HIV-infected children, more serious conditions can occur. HIV encephalopathy (stage 4) is a severe manifestation of the effect of HIV on the brain and is heralded by several features, including failure to attain or loss of developmental milestones or intellectual ability, symmetric motor deficits accompanied by other neurologic findings (ie, ataxia, gait disturbances, abnormal reflexes, or paresis), and impaired brain growth. Loss of milestones in an infant or young child is a particularly common presentation of HIV encephalopathy in developing countries and, while not specific to HIV infection, should raise a strong warning for the possibility in areas where HIV infection is common. It

is not uncommon for signs and symptoms of HIV encephalopathy to resolve considerably with ART.

Many different opportunistic infections further characterize clinical stage 4 and represent the presence of severe immunocompromise; all are clinical indications for ART. While the highest incidence of *Pneumocystis* pneumonia is seen among HIV-infected infants, it is also common in immunocompromised HIV-infected children beyond infancy, particularly when CPT is not being taken. A normal chest radiograph is often seen, even when tachypnea, dyspnea, and hypoxia are prominent. Table 28-3 notes WHO recommendations for CPT use. Co-trimoxazole preventive therapy should be administered daily; intermittent CPT has been associated with higher rates of invasive bacterial disease than daily CPT.[63] *Pneumocystis* pneumonia treatment includes a 21-day course of high-dose cotrimoxazole.

Cryptosporidium parvum causes severe and persistent diarrhea in immunocompromised children, and case fatality rates can be high. While nitazoxanide has been shown to effectively treat *Cryptosporidium* in immunocompetent children and adults,[64] response to nitazoxanide has not been consistently demonstrated in immunocompromised children. Even high doses given for up to 28 days have been ineffective in clinical trials in sub-Saharan Africa.[65] *Cryptosporidium* generally responds to the immune restoration effected by ART.

While rarer in children than adults, cryptococcal meningitis presents similarly in both groups as a subacute but severe meningitis and can be life threatening. Ideal treatment includes an initial therapy of amphotericin B plus 5-flucytosine (5FC) for 14 days, followed by oral fluconazole for 8 to 10 weeks, and then continuation therapy. Where 5FC is not available, oral fluconazole should be combined with amphotericin B in initial therapy.[66] Amphotericin B is not available in many developing countries, and oral fluconazole is the only agent available to treat cryptococcal meningitis; case fatality rates tend to be higher with this approach.[66] Markedly increased intracranial pressure is common with cryptococcal meningitis, with opening pressure often quite high on initial lumbar puncture. Intracranial pressure should be monitored with repeated lumbar puncture, especially during the first 2 weeks of therapy. Fluconazole is continued as secondary prophylaxis after treatment until immune restoration takes place with ART and patients are stable on therapy for several months. Guidelines for primary prophylaxis in children and for discontinuation of secondary prophylaxis in children 5 years and younger are not clearly defined.

Kaposi sarcoma is an unusual but common (especially in sub-Saharan Africa) malignant manifestation of an infection with human herpesvirus 8, primarily involving skin but also associated with severe disease in the lungs, gastrointestinal tract, liver, and spleen. Mucocutaneous lesions are usually a ruddy brown or purple and may be flat, raised, or nodular on any skin surface or inside the mouth. Lymphadenopathic forms may also occur. Visceral disease is frequently fatal. Antiretroviral therapy is often effective for Kaposi sarcoma, but chemotherapy is frequently required, especially when there is visceral involvement.

Globally, for HIV-infected and uninfected children alike, severe bacterial infections such as diarrhea and pneumonia are responsible for most child deaths outside the neonatal period. In a given area, rates of diarrhea tend to be more common in HIV-infected children than uninfected children and bacterial etiologies are common. Interventions directed at diarrhea prevention may be particularly likely to benefit HIV-infected children.[67]

HIV-infected children experience pneumonia more frequently than uninfected children and have a higher risk of severe disease even when on ART and no longer immunocompromised.[68] Standard approaches to managing pneumonia in children require modification in areas of high HIV prevalence with the addition of *Pneumocystis* pneumonia treatment (high-dose CPT) to empiric broad-spectrum antibiotics for infants or children not taking *Pneumocystis* prophylaxis.[68]

While duration of diarrhea and pneumonia episodes tends to be longer in HIV-infected children, short-term multi-micronutrient supplementation containing vitamins A, B, C, D, E, and folic acid, along with iron, copper, and zinc, has been noted in HIV-infected children to reduce duration of illness and length of hospitalization associated with these 2 important diagnoses.[69]

ANTIRETROVIRAL TREATMENT

While nutritional support and prophylaxis against opportunistic infections are very important for HIV-infected children, effective ART is the key to restoring health and its long-term maintenance. Highly active ART has been available in developed countries since the latter part of the 1990s but only recently became freely available in many developing countries, including high-prevalence sub-Saharan Africa. Pediatric ART programs have generated notable successes across diverse developing countries.[70–73] Even in rural areas and primary care settings in resource-poor countries, good clinical outcomes of ART on HIV-infected children have been noted.[74,75] Antiretroviral therapy reduces incidences of opportunistic infections and tuberculosis (TB) in HIV-infected children[76] and

assists in restoring normal growth.[77] As mentioned earlier, ART dramatically reduces the mortality for HIV-infected children.[2] In resource-limited settings, more than half of the deaths of children who were on ART occur in the first 3 months[73]; young age, malnutrition, and low CD4 counts are associated with a higher risk of early death when on ART.[72,78] Early HIV diagnosis and treatment are clearly important, but the number of infants and young children enrolled in most pediatric ART programs is low in developing countries[74]; therefore, early identification and follow-up of HIV-exposed infants is critical.

Antiretroviral therapy is not curative. Effective ART results in prolonged suppression of HIV replication, which allows immune function to be restored in most cases.

Antiretroviral therapy efficacy is measured through 3 parameters with many clinical benefits: clinical, immunologic, and virologic. Immunologically, CD4 counts generally rise, often to non-immunosuppressed levels. Virologically, HIV RNA levels decline and are ideally undetectable within the first 6 months of ART initiation. Therefore, failure to achieve these parameters or regression after initial response are the hallmarks of ART failure.

Eligibility and Choice of Regimen

Clinical and immunologic parameters are used to determine ART eligibility for children older than 60 months, while it is recommended that ART be initiated in infants and children younger than 60 months at the time of diagnosis, given the unreliability of clinical and immunologic markers of disease progression in young children.

Based on the mechanism of action, there are multiple categories of antiretrovirals. Unfortunately, options for children remain limited compared with options for adults, particularly in developing countries. Many existing antiretrovirals do not have pediatric formulations or approval for use in children. The WHO has placed emphasis on increasing pediatric antiretroviral options.

To lower the chance of resistance, antiretrovirals are used in combination with at least 3 different antiretrovirals active at 2 or more distinct sites of action in the HIV life cycle. Standard ART combinations generally include a backbone of 2 nucleoside reverse-transcriptase inhibitors plus a non-nucleoside reverse-transcriptase inhibitor or a protease inhibitor. Based on availability and feasibility considerations in resource-limited settings, WHO recommends choice of ART in children be stratified by age, with children younger than 3 years following certain recommendations and children older than 3 years following others. These are summarized in Box 28-6.

Box 28-6. World Health Organization Recommendations for Antiretroviral Therapy Strategized by Age in Children

ANTIRETROVIRAL THERAPY FOR CHILDREN <3 y

A lopinavir/ritonavir (LPV/r)-based regimen should be used as first-line antiretroviral therapy (ART) for all children infected with HIV <3 y (36 mo), regardless of non-nucleoside reverse-transcriptase inhibitor (NNRTI) exposure. If LPV/r is not feasible, treatment should be initiated with a nevirapine (NVP)-based regimen (*strong recommendation, moderate-quality evidence*).

Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virologic suppression is sustained (*conditional recommendation, low-quality evidence*).

For infants and children infected with HIV who are <3 y, abacavir (ABC) + lamivudine (3TC) + zidovudine (AZT) is recommended as an option for children who develop tuberculosis (TB) while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted (*strong recommendation, moderate-quality evidence*).

For infants and children infected with HIV who are <3 y, the NNRTI backbone for an ART regimen should be ABC or AZT + 3TC (*strong recommendation, low-quality evidence*).

ANTIRETROVIRAL THERAPY FOR CHILDREN ≥3 y

For children infected with HIV who are ≥3 y (including adolescents), efavirenz (EFV) is the preferred NNRTI for first-line treatment and NVP is the alternative (*strong recommendation, low-quality evidence*).

Special note: In determining the choice of NNRTI for first-line therapy, national programs should consider the dosing characteristics of EFV (once daily) and NVP (twice daily) and how this aligns with the NNRTI backbone. For example, NVP may be a better choice if the recommended regimen is a twice-daily option using a fixed-dose combination.

For children infected with HIV who are 3–<10 y (or adolescents <35 kg), the NNRTI backbone for an ART regimen should be one of the following, in preferential order:

- ABC + 3TC
- AZT or tenofovir disoproxil fumarate (TDF) + 3TC (or emtricitabine [FTC])

(*Conditional recommendation, low-quality evidence*).

Special note: Consideration should be given to the relative merits of ABC versus TDF versus AZT for this population. There is no definitive evidence to make a preferred recommendation, and each option has its respective risks and benefits. ABC can be used once daily, is available across age groups as a fixed-dose combination with 3TC, and harmonizes with TDF from a resistance perspective. AZT has been widely used and is available as dual and triple fixed-dose combinations with NVP but is dosed twice daily and can cause severe anemia. TDF has recently been approved for use in children; advantages include once-daily dosing. However, pediatric TDF formulations are not widely available, experience with TDF in children is limited, and there are concerns about the long-term effects of bone toxicity. Considerations that support the adoption of TDF as the national recommendation include the national program use of TDF for adults and pregnant women and a suitable TDF fixed-dose combination formulation for children being available.

For adolescents infected with HIV (10–19 y) weighing ≥35 kg, the NNRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order:

- TDF + 3TC (or FTC)
- AZT + 3TC
- ABC + 3TC

Box 28-6. World Health Organization Recommendations for Antiretroviral Therapy Strategized by Age in Children, continued

(*Strong recommendation, low-quality evidence*).

Special note: TDF-containing fixed-dose combinations are currently only available in adult, un-scored tablets for once-daily use. At or above 35 kg, the dose of TDF in adult dual and triple fixed-dose combinations and the dose of EFV in adult triple fixed-dose combinations are acceptable for use in adolescents. ABC or boosted Protease inhibitors can be used in special circumstances.

From World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva, Switzerland: WHO Press; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en. Accessed July 15, 2015.

Adherence

Adherence to therapy is the critical factor in determining how well a child does on ART. Adherence between 95% and 105% of expected doses is required to maintain effect without developing antiretroviral resistance (seen with lower rates of adherence) or toxicity (more likely with antiretroviral overdosing); adherence rates for each antiretroviral should be calculated and any discrepancies addressed at each visit.

Achieving good adherence is not easy for children and families. Taking multiple medications at different times, sometimes in coordination with meals, on a perpetual basis is complex. Early and ongoing counseling is critical, as is the responsibility of the entire health care team. Problems with transportation to the clinic, lack of support systems, and stigma should ideally be addressed prior to initiating ART and anticipated during ongoing supportive adherence counseling for those patients on ART. An age-appropriate disclosure process is an important component of adherence support, particularly for older children.

Monitoring

Infants and children on ART are followed for clinical, immunologic, and virologic response at regular intervals. The potential for ART to cause toxicity is also monitored. Early responses to ART are especially important. A gain in CD4 percentage in the first 6 months of ART has shown to predict subsequent ART outcomes, as has weight gain; children who respond poorly in these parameters early on are at higher risk of viral non-suppression, treatment failure, and death.[79]

Ideally, baseline values for viral load, CD4, hemoglobin, liver enzymes, and blood urea nitrogen and creatinine should be obtained prior to ART initiation and followed on a regular basis at least every

6 months, often more frequently early on, and as determined by the presence of symptoms or need to follow up on any toxicity noted.

Antiretrovirals commonly used in developing countries have characteristic toxicities: anemia with AZT; hepatitis and allergic skin reactions, including Stevens-Johnson syndrome (rarely), with NVP and EFV; lipodystrophy and peripheral neuropathy (less commonly in children than adults) with stavudine; severe systemic hypersensitivity (although less commonly in African children)[80] with ABC; dyslipidemia with LPV/r; renal insufficiency with tenofovir disoproxil fumarate (TDF); and psychologic side effects with EFV. Management of specific toxicities depends on their severity; single-drug substitutions (swaps) may be carried out when necessary, such as NVP for EFV-associated psychologic effects. Severe toxicity may merit complete ART suspension. Lactic acidosis can be seen with any ART regimen (generally after >4 months on ART) but is most common with regimens containing stavudine or didanosine that are no longer recommended. Management is supportive.

Data from large pediatric treatment programs in resource-limited settings have shown toxicity-related ART regimen change to be uncommon, which generally suggests good tolerability of WHO-recommended first-line regimens, including those containing NVP.[81,82]

Treatment Failure

Therapy is changed to second-line treatments when first-line ART fails; however, these treatments are not consistently available in all developing countries. While national policies differ among developing countries, the WHO defines ART failure as outlined in Box 28-7.

- *Clinical failure:* Appearance or reappearance of WHO stage 3 or 4 events (clinical manifestations)
- *Immunologic failure:* Developing or returning to age-related immunologic thresholds

The importance of ensuring treatment adherence for a child failing ART is vital. Most treatment failure is due to non-adherence, and many failing children's therapy can be effective (even on a current line of therapy) if adherence can be restored. Changing therapy lines when children are non-adherent will swiftly lead to failure of the second-line regimen, again due to non-adherence.

Treatment-adherent children who are failing therapy are presumed to have antiretroviral resistance. Proving this with a resistance test, while perhaps ideal, is not essential; effective second-line regimens can be predicted from first-line drug exposures, as resistance tests are not available in many resource-limited settings. Second-line therapies use at least 2 drugs expected to be effective with LPV/r generally included in place

Box 28-7. World Health Organization Definition of Antiretroviral Therapy Failure

Viral load is recommended as the preferred monitoring approach to diagnose and confirm antiretroviral treatment failure (*strong recommendation, low-quality evidence*).

If viral load is not routinely available, CD_4 count and clinical monitoring should be used to diagnose treatment failure (*strong recommendation, moderate-quality evidence*).

Special notes: Treatment failure is defined by a persistently detectable viral load exceeding 1,000 copies/mL (ie, 2 consecutive viral load measurements within a 3-month interval, with adherence support between measurements) after at least 6 months of using antiretroviral drugs. Viral load testing is usually performed in plasma; however, certain technologies that use whole blood as a sample type, such as laboratory-based tests using dried blood spots and point-of-care tests, are unreliable at this lower threshold, and where these are used, a higher threshold should be adopted.

Viral load should be tested early after initiating antiretroviral therapy (at 6 months) and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD_4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm virologic failure where possible.

From World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva, Switzerland: WHO Press; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en. Accessed July 15, 2015.

of NVP or EFV, and vice versa, and ABC or AZT in place of the other. Lamivudine is maintained, as most resistant viruses have a particular mutation to 3TC (known as M184V) that reduces their pathogenicity; maintaining 3TC will help maintain this less virulent-resistant strain of HIV. Newer antiretrovirals, such as darunavir (latest-generation protease inhibitor) and raltegravir (integrase inhibitor), while not part of standard ART approaches in developing settings, are used in some settings, where available, as part of salvage therapy after second-line ART failure.[83]

Immune Reconstitution Syndrome

Immune reconstitution syndrome (IRS) is a common complication of ART in the developing world in which a patient develops a paradoxic worsening of symptoms soon after initiating ART. Immune reconstitution syndrome is caused by ART awakening the child's immune system in the presence of an occult infection (often an opportunistic infection) not clinically apparent at the time of ART initiation, to which the awakened immune system reacts. Immune reconstitution syndrome frequently resembles the naturally occurring infection itself, such that, for example, a reaction to occult pulmonary TB after initiating ART presents with pulmonary symptoms and a reaction to occult central nervous system (CNS) cryptococcal infection presents with neurologic symptoms.

Other common underlying infections unmasked by ART are hepatitis C, cytomegalovirus, and varicella-zoster virus. Reactions to BCG vaccine are also common.[84]

Immune reconstitution syndrome occurs in as many as 40% of HIV-infected patients with ART initiations,[85] usually within 12 weeks of therapy initiation. Immune reconstitution syndrome is more common with advanced HIV disease, particularly when initial CD4 counts are quite low; improvement in CD4 count in concert with symptoms is a hallmark of IRS diagnosis. Immune reconstitution syndrome management depends on its severity; while generally mild and self-limited, IRS can be life threatening. Treating the underlying infection (eg, TB, *Cryptococcus*) is essential. Antiretroviral treatment can be continued in most cases. Steroids to control IRS-associated inflammatory processes may be required in more serious cases; ART is discontinued when life-threatening IRS (particularly pulmonary and CNS) is present.

Scaling Up Pediatric Antiretroviral Therapy Programs

Children are generally underrepresented in ART programs in developing countries compared with adults. Children and those living in rural areas have been specifically identified as challenges to the goal of universal access to ART.[2,86] Particularly where there is high HIV prevalence and a limited number of practitioners, physician-based models of care are unlikely to provide the universal access to HIV care and treatment that is required. Task shifting is an increasingly used method for addressing such human-resource limitations and for facilitating decentralization of services. While legitimate concerns exist over the quality of task-shifted care,[87] many developing countries have few options other than task shifting for immediate rapid scale-up of care and treatment programs.[7,88] Shifting of tasks to nurses and other nonphysician clinicians in Africa in the care and treatment of HIV (especially ART initiation and monitoring) has generally been favorable[89] and shown to increase the number of patients on ART and aid decentralization of services[88–90]; however, appropriate training and support for task-shifted personnel is crucial. For example, in a South African study, ART monitoring by a trained nursing cadre was non-inferior to that monitored by physicians,[91] while the quality of HIV care provided by nonphysicians in Mozambique was substandard, leading to the revision of nonphysician scope of practice and training.[92] In high-prevalence settings of pediatric HIV, effective strategies to rapidly develop quality, sustainable, task-shifted capacity for care are urgently needed. Clinical side-by-side mentoring of nonphysicians by skilled practitioners is used in some developing countries, including rural primary health care clinics.[93,94]

IMPORTANT COINFECTIONS

Tuberculosis

Tuberculosis is by far the most important coinfection in HIV-infected individuals. After being on the retreat for decades in the face of improved public health conditions in many lower-income countries, TB has surged in recent years, particularly in areas of high HIV prevalence. Tuberculosis is well-adapted to take advantage of immunosuppressive effects of HIV on individuals and the strain placed on national health systems by the HIV epidemic; where resources are limited, health authorities struggle with the challenge of addressing twin epidemics. Consequently, TB coinfection with HIV is common. In some countries, HIV prevalence in newly diagnosed TB cases exceeds 50%, and in HIV-prevalent areas, it is recommended to screen all new TB diagnoses for the presence of HIV infection.[95]

HIV-infected children are particularly susceptible to severe forms of TB, including TB meningitis, which has a high mortality rate. Adding to this susceptibility is the fact that while BCG protects against severe forms of TB in young children, it is not given to HIV-infected infants because of the risks of disseminated BCG disease (which carries a mortality rate >70%)[47]; data also suggest that due to HIV effect on T-cell response in infected infants, BCG may offer little, if any, benefit to HIV-infected infants.[48] Symptomatic HIV-exposed infants are also not offered BCG, while healthy-appearing HIV-exposed infants are immunized.

While treatment of TB in HIV-infected children is the same as in noninfected children, there are special considerations with the coadministration of ART with antituberculosis drugs (Table 28-4). Rifampicin can lower levels of NVP and LPV/r below therapeutic margins, increasing the chance of resistance developing to these antiretrovirals. Accordingly, when co-therapy is given, consideration is given to triple nucleoside regimens (AZT + 3TC + ABC) or to the substitution of EFV for NVP (not for children <3 years who weigh <10 kg, for whom EFV is not indicated) and, in some cases, for LPV/r, or additional ritonavir to LPV/r, to achieve the full therapeutic dose. Close scrutiny for the development of hepatotoxicity is important given the propensity of antituberculosis therapy, EFV, and LPV/r to affect the liver.

Extrapulmonary forms of TB (eg, lymph node, abdominal, CNS) are more common in HIV-infected children; clinicians practicing in HIV- and TB-prevalent areas should maintain a high index of suspicion for both. In many developing countries, diagnostic modalities for TB diagnosis are limited, and treatment is often initiated based on clinical

Table 28-4. Recommended Regimens for Children and Adolescents Initiating Antiretroviral Therapy While on Tuberculosis Treatment

Recommended regimens for children and adolescents initiating ART while on TB treatment[a,b]		
Younger than 3 years		Two NRTIs + NVP, ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[c]
3 years and older		Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)[c]
Recommended regimen for children and infants initiating TB treatment while receiving ART[a]		
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)	Younger than 3 years	Continue NVP, ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[c]
	3 years and older	If the child is receiving EFV, continue the same regimen If the child is receiving NVP, substitute with EFV or Triple NRTI (AZT + 3TC + ABC)[c]
Recommended regimen for children and infants initiating TB treatment while receiving ART[a]		
Child on standard PI-based regimen (two NRTIs + LPV/r)	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC)[c] or Substitute NVP for LPV/r, ensuring that dose is 200 mg/m^2 or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose[d]
	3 years and older	**If the child has no history of failure of an NNRTI-based regimen:** Substitute with EFV[e] or Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose[d] **If the child has a history of failure of an NNRTI-based regimen:** Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r consider adding RTV to achieve the full therapeutic dose[d] Consider consultation with experts for constructing a secondline regimen

Table 28-4. Recommended Regimens for Children and Adolescents Initiating Antiretroviral Therapy While on Tuberculosis Treatment, continued

[a] Ensure optimal dosing of rifampicin based on new dosing guidelines (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

[b] Substitute ARV drugs based on an age-appropriate ARV regimen in line with nationally recommended first-line ART.

[c] Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI- or NNRTI-based regimen should be restarted when rifampicin-based therapy ends. Based on the findings from the ARROW trial (*163*), this regimen should be considered as the preferred option for children younger than three years who are receiving a LPV/r-based regimen when starting TB treatment. The United States Food and Drug Administration approval for the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg offers a potential alternative to the triple NRTI approach. An EFV-based regimen in children under 3 years is still not recommended as pharmacokinetics data are needed to ensure that the co-administration of rifampicin does not decrease drug levels below the therapeutic level. Triple NRTI should also be considered as the preferred regimen for children older than 3 years with a history of failure on a NNRTI-based regimen.

[d] Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.

[e] Substitution with EFV should be considered as the preferred option (*179*), and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.

From: World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection.* Geneva, Switzerland: World Health Organization; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/en. Accessed June 10, 2015.

diagnosis and supportive investigations.[96] Tuberculosis meningitis, in particular, carries a high fatality rate and risk of severe sequelae in survivors; empiric treatment, when suspected, may be lifesaving.

Malaria

Malaria is more common and more severe in people with HIV infection.[97] Incidence in a given area may be as high as 2-fold or more in HIV-infected individuals, with higher parasitemias.[97] Mortality and severe morbidity tend to be more common among persons with HIV infections and more so in areas where malaria transmission is less intense and individual immunity to malaria may not be present.[98]

Co-trimoxazole preventive therapy is beneficial to HIV-infected children in malaria-endemic areas because, in addition to protection against opportunistic infections and serious bacterial infections, it also reduces the risk of malaria.[2] Co-trimoxazole preventive therapy remains very effective in preventing malaria even where folic acid antagonist resistance-mediating mutations in *Plasmodium* are common.[99]

Use of insecticide-treated bed nets by all persons is critical in malaria-endemic areas because they reduce incidence, morbidity, and mortality of malaria in children and adults[100,101] and are a priority intervention for improving child survival.[33] Their use is particularly important for HIV-infected pregnant women, as placental malaria is associated with a substantial risk of HIV MTCT.[102] Intermittent preventive treatment with 2 doses of sulfadoxine-pyrimethamine during pregnancy has also been

shown to reduce placental malaria but is less effective in HIV-infected women than uninfected women; a higher sulfadoxine-pyrimethamine dosage (eg, monthly administration) is recommended for HIV-infected pregnant women.[103]

Hepatitis B and C

As many as 10% of HIV-infected children in developing countries are coinfected with hepatitis B virus (HBV), the vast majority infected through MTCT.[104] Administration of HBV vaccine at birth alone is 70% to 75% effective for preventing MTCT of HBV, and the addition of hepatitis B immunoglobulin at birth brings efficacy to 95%[105]; these have particular utility in HBV-prevalent settings. In areas of higher hepatitis B prevalence, HIV-infected infants and children should be screened for hepatitis B infection, as should all HIV-infected infants and children with otherwise unexplained liver enzyme elevations.

Diagnosis of hepatitis B coinfection has implications for ART. Lamivudine has activity against HBV and is part of all standard first- and second-line ART. As HBV may develop 3TC resistance when 3TC is used without a second drug with anti-hepatitis B activity,[106] use of TDF (also active against HBV) as part of ART along with 3TC (or emtricitabine, also active against hepatitis B) is preferable for hepatitis B–coinfected patients.

Another important reason for knowing hepatitis B status in managing children's ART is that hepatitis B–infected children are at risk for a flare of underlying quiescent hepatitis, including fulminant hepatic failure and death (in some cases), when ART containing antiretrovirals with anti-hepatitis B activity is suddenly withdrawn.[107]

Hepatitis C coinfection with HIV in children is uncommon. When present, management does not differ from that of non–HIV-infected children.

ADOLESCENCE AND PSYCHOSOCIAL ISSUES

The special needs of HIV-infected adolescents are attracting more attention in developing countries' responses to pediatric HIV.[108] As ART programs expand and fewer perinatally infected children die from HIV infection, countries are experiencing growth in adolescent HIV numbers, augmented by sexually transmitted infections among young persons.[109,110] In high-prevalence settings, undiagnosed HIV in adolescents is not uncommon,[111] and a high proportion of adolescents admitted to hospitals are HIV infected with common admission diagnoses including TB, cryptococcal infection, pneumonia, and sepsis.[112] A clear role can be seen for expanded efforts in high-prevalence settings to identify HIV-infected adolescents.

Data suggest that adolescents may be less likely to maintain effective responses to ART than younger children, which is generally related to problems with non-adherence to antiretrovirals[113] and psychosocial concerns, particularly depression.[108,114] Depression and anxiety are also common in caregivers of adolescents and are positively associated with adolescents' difficulties in psychosocial functioning.[114] A family-centered approach to HIV infection has been suggested to offer many benefits to caregivers and children alike, including the opportunity to offer family therapy or other group approaches to managing psychosocial difficulties.[114,115] It has been suggested that screening for and treating depression should be part of standardized packages of services offered for families coping with HIV infection in resource-limited settings.[115]

Disclosure of HIV status is a difficult issue in the field of pediatric HIV in higher- and lower-income countries. Caregiver reluctance to disclose HIV status to a child or an adolescent is often related to fear of stigmatization and discrimination, which are powerful cultural issues in many developing countries.[108] However, disclosure is important for HIV-infected children and adolescents, as it is associated with elevated self-esteem, willingness to accept treatment, and adherence to ART.[108] Health care professionals are recommended to assist caregivers with a stepwise approach to disclosure from an early age using age-appropriate language and concepts.[108,112]

A holistic approach to developing life skills compatible with long-term health is important for adolescents with HIV infection. Generally, in developing countries, there is a lack of accurate and youth-friendly information available to HIV-infected adolescents on how to live a healthy life. Efforts are underway in some settings to address this with culturally relevant, targeted informational materials.[116] Structured peer support groups are used in some adolescent treatment programs and offer a venue for developing confidence in disclosure and peer relationships, as well as an opportunity to deliver an educational program focused on life skills.[117] Such support may help ART programs in lower-income countries deliver better outcomes for this challenging group of patients. In a study comparing virologic responses of children and adolescents in Uganda with those in the United Kingdom and Ireland, the superior virologic response seen in Ugandan adolescents was attributed in large part to successful adolescent support programs.[118]

IN PERSPECTIVE: THE GLOBAL RESPONSE TO PEDIATRIC HIV IN DEVELOPING COUNTRIES

In recent years, major strides have been made in the effort to address the effect of the global HIV epidemic on children and families. It has been shown that perinatal transmission can be markedly reduced and children can be broadly enrolled into effective treatment programs, even in very resource-poor settings. In many locales, the tide is turning against new child HIV infections; in 7 hard-hit sub-Saharan African countries (Botswana, Ethiopia, Ghana, Malawi, Namibia, South Africa, and Zambia), there are now 50% fewer new child infections annually than in 2009.

Treatment is cost-effective.[119] And treatment itself works in children. Around the world, hundreds of thousands of previously ill children have had their health restored and been able to resume normal lives. In Africa, many caregivers cite their child's ability to return to school as their greatest source of satisfaction with the child's care.

Yet HIV-infected children and their families remain among the most vulnerable members of our global community. Many countries where HIV is prevalent have multiple competing and critical priorities, of which HIV is one. Resources are limited and sustenance of current programs is a daunting challenge, never mind expansion to those still in need.

It is said that every nation walks on its children's fragile feet. This is perhaps nowhere more true than in the regions markedly affected by HIV. The continued effort to bring HIV prevention, care, and treatment to all children and families in need keeps the promise of an HIV-free generation and a healthy future for children and families coping with HIV challenges.

KEY POINTS

- HIV is a major cause of death where prevalence is high, such as in sub-Saharan Africa, where more than 90% of HIV-infected children reside, and millions of children worldwide have been orphaned by HIV.
- Despite substantial progress in recent years, children remain underrepresented in care and treatment programs compared with adults.
- The vast majority of pediatric HIV infections are due to MTCT; with a strong MTCT prevention approach, including opt-out HIV testing in pregnancy and expanding availability of ART to all pregnant women, developing countries can realize rates of MTCT below 2%.
  - —The broadening of MTCT prevention recommendations to Option B-plus is a major advance for the global goal of eliminating pediatric HIV and promoting maternal survival.
  - —Pediatric HIV infections are decreasing.

- Decisions on feeding modality (breastfeeding versus formula-feeding) should center on child survival considerations, rather than strictly on the likelihood of HIV transmission; HIV-exposed infants should only formula-feed if all of the WHO conditions needed for an HIV-positive woman to safely use formula-feeding are present, a rare happenstance in the developing world, where most HIV-exposed infants will do better with breastfeeding
- Co-trimoxazole preventive therapy is a key yet underused intervention for HIV-exposed and HIV-infected infants and children.
- Health care professionals in developing countries should maintain a high index of suspicion for clinical signs and symptoms indicative of HIV infection, particularly in HIV-prevalent settings; provider-initiated testing and counseling in health settings is a key strategy to increase identification of HIV-infected children.
- Antiretroviral therapy is effective and lifesaving in infants and children; HIV-infected infants and children younger than 60 months should be initiated on ART regardless of clinical stage or CD4 count.
- Adherence to therapy is the critical factor in determining how well a child does on ART; age-appropriate disclosure process is a critical component of adherence support, particularly for older children, and should be part of every clinic visit.
- Tuberculosis is the most important coinfection for HIV-infected individuals; HIV-infected children are particularly susceptible to severe forms of TB and should receive isoniazid when indicated.
- HIV-infected adolescents require special attention with a particular focus on psychosocial concerns.

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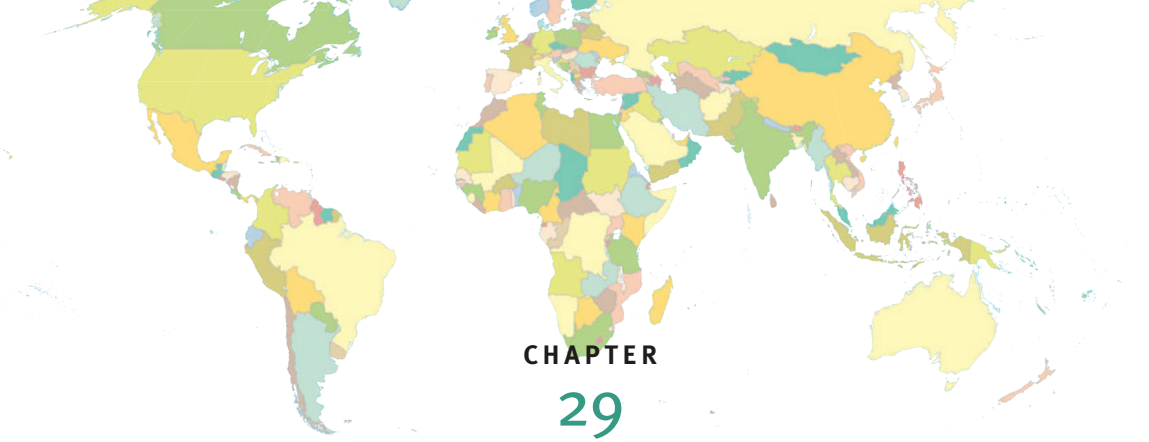

CHAPTER

29

Infection Control

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INTRODUCTION

Communicable diseases are a major cause of morbidity and mortality across the world, accounting for approximately 12 million deaths per year.[1] Ninety-five percent of these deaths are clustered in resource-limited countries. In fact, infection accounts for one-third to two-thirds of deaths annually in certain regions such as Asia and Africa. Children remain disproportionately affected, with 50% of pediatric demise attributable to diarrheal and respiratory illnesses, resulting in greater than 2 million deaths per year.[2] Neonatal infections and deaths in resource-limited countries are approximately 3 to 20 times higher than in the United States. Additionally, there are nearly 1.4 million hospital-acquired infections (HAIs) ongoing at any given time. Disparities in rates are significant, with higher-income countries showing approximately 10% of patients affected compared with 25% HAIs in countries with limited resources.[3]

As medical and surgical technologies continue advancing, the number of HAIs is likely to continue climbing and result in even greater disparities because of distinct differences in stimuli to address them. Infection control issues in developing countries become more pronounced as the global village shrinks with regard to diagnosis and possible interventions. In addition, unless there is strict adherence to infection control measures, a rise in medical tourism in many countries will result in the spread of highly resistant organisms.[4]

Addressing infection control concerns poses challenges in resource-limited countries that are somewhat reminiscent of hurdles faced and overcome in industrialized nations 30 to 50 years ago. Strategies employed for infection control in developing countries cannot be addressed with a one-size-fits-all approach, as disease profiles and resources differ markedly among developing economies.[5] The availability of good health care is inversely proportional to the population needs in such areas, and health systems are weakest where the burden is the greatest.[6] Physical distance between areas, dissimilar cultures, language, extensive movement, and variable states of socioeconomic development accentuate disparities. Emphasis on cost containment as a short-term goal may overshadow long-term gains that could be realized from basic infection prevention. From a cultural perspective, there may be an underlying acceptance of disease and inevitable death in a deprived society, which makes redistributing resources a reactive attempt at a cure instead of a proactive attempt at prevention that is difficult to achieve.

Close to 10 years ago, the World Health Organization (WHO) launched an alliance focused on increasing patient safety with improving infection control as a major initiative (www.who.int/patientsafety/en).[7] While many countries are now active participants within the alliance, for countries with limited resources, the unique issues that present themselves in infection control within their health care settings and the viability of various interventions must be examined first before full participation can be considered.

GENERAL ISSUES IN RESOURCE-LIMITED COUNTRIES

Certain overarching issues in developing countries contribute to challenges on every level, including infection control. Poverty remains widespread and far reaching, resulting in many challenges, including lack of access to health care and limited facilities and programs even where clinics and hospitals do exist. Lack of clean water and appropriate sanitation remain significant issues in resource-limited countries, with 2.4 billion people worldwide without basic sanitation and another 1.1 billion without access to safe water.[8] Without these resources, infection will continue to be pandemic and a major cause of death in the developing world.

Lack of government oversight remains a barrier to infection control in lower-income countries as well. In many regions, a very small percentage of the gross national product (often <5%) is set aside for infection prevention initiatives, and health care budgets for developing countries are staggeringly small compared with the industrialized world. Governmental priorities often mandate that funds be used to service growing international debt and not to support health care systems,

which results in a lack of overall political support for programs. There is generally no oversight or accreditation system for health care facilities, nor are there mandates for hospital infection control, surveillance activities, or staff training. There is also poor donor organization, a lack of nongovernmental organizations (NGOs) to address needs, and a discontinuous commitment due to frequent civil issues, which can derail health care initiatives and agendas.

More specific issues can be encountered within the hospital environment itself (Box 29-1). Surveillance of infections and their evolution is seriously lacking. As infections vary from region to region, even defining what should be tracked poses nearly unlimited difficulties. Additionally, limitations in laboratory and information technologies make getting data and maintaining and circulating them significant obstacles. Lack of microbiological support in many areas of the world makes available data difficult to translate into useful clinical information. There is a paucity of infection control experts to craft interventions to affect practice and culture change based on available data; thus, no outlets are offered for lessons that could be learned from surveillance in resource-limited countries. Crowded living environments and health care facilities contribute to the spread of disease and acquisition of HAIs. Economic constraints and rewards for cost-containment evidence may be responsible for the reuse of disposables, which can contaminate stock supplies—rinsing and reusing items such as gloves, requiring families to provide care items that disrupt supply chains, and pooling items, such as drugs and syringes, for

Box 29-1. Factors Associated With Nosocomial Infections in Countries With Limited Resources

- Lack of clean water and appropriate sanitation
- General lack of availability of antiseptic gels
- Absence of governmental oversight
- Insufficient personnel trained in infection control
- Limited financial resources dedicated to infection control
- Lack of surveillance and microbiological support
- Reuse of single-use medical equipment (eg, endotracheal and gastric tubes)
- Improper sterilization of medical equipment
- Overcrowding
- Overuse or suboptimal dosing of antimicrobial agents leading to resistance
- Contamination of multiuse antiseptics and disinfectants
- Contamination of intravenous solutions and aggregates
- Unavailability of negative-pressure isolation rooms
- Poor facility infrastructure (eg, poor ventilation, lack of air-conditioning)
- Limited access to personal protective equipment (eg, masks, respirators, gowns)

later use. There are no established standards for reusing items, but even with single-use items, issues exist with location and maintenance of waste containment facilities.[9]

Familiar themes exist when comparing issues in countries with limited resources with lessons learned in industrialized nations. Hand hygiene poses issues in every health care setting around the globe. Multiple studies show that compliance rates vary but are usually less than 40% regardless of the country observed. Educational efforts reported in higher- and lower-income countries show effectiveness, but improvements have been transient. Epidemics have forced improved hand hygiene but only for short periods. In all societies, there is some thought that germs are abstractly viewed and that a fear of illness or disease does not stimulate hand washing. Structural issues like a lack of sinks and cultural norms that are less likely to endorse alcohol-based hand rubs often contribute to poor compliance as well.[10] Additionally, emergence of resistant pathogens presents new challenges in infection management across the globe.

Issues that confront the industrialized world, such as indiscriminate antibiotic use or overuse in hospitals or suboptimal antibiotic dosing resulting in selective pressure on endogenous flora, are often accentuated in resource-limited settings. Antimicrobial agents are frequently available in hospitals with very few other resources. Coupled with the over-the-counter supply of medications, selective pressure in the developing world is much greater than that seen even in industrialized nations. Effective treatment may be halted because of the expense of newer agents to fight multidrug-resistant (MDR) organisms. Even when agents are available, lack of quality assurance programs addressing drug production allow for suboptimal effectiveness and concentration, adding to the development and sustenance of resistant bacteria. With high population density and migratory population shifts and medical tourism, the spread of MDR disease is likely to continue expanding and increasing on a multinational level as well.[4,11,12]

SPECIFIC ISSUES FOR INFECTION CONTROL

There are some common or recurrent communicable diseases encountered in resource-limited settings that present specific challenges for infection control purposes. According to National Nosocomial Infections Surveillance data, HAIs, including catheter-associated bloodstream infections, catheter-associated urinary tract infections, and ventilator-associated pneumonias, are in the 90th percentile in lower-income countries compared with the United States, despite the fact that surveillance is often suboptimal.[13] Nosocomial infections can occur in as many as

25% of hospitalized patients in resource-limited settings. Reasons for this high number are likely multifactorial in etiology and include, but are not limited to, universal use of open infusion systems as opposed to closed systems, which are the standard of care in higher-income countries; unavailability of clean water or other materials to clean central venous line hubs and caps prior to access; less frequent changing of administration sets due to lack of supply; infusate contamination caused by less trained personnel, unclean water for mixing, or homemade infusate brews that have no quality assurance and a higher risk of contamination; and few recommendations or guidelines for device use in countries where such items are available but experience in actual use is limited. Introducing infection-control programs, even in a limited fashion, results in a decrease in HAIs.[14,15] Implementation of the International Nosocomial Infection Control Consortium multidimensional approach on central-line–associated bloodstream infections (CLABSI) in India resulted in a 53% reduction in infections.[16]

Diarrheal Diseases

Diarrhea is one of the most common diseases encountered in the developing world. In general, diarrhea is considered an expected childhood malady with less risk of long-term adverse consequences. This can lead some parents to be less interventional than with illnesses with a high likelihood of poor outcomes. However, diarrheal illnesses result in a significant number of deaths globally each year, with rotavirus accounting for approximately one-fifth of the total number. Despite studies that suggest hand hygiene alone can prevent 30% to 47% of diarrheal illnesses, compliance is marginal. Additionally, the nosocomial resistance of nonviral pathogens appears to be increasing because of inherent risk factors in the living and hospital environment, including malnutrition, crowding, lack of availability or knowledge on the use of personal protective equipment, and overuse of antibiotics.[15]

Tuberculosis

Tuberculosis (TB) is a particularly challenging issue with regard to infection control in all hospitals. Precautions considered appropriate in higher-income countries include private negative-pressure isolation rooms with personnel garbed in protective items, such as N95 respirator masks, gowns, and gloves. Many institutions mandate fit-testing masks and limiting adult visitation pending testing and treatment. In resource-limited settings, negative-pressure rooms are difficult to provide. Air circulation generally depends on cross ventilation from open windows without screens. A general rule of TB isolation in many resource-limited

facilities includes separating patients in distant areas of the ward with open windows on both sides of the patient care area to allow cross ventilation. Although this may provide some protection to patients in other parts of the ward, crowding, bed sharing, and delayed time to diagnosis make person-to-person transmission likely. The spread of MDR TB can occur even with attempts at isolation. It is estimated that even when protective items are available for staff use, most staff are poorly trained and supported, with only 10% reporting formal training. The result is that the highest exposure areas are often magnified by the least infection control.[17]

Recent strategies have highlighted the need for well-integrated approaches for disease management in resource-limited countries, using TB management as the template. The large number of medical and social comorbidities seen in this population, such as HIV, malnutrition, and substance use, illustrates the need for synergistic approaches to disease screening, monitoring, and care coordination. This strategy could potentially alleviate redundancy of government resources needed to screen and monitor, which may assist in disease eradication.[17]

Hemorrhagic Fevers and Emerging Pathogens

Hemorrhagic fever, also common in these settings, has the potential for person-to-person spread as well as percutaneous spread to health care workers. Frequently, families are charged with burial preparation, which can further spread the disease even after the patient dies. Lack of rapid diagnostic techniques and isolation facilities, crowding, inconsistent use of universal precautions, and a paucity of waste disposal techniques contribute to continual spread of these organisms.[18–20]

Recently, health care workers in Saudi Arabia became infected with Middle East respiratory syndrome coronavirus. Poor adherence to infection control measures was a contributing factor for infection.[21,22]

NEONATAL CARE

One area that poses incredible challenges in resource-limited countries is neonatal care and nurseries. In these settings, intrapartum and postpartum care present infection control issues. Infections in newborns are 3 to 20 times higher than in industrialized settings and are the major cause of death, accounting for 1.6 million per year or about 40% of total annual neonatal deaths. Seventy-five percent of these deaths are concentrated in Asia and sub-Saharan Africa.[23] Survival is generally only thought to be possible with a gestational age older than 30 weeks and a birth weight of a minimum of 1,000 g. Many children with complicated

issues are unable to be supported because of a lack of needed technology, such as ventilators, central lines, and total parenteral nutrition, or staff with knowledge to use such items when they are available. In areas that may have access to the necessary technology, infections are still higher than in industrialized countries. Socioeconomic level clearly influences device-related infections in this population.[24]

Lack of appropriate prenatal care is a setup for poor neonatal outcomes. Many vitamins and nutrients (eg, folate) that are regularly in supplements or food in higher-income countries are lacking in lower-income countries, resulting in higher birth defects, lower birth weight, and increased risk of neonatal complications. Lack of appropriate hygiene during labor and delivery further complicates risks. Nearly 60% of births occur in the home in resource-limited settings and are usually facilitated by traditional birth attendants, who are often not trained outside of lore passed through generations. When deliveries do occur inside hospitals, there are often frequent vaginal examinations before delivery, misuse of antibiotics, and failure to recognize and respond to chorioamnionitis in rapid fashion.[25] Many of the same issues exist in special care nursery settings as in the rest of the hospital, such as poor hand hygiene, crowding (sometimes with multiple babies per cot), lack of isolation areas (mothers often reside in same area as tens of babies), and shared equipment. The cost of diapers is too high for many facilities or families and are rarely used, resulting in frequent soiling and improper cleaning of cots between patients. Reusing other items of expense or in short supply also contribute to the list of concerns, most commonly latex gloves, which are often rinsed and air-dried between use, or a single stethoscope used for multiple babies. Additionally, some items, such as povidone-iodine or intravenous solutions, are pooled as stock items for use over the entire nursery, which can affect multiple babies once contaminated.

Pneumonia and bloodstream infections are the most common nosocomial infections reported in neonatal intensive care units (NICUs).[26] Most nursery infections are caused by gram-negative rods; the most common organisms are *Klebsiella, Pseudomonas, Enterobacter,* and *Escherichia coli*. Of concern with gram-positive organisms is that 56% of all staphylococcal isolates are now methicillin resistant, and vancomycin-resistant *Enterococcus* appears to be an emerging threat. The most likely source appears to be the hands of health care workers and overuse of broad-spectrum antibiotics resulting in MDR organisms. Approximately 70% of identified pathogens in some nurseries would not be covered by WHO-recommended empiric antibiotic therapies of ampicillin and gentamicin, resulting in late or inadequate treatment of neonatal infections.[27]

OTHER CHALLENGES

Other communicable diseases have been endemic and problematic in these countries for decades, including malaria, streptococcal infections, respiratory infections (eg, respiratory syncytial virus), skin diseases (eg, scabies, impetigo), and trachoma.[28] The acute disease may often be self-limited but present long-term post-infectious complications and resultant long-term financial burdens from therapy or complications. Lack of hygiene, crowding, and poor access to appropriate drug therapy add to issues of disease that often receive very little funding or programmatic consideration because of the perception that these illnesses are common and minor compared with others such as HIV.

GENERAL PRINCIPLES FOR INFECTION CONTROL INTERVENTIONS

All interventions undertaken in developing countries must be simple, inexpensive, and practical under each region's limitations. One major requirement is a declaration of commitment and focus on infection control. The WHO made a public commitment in 2004 by establishing the World Alliance for Patient Safety. The WHO created this international alliance and then issued the Global Patient Safety Challenge to fight health care–associated infections.[7,29] In effect, this challenge would stimulate the development of infection control programs by focusing on a number of critical factors in safety, including safe handling of blood injections, clinical procedure, clean water, sanitation and waste management, and hand hygiene. Early information shows success in the challenge of increasing hand hygiene in Mali, Africa, when components were introduced as a bundle.[30,31] In a recently published study, hand hygiene compliance increased from 51% before intervention to 67.2% after intervention.[31] Further, in Colombia, adherence to hand hygiene increased by 55% with the implementation of a multidimensional strategy.[32] Compliance had a greater effect in low- to middle-income countries than in high-income countries. Increasing the number of trained specialists is an additional element that needs to be addressed to develop infection control programs in health care facilities. There is little interest in pursuing further training because infection control is not recognized as a specialty in its own right and carries no financial or professional incentive in resource-limited areas.

Educational initiatives for health care workers are also critical to the success of infection control. Improving training programs as well as increasing access to computers and information technology support will allow for remote learning to supplement current programs. Whether such programs should focus on nursing or physician resources is unclear,

but they should likely involve both if feasible.[33] Public health campaigns are also necessary to clarify expectations for patients who receive services and increase support for infection control exercises. Multimedia campaigns, tax subsidies, and tax relief may work in combination to provide stimuli for increasing medical personnel and public appreciation of the potential effectiveness of infection control programs.

Facility improvement and sanitation concerns are clearly basic problems that must be addressed but which may be of such an extreme scope that they are difficult to solve. Operational costs for facilities are often borne by patients and families, which leaves little to no room for capital improvements. Sanitation issues generally require large-scale interventions and huge investments over a long period. As funding decisions are usually made ad hoc, priorities may not be congruent with a particular area's need because infection control is usually a low priority. Every initiative requires money and although spending on global health initiatives significantly increased from 12% to 37% from 1992 to 2003, committed resources fall well short of needed funds.

Diseases may compete with one another for funding, and monetary support may often follow specific initiatives, resulting in disproportionate funding for illnesses that resonate with donors but may not correlate with actual burden of disease. Additionally, influences, such as national security needs or perceived threats and socialization patterns that stimulate desire to follow global health policy, may redirect donors as well as recipient countries from the initial agenda. For these reasons, a balance must be struck with respect to recipient need, provider interest, and global policy mandates.[34] As funding becomes more competitive, unique ideas that expand on existing programs, involve outreach, or make use of one of the largest resources in the developing world—workforce—may have added advantages. Cost-effectiveness evaluations of funding initiatives should include longitudinal evaluation of infection control programs and facility improvements compared with long-term treatment costs of nosocomial infections. In addition, preferential consideration should be given to ideas that involve infection prevention.[35]

The overarching goal should be to develop realistic guidelines for implementation that are acutely aware of resource limitations in a particular setting. Most guidelines are copied from resource-rich countries and so, by definition, generally require major infrastructure, expertise, and funding for implementation. Additionally, cultural and language differences need to be addressed. There is a pressing need to modify existing guidelines to fit economic and practical limitations in individual settings to be effective. Major improvements in surveillance

will be necessary to delineate the needs and limitations of practice in such settings.

SPECIFIC INTERVENTIONS FOR INFECTION CONTROL

Several specific interventions have been advocated for implementation in lower-income countries. The easiest and most economical intervention appears to be increasing emphasis on hand hygiene. Hand washing is simple, standardized, and low cost and has data to support its effectiveness, making it optimal for implementation in deprived settings. As noted in multiple studies, compliance continues to be low. Hand hygiene needs optimal promotion to be a successful intervention. There has been variable commitment to hand washing by health care administrators, government officials, and NGOs. Implementation of hand hygiene strategies in countries with limited resources is feasible and sustainable over time.[31,32] Since WHO launched its Clean Care is Safer Care campaign almost 10 years ago, 130 WHO member countries, millions of health care professionals, and tens of thousands of health care facilities have demonstrated a commitment to improve hand hygiene (www.who.int/gpsc/pittet_message/en).

Soap and alcohol-based hand gel are not reliably available in public institutions, including schools and hospitals, which are missed opportunities to underscore hygiene as a priority. In developed countries, gels have been touted as superior to soap and water, especially from a compliance standpoint. These commercially produced gels are too expensive for use in the developing world, but local production of ethanol hand rubs may be a practical alternative.[36] Combining hand rubs with education to create a culture of "everyone is doing it" may be an effective strategy in resource-limited countries.

Additionally, improving isolation procedures may go hand in hand with hand hygiene. Simple interventions, such as isolating, improved use of protective items (eg, gloves, masks), and cough etiquette, are inexpensive and have great potential for effect. Escombe et al showed that opening windows and improving natural ventilation improves TB organism counts on wards without any required reconstruction.[37]

Maximizing the benefits of existing programs may be another cost-effective option. The most obvious option may be extending immunization programs because they are extremely effective in disease control, fairly well respected globally, and more substantially funded than other programs. Efforts should include attention to supply, formulation regulation, distribution, cost, and a post-market safety profile.[38] Other options, including point-of-use disinfection, bleaching vessels for storage, distributing oral rehydration solution recommended by WHO, and extending

the use of permethrin-impregnated bed nets, may tremendously affect associated illnesses.[39] Outreach workers could be easily and inexpensively inserted into all of these programs to reach more patients.

In the age of technology, expanding electronic medical records may improve surveillance activities in resource-limited locations. While this would potentially allow better compliance to the WHO call for increased reporting, it may also benefit epidemiologic pattern delineation in parts of the world that have had difficulties describing the disease burden locally. The potential applications of open source software tailored to specific regional needs are being explored.[40]

An alternative to creating new initiatives is risk reduction. Unsafe injection practices remain a major issue in resource-limited settings. Approximately 8 to 12 billion injections are given each year, with sick patients likely to receive 10 to 100 times more injections per year than healthy persons. Estimations show that 50% to 90% of injections are given for therapeutic purposes and as many as half of these injections are likely unnecessary and primarily used for mild diarrhea, fever without other symptoms, colds, or fatigue.[41,42] As in higher-income countries, injections are often given at the demand of patients or families or because of economic incentives. Many of these injections are administered by doctors untrained to provide them or family and friends who do not know proper technique.

Needles are frequently used on multiple consecutive patients without proper sterilization and then improperly disposed without sharps or biohazard containers. Implementing single-use syringes that will not plunge more than once has been advocated; they are easy to use and could be distributed through current immunization programs. Limitations include cost, as they are only beneficial if immunization sites are very busy and are not amenable to bacille Calmette-Guérin or reconstitution of all vaccines.[43] They also require adequate disposal; thus, working toward the goal of needleless systems should continue in all countries. Vacating use of multidose vials is also an appropriate intervention but may not be cost-effective in many economically deprived settings. Additional risk-reduction measures, such as needle exchange programs and condom distribution, may be undertaken; however, cultural or religious tenets in a particular area may influence the acceptance of such programs.

Interventions specifically geared to nurseries present an area unto themselves because of the previously described issues that are highly associated with neonates. Reducing maternal vaginal examinations and recognizing and treating chorioamnionitis early may decrease vertical transmission of disease. Exclusive breastfeeding, kangaroo care, a

checklist for nursery staff about routine infection control practices, and optimal timing of discharge to avoid HAIs may be beneficial. Increasing personnel training on hand hygiene and cleaning equipment may have even longer-lasting effects in the nursery setting, as staff numbers tend to be limited with lesser turnover. Implementation of multidimensional infection control strategies have been shown to reduce the incidence of ventilator-associated pneumonia and CLABSI in NICUs in countries with limited resources.[44,45]

Broader interventions may be ideal. Improving sanitation by increasing positive pressure in water treatment plants, supplying free soap, and using ultraviolet light sources or natural sunlight for water sanitation could have far-reaching effects even beyond the hospitalized population.

Controlling the spread of MDR organisms globally is certainly an item on the global health agenda. In resource-limited settings, increasing the role of the chemist or pharmacist in responsible antibiotics use will be necessary as long as antibiotics are available over the counter. Cycling and combination therapy have been suggested as possible strategies as well, but there are not enough data to assess the potential adverse effects of such practices in developing countries or if data on these strategies in the developed world translate to use elsewhere.[46] Antibiotic restriction has shown some benefits with decreased costs and reduced resistance in the short term. Whether these effects are sustainable is unknown, as changes in the antibiogram in any institution can take prolonged periods to show true shifts. Additionally, restriction programs require subspecialists to be available 24 hours a day, 7 days a week, and a continuous supply of alternate antibiotics, neither of which may be possible in particular settings. Additionally, there is no clear evidence in any setting that restriction programs affect lengths of stay or case fatality rates, which is the desired outcome of any intervention.[47]

KEY POINTS

- Many challenges exist with infection control issues and prevention strategies in resource-limited countries.
- Increased emphasis on hand hygiene, proper sterilization of medical equipment, appropriate use of antimicrobial agents, and recruitment and training of specialized personnel are necessary in many lower-income countries.
- A focus on infection prevention can be financially feasible for countries with limited resources and may reduce morbidity and mortality.

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CHAPTER

30

Pediatric Cardiology

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INTRODUCTION

Heart disease in children is primarily congenital in origin in all regions of the world. Resource-limited countries bear a greater burden of congenital heart disease (CHD) because they have a greater proportion of the world's population. Most estimates of the incidence of CHD are from population studies in developed countries. The true incidence in resource-limited countries is unknown, as much CHD remains undiagnosed and unreported.

Other significant causes of heart disease in resource-limited countries are rheumatic heart disease (RHD), dilated cardiomyopathy (DCM), Chagas disease, Kawasaki disease, and infective endocarditis (IE).

Rheumatic heart disease is the most common acquired heart disease and is largely preventable. It is the most important sequel of acute rheumatic fever (RF). Its occurrence is limited to densely populated and resource-limited areas of the world with rare exceptions. Dilated cardiomyopathy is the most common type of cardiomyopathy. Resource-limited countries see a higher incidence of DCM secondary to hypocalcemia and myocarditis. Chagas disease is a common cause of myocarditis and cardiomyopathy in South America. Kawasaki disease is the most common cause of pediatric vasculitis globally. It has debilitating consequences for the coronary arteries. Infective endocarditis remains an important contributor to morbidity and mortality associated with CHD and RHD in the third world. This

chapter presents an overview of these heart diseases as encountered in resource-limited countries.

CONGENITAL HEART DISEASE

Congenital heart disease is the most common birth defect. The spectrum of CHD is huge; there are vast differences in severity; and there is no single treatment pathway. Treatment is expensive and, for many types of defects, there is a narrow treatment window. Most common CHD has excellent prognosis if treated in a timely fashion. However, if left untreated, it may be life threatening or debilitating with early mortality or morbidities related to chronic heart failure, cyanosis, or pulmonary hypertension.

Mortality related to CHD has improved dramatically in the Western world. Thus, focus there has shifted to antenatal prevention and treatment of CHD and refining treatment techniques postnatally to improve morbidity. However, the scenario is drastically different in resource-limited countries. Most CHD remains undiagnosed; CHD that is diagnosed may not get treated in time to prevent significant morbidity. When treated, accessibility and resources may prevent families from following up appropriately. While fetal echocardiography is now making an appearance in larger cities in resource-limited countries, it has yet to make a significant contribution toward early diagnosis. There is also scarcity of data about CHD in resource-limited countries.

Epidemiology

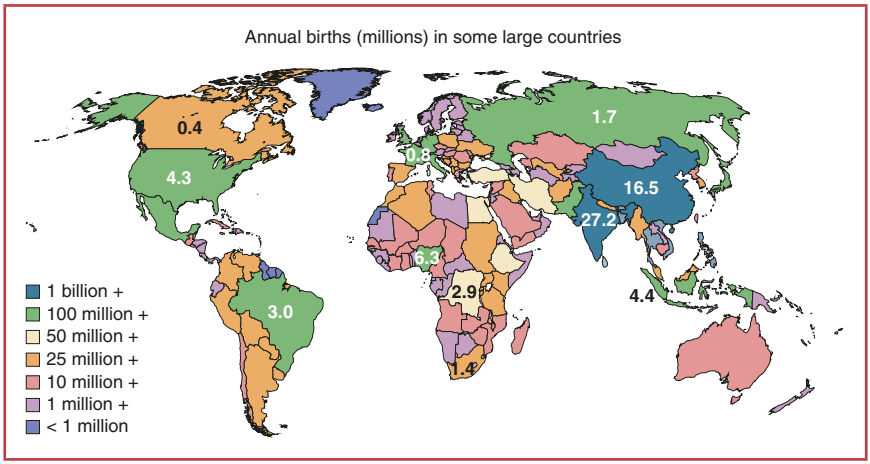
The incidence of CHD is 10 to 12 cases per 1,000 live births. Incidence does not vary from one part of the globe to another, but relative incidences of different types of CHD may vary (Figure 30-1).[1]

The prevalence of uncorrected CHD is far higher in resource-limited countries compared with developed countries; each day, an outpatient clinic routinely has 10% to 20% of such children older than 2 years. The etiology of CHD is multifactorial, with genetics one of the factors. Consanguinity is prevalent in people of certain regions and ethnicity in North Africa, West Asia, and the Middle East. There is a reported higher incidence of CHD in such populations.

Detection

The biggest challenge for resource-limited countries is timely detection of CHD. Congenital heart disease presents in a variety of ways. Congenital heart defects are always in the top 3 differential diagnoses in neonates who collapse or show severe cyanosis. It is essential to perform an echocardiogram on the baby. But accessibility to a qualified

Figure 30-1. World Map With Annual Births With Congenital Heart Disease per 1 Million Population



The key indicates the population ranges of the different countries, with China and India each having more than 1 billion inhabitants.

From Hoffman JIE. The global burden of congenital heart disease. *Cardiovasc J Afr.* 2013;24(4):141–145.

Data from United Nations Statistics Division. Annual number of births. http://data.un.org/Data.aspx?d=SOWC&f=inID%3A75. Accessed June 11, 2015. Map from Wikipedia. World population. http://en.wikipedia.org/wiki/World_population. Accessed June 11, 2015.

practitioner who will perform an echocardiogram and give the diagnosis is extremely poor for a variety of reasons. Because a large proportion of neonatal admissions occur in small stand-alone neonatal intensive care units, babies delivered here seem to be at a disadvantage in the absence of a reliable emergency transport service if required. Screening all neonates with pulse oximetry at discharge from the hospital is now mandatory in most of the United States. This simple test helps pick up critical cyanotic congenital heart defects when a patient with a failed pulse oximetry test result is referred for an echocardiogram. This program is not yet a reality in resource-limited countries. In addition, another simple safety net in the United States is the mandatory 7-day follow-up visit of a newborn if the newborn is discharged home within 36 hours of birth.

Detection of large shunt-type CHD (atrial septal defect [ASD]; ventricular septal defect [VSD]; patent ductus arteriosus [PDA]) in a newborn is based on a high index of suspicion when faced with repeated respiratory tract infections and failure to thrive. The high prevalence of malnutrition and lack of sanitation and immunizations in resource-limited countries may decrease the index of suspicion for CHD as the

cause. Diagnosis of murmur-producing lesions is less challenging. However, not all CHD is associated with significant murmurs.

Detecting CHD with reduced pulmonary blood flow is based on the amount of visible cyanosis (apart from the diagnostic cyanotic spells). Cyanosis is hard to recognize in babies with dark skin. Most health care practitioners see 50 to 100 patients daily in the outpatient clinic, and there is often no continuity of care. Only extreme diligence and adequate support staff in a well-lit environment can result in identifying newborns with cyanotic CHD.

Antenatal Detection

Antenatal detection is possible for most major CHD. Fetal echocardiography is the modality offered to high-risk fetuses, which should be performed at 18 to 20 weeks' gestation. However, most CHD occurs in low-risk fetuses; hence, the assimilation of the echocardiographic 4 chamber and 5 chamber screening views in the standard anomaly scan of the fetus. Fetuses with abnormal views are then referred to the fetal echocardiographer for details and parental counseling. Antenatal diagnosis of major CHD has affected the incidence of certain types of CHD (eg, hypoplastic left heart syndrome [HLHS], single ventricles) postnatally (especially in parts of Europe) as a percentage of families opt to terminate pregnancy.[2] Congenital heart disease with an unstable neonatal course may have improved outcomes if antenatally diagnosed. Antenatal detection rates vary from 30% to 50% for major CHD in North America and most of Europe. The antenatal detection rate is abysmally low in resource-limited countries. The reasons are manifold and include nonavailability of anomaly scans for most pregnant women, lack of knowledge of screening echocardiographic views, and severe shortage of personnel trained in fetal echocardiography, along with lack of public awareness of this test.

Management

Effect on the Family

The family of a baby just diagnosed with a major CHD is shattered. Given privacy and time, the family adjusts to the situation and makes a decision on further care based on the information that the doctor offered. In a resource-limited country like India, the medical condition of the baby is just one of the factors that the family considers. There is still a widespread bias in certain regions against a female newborn, which may manifest as opting for comfort care only or half-hearted efforts at fund-raising. Families worry about social ostracism and stigma

associated with an "imperfect" baby. Guilt owing to their belief that it was the mother's fault adds to their woes. Parents voice concerns about their newborn son's potential for growing up as a working member of society or their newborn daughter's potential to become a mother in the future. Even the scar caused by the sternal incision is an issue for the family of a female baby. Families also seek a "guarantee" that the treatment offered will "cure" their baby and that there will be no risk of death.

The practice of non-allopathic medicine is widespread in India and many parts of Asia, and many families seek advice from these practitioners. In a lesion, such as a large VSD, time spent on waiting for medications to close the hole can make the difference between straightforward closure versus inoperability. Approximately 70% of the population in Ghana depends exclusively on traditional medicine for their health care. There is approximately one non-allopathic medicine practitioner for every 400 people, compared with one allopathic doctor for every 12,000 people in Ghana.

The average resource-limited country family's biggest concern is to raise enough funds for medical care. Government-run insurance schemes are still limited to isolated pockets in resource-limited countries. The schemes should ideally ensure that the newborn gets treatment essentially free of cost.

Trained Specialists

There is a severe shortage of trained personnel (Table 30-1).[3] A typical center in a resource-limited country that performs 400 pediatric cardiac surgeries a year is manned by 2 pediatric cardiologists, 2 surgeons, 2 anesthesiologists, and 1 or 2 intensivists. The cardiologists are expected

Table 30-1. Ratio of Cardiac Surgeons to Population on Different Continents

CONTINENT	RATIO OF CARDIAC SURGEONS TO POPULATION
North America	1:3.5 million
Europe	1:3.5 million
South America	1:6.5 million
Asia	1:25 million
Africa	1:38 million

From Hoffman JIE. The global burden of congenital heart disease. *Cardiovasc J Afr.* 2013;24(4):141–145.

to be as competent in echocardiography as interventional catheterization and intensive care medicine. Fellowships in each subspecialty are hard to come by or nonexistent. Pediatric cardiac anesthesia training is imparted as a part of the adult training course. In most units (other than dedicated pediatric cardiac units), surgeons or anesthesiologists provide postoperative care—a practice with lots of lacunae. Input from pediatricians and neonatologists helps improve the care delivered and is becoming the norm in most dedicated pediatric cardiac units, as seen in other leading centers of the world.

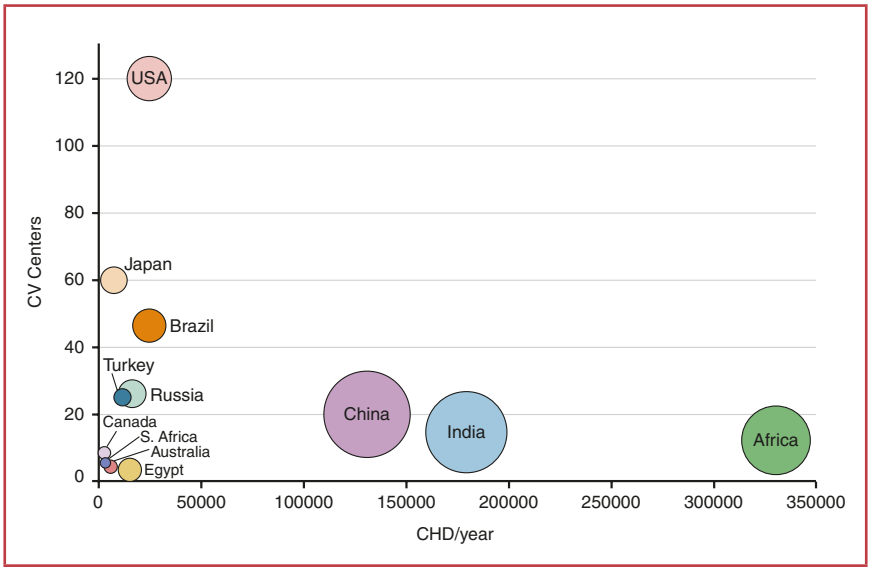
There is a new Internet-based initiative in India that hosts biweekly pediatric cardiac lectures for students across India and parts of Africa (http://heartstrings.linkstreetlearning.com) that makes learning a bit more uniform across centers. Nursing care is a challenge, as the training period is long and hospitals have to compete with hospitals in the Arabian Gulf, as well as parts of Europe, Canada, and the United States, to retain their trained nurses.

Infrastructure/Equipment and Practices in Centers

There is an obvious shortage of pediatric cardiac centers in resource-limited countries (Figure 30-2). Approximately 1,300 patients (out of an estimated 4,500 requiring surgery) were operated on for CHD in South Africa.[4] Eight hundred of the surgeries were in public service hospitals, which serve close to 85% of the population. Disregarding the accumulated backlog of untreated CHD, every year more than 3,000 children die or remain disabled from their congenital heart condition in South Africa. Data are scarce from the rest of Africa or Asia. Until recently, Nigeria, the most populous country of Africa, did not have a pediatric cardiac center. Most patients still must travel abroad for treatment or wait for periodic missions from developed countries.[5] Pediatric cardiac surgical programs in resource-limited countries vary in the resources available to their patients. At certain select hospitals, one may find facilities equivalent to those in developed countries. However, most centers do not have dedicated operation theaters, biplane catheterization laboratories, or pediatric cardiac intensive care units.

Most pediatric cardiac outpatient departments function with a sole dedicated echocardiography machine. In sub-Saharan Africa, access to an echocardiography machine with a pediatric probe is difficult. An adult probe has a larger footprint that does not fit in a baby's rib spaces. Also, the resolution is lower than the pediatric and neonatal probe. All of this contributes to higher diagnostic inaccuracy. Sedatives are the rule for an echocardiography examination for infants and children 6 months to 2

Figure 30-2. Distribution of Cardiovascular Centers in Select Countries and Continents (Bubble Area Proportional to Population)



From Hoffman JIE. The global burden of congenital heart disease. *Cardiovasc J Afr*. 2013;24(4):141–145.

years of age because time is at a premium in most resource-limited countries. The number of cardiac catheterization laboratories is low compared with the need. Time is also at a premium for pediatric cardiac catheterization studies, as there is usually a line of waiting adult cases after the pediatric case in the shared catheterization laboratory. Catheters and wires are used sparingly, as each extra piece will result in more cost to the patient. The whole range of catheters and wires that are useful in pediatric interventions are not available. Most pediatric cardiologists in resource-limited countries have become adept at completing entire diagnostic studies with barely 2 low-cost adult catheters and a wire. A number of studies have been published from centers in resource-limited countries that describe innovations in the catheterization laboratory that minimize cost or time or simplify the procedure.[6] Biplane catheterization laboratories are rare. The alternative monoplane catheterization laboratory has the disadvantage of less safety in complex interventional cases and more radiation and contrast use. Innovative use of the echocardiography machine in conjunction with catheterization has reduced the disadvantage of working with a monoplane machine.[7]

Pediatric Cardiac Operating Room and Intensive Care Unit

A few units in the developed world are moving toward hybrid suites, ie, operation theaters that are also cardiac catheterization laboratories, so that optimal care can be delivered. There is a trend toward unifying cardiac catheterization laboratories with noninvasive imaging (magnetic resonance imaging and computed tomography scanning). On the other hand, very few centers in resource-limited countries even have a dedicated pediatric cardiac operating room. It is the norm in many places to share adult facilities to perform surgery and deliver postoperative care. This may make sense in terms of investing less in infrastructure and personnel; however, it compromises quality of care, particularly in neonates and very young infants. Many practices have had to resort to decreased surgical costs and extending the life of some expensive instruments, decisions that may not be acceptable in developed countries.[8] One example is reusing disposable equipment, such as perfusion cannulas and cardiac catheters, after they are cleaned and sterilized with alcohol. This has proven to not be detrimental in most patients and largely offsets costs. Intensive care units also have shortcomings pertaining to infrastructure and staff shortages.[9] Perioperative sepsis and nosocomial infections are a big concern. Total parenteral nutrition is not available routinely. Portable chest radiograms are a rarity in many regions of the developing world. Ancillary service providers, such as blood banks, suffer from acute shortages of blood products and related testing. Issues such as power shortages or surges are nearly nonexistent in the developed world but are routine in resource-limited countries, especially in parts of Africa, and greatly impede successful operation of pediatric cardiac surgery programs.

Preoperative Management

Prostaglandin E_1 (PGE_1) infusion keeps the ductus arteriosus open and is lifesaving for neonates with duct-dependent CHD. It is discontinued once the neonate undergoes the indicated surgery or cardiac catheterization procedure. Although PGE_1 infusion is available in resource-limited countries, the cost is a deterrent to many. It is not manufactured locally in most of Africa and must be imported on a case-by-case basis. Emergency transport services are primitive. Pediatric transport ventilators are rare. Even transport-friendly infusion pumps are hard to obtain. It is common for doctors to use the Ambu bag to transport patients long distances, even from one city to another. Most infants with large left-to-right shunts are diagnosed late (ie, in late infancy). They are deficient in calories as well as vitamins, minerals, and iron. This contributes

significantly to perioperative morbidity. Although many governments in resource-limited countries have good immunization outreach clinics, most practitioners put off immunizing infants with undiagnosed CHD because most of these infants have acute respiratory tract infection at every visit to the clinic. So the baby with a large shunt who needs immunization the most is denied it.

Management of Specific Congenital Heart Disease

Acyanotic Heart Defects

Most acyanotic heart defects, such as PDA, ASD, and VSD, are managed in resource-limited countries in a manner similar to the developed world. The principles of management are early diagnosis and early treatment. Failure to diagnose and treat early results in failure to thrive, congestive heart failure, and pulmonary vascular obstructive disease. Oral ibuprofen is used to close the PDA in a premature neonate. Device closure is the standard treatment offered to patients with (suitable) ASDs. Families may opt for surgical closure if funds are an issue because the device cost is considerable. Unlike in the developed world, the consumable item—the device—contributes to the treatment cost the most. In Africa, the paucity of catheterization laboratories makes transcatheter closures a rarer option. Infants with large VSDs are electively operated on by age 3 months in dedicated pediatric cardiac centers, but patients at many public hospitals end up waiting for months for their turn. Public service hospitals often do not have the expertise or facilities needed to perform surgery on infants who weigh less than 10 kg. As discussed earlier, the reasons for the 10-kg barrier are multiple: scarcity of trained pediatric cardiac surgeons and pediatric anesthesiologists, intensive care management not geared to handle an infant, and infrastructural deficiencies. Families of infants with large VSDs throng the outpatient departments of hospitals with complaints of failure to thrive, repeated lower respiratory tract infections, and congestive heart failure even after diagnosis. In a study from Uganda, 35% of admissions in the pediatric age group for congestive heart failure were due to untreated CHD.[10] It is common to encounter a 6-month-old with a large VSD who weighs just 3 kg. Aortic or pulmonary valvular stenosis is dealt with by balloon angioplasty, as is the norm throughout the world.

Complex Congenital Heart Defects

The anatomy and correction of complex congenital heart defects are complicated. Surgery is lengthy, which precludes it from taking place in many resource-limited countries, especially in Africa.

A long cardiopulmonary bypass time requires a lot of scarce additional resources.

Tetralogy of Fallot

This is a tetrad of a large subaortic VSD, overriding the aorta, pulmonary stenosis, and right ventricular hypertrophy. Murmur and cyanosis are the common reasons patients are referred to a pediatric cardiac center. Some patients present in a cyanotic spell. In resource-limited countries, VSDs in many patients are detected during evaluation for a stroke or brain abscess. Strokes and abscesses are complications of a hypercoagulable state, microcythemia, iron deficiency anemia, or dehydration. Many infants are placed on beta-blocker therapy, which is believed to relieve infundibular spasm and hence prevent cyanotic spells. The infant is offered complete corrective surgery around 1 year of age. The comfort level of centers in resource-limited countries is slowly increasing; some centers offer low-risk repair at age 6 months. This is in contrast with practice in the United States, where surgery is offered at 4 months of age (or earlier). There is probably a higher proportion of infants and children receiving a Blalock-Taussig (BT) shunt (innominate artery to pulmonary artery graft), for which the reasons are multiple: the BT shunt operation in an older infant or child is relatively simpler compared with a complete intracardiac repair; many infants and children present in a severe unresponsive spell (a BT shunt is believed to be a less-risky option in such children); the branch pulmonary arteries may be hypoplastic; and there may be a major coronary crossing the right ventricular outflow tract, which precludes dissection and resection of the area below the coronary. Definitive repair consists of avoiding resection of the area and instead placing a conduit from the right ventricle to the main pulmonary artery apart from VSD closure. Placing a BT shunt in such an infant ensures that the infant gets a chance to grow and the largest possible conduit in the final corrective surgery. Patients who required a trans-annular patch as part of their obligatory repair have significant pulmonary regurgitation, which ultimately requires pulmonary valve replacement years later. Close follow-up is essential.

Transposition of the Great Arteries With an Intact Ventricular Septum

Transposition of the great arteries (TGA) with an intact ventricular septum is the most common cause of cyanosis in the newborn. There is ventriculo-arterial discordance that leads to deoxygenated blood finding its way back to the aorta and oxygenated blood routing back to the lungs. Survival after birth depends on mixing at the ASD or PDA level. The definitive repair is arterial switch surgery; this is routinely performed

at some dedicated private sector centers across India with results comparable to that in the Western world. An arterial switch procedure has not been performed to date in Ghana. Kenya's first such procedure was performed in 2009. For best results, the arterial switch for an isolated TGA has to be performed in the first few weeks of life. If the surgery is not performed in time, the left ventricle becomes deconditioned and unfit to withstand the switch. In such cases, the newborn is offered atrial switch surgery. This surgery has good short-term results, but there are long-term concerns for atrial arrhythmias and intracardiac obstructions to flow within the venous circuit. The atrial switch is rare in the developed world but is still common in resource-limited countries. Reasons for this include late detection of CHD due to the absence of screening protocols for cyanosis at birth, low rate of follow-up with physicians for the well-child visit, lack of awareness about treatment options of TGA among physicians, and high cost of the surgery. The cost of performing a neonatal arterial switch is twice as much as surgery for an ASD or VSD.

Coarctation and Interrupted Arch Repair

Neonatal coarctation of the aorta or interrupted aortic arch presents with circulatory collapse once the ductus arteriosus constricts within the first 3 days of life. Prostaglandin E_1 infusion is a lifesaving temporizing measure. Corrective surgery is performed as soon as feasible. The nonsurgical option of balloon angioplasty for neonatal coarctation is resorted to more often in resource-limited countries because neonatal coarctation is detected and salvaged late, at which time the left ventricle is severely dysfunctional and surgical risk is higher. The other reason is that balloon angioplasty is more widely available.

Single Ventricle

These include a wide variety of defects where a complete, corrected 4-chamber heart is not the management goal. All forms of tricuspid atresia, double-inlet ventricles, severe right or left ventricular hypoplasia, and certain CHD with complex non-routable VSDs all fall under needing a single ventricular repair. Repair for these conditions is essentially a staged palliation called the Fontan procedure, which is accomplished in 3 stages. The first stage is placing a systemic pulmonary shunt if there is pulmonary stenosis or atresia or a pulmonary artery band if there is excessive pulmonary blood flow in the neonatal period or early infancy. The second stage is surgically rerouting the superior vena cava to the pulmonary artery (Glenn operation) at 6 months of age. The final stage is rerouting the inferior vena caval blood to the pulmonary artery with a conduit, which is performed at 4 years of age or when the patient weighs

15 kg, whichever is earlier. The typical Asian or African child is older, compared with the average American or European child, by the time his or her body surface area is adequate for an adult-sized conduit. This implies that the interval between Glenn and Fontan completion may be longer, leaving the child's heart susceptible to the effects of cyanosis and polycythemia for a longer time. The palliation offered by a Fontan operation has transitioned lots of affected children into adulthood with lives of good quality. However, this may not be said for other forms of a univentricle heart with heterotaxia or those associated with a common atrioventricular valve.

Hypoplastic Left Heart Syndrome

The palliation of HLHS has elicited much controversy across the world. In the developed world, various options for the affected family include pregnancy termination (when diagnosed antenatally), comfort care, 3-staged palliative surgery, or heart transplantation. Antenatal diagnosis of this major disease is still a distant reality in resource-limited countries. Surgery is a multistage palliation (not a total correction) that uses extensive resources. While many children with potentially curable lesions await surgery, priority for HLHS surgery is slow even in established pediatric cardiac centers in resource-limited countries. Notwithstanding this reality, a few private pediatric units have attempted this palliation with results that are improving with increasing experience.[11] Surgery for most children was funded by their families after prolonged counseling sessions about surgery stages and long-term issues.

Conditions Requiring Placement of a Conduit

Much CHD requires conduit placement as part of the treatment strategy. The best conduits in terms of longevity are pulmonary allografts, aortic allografts, and bovine jugular vein conduits. The problem with conduits is their absence of growth and degeneration, making another operation necessary; factors such as pulmonary artery hypertension, stenosis, or infections also reduce their longevity. Allografts are hard to come by in resource-limited countries, as most centers do not have access to allograft banks. Most units have to make do with commercially available Contegra conduits or various adaptations of a bovine pericardium sheet rolled into a conduit with 2 valve leaflets stitched inside. Contegra conduits are very expensive. A common strategy to minimize the number of times a conduit is changed is to postpone conduit implantation to an age when an adult-sized or near adult-sized conduit can be implanted. Bilateral BT shunts, cavo-pulmonary connections when the child outgrows initial palliation, and other surgical techniques are employed.

However, anatomy dictates feasibility of the planned repair in each of these instances.

Follow-up of Patients With Repaired Congenital Heart Disease

Most patients who had interventions or surgeries for CHD need long-term follow-up. It is important to monitor their somatic growth, echocardiographic and electrocardiographic changes, neurodevelopmental outcome, and tolerance of physical stress and other expectations of adulthood and beyond. Patient follow-up is difficult in resource-limited countries. Extensive counseling and education about the need for long-term follow-up seems to be the most effective strategy to motivate families to travel to the center from villages that may be hundreds of miles away. The burden of grown-up CHD (GUCH) is reported to have increased in the developed world, as the population of patients being treated is growing. Centers have prepared for this and have specialist clinics in place. The GUCH population in resource-limited countries is still made up of untreated patients. Many patients who were diagnosed with CHD in childhood present for primary correction in adulthood because they did not receive treatment at the time of diagnosis due to financial constraints, misguided advice, or minimal symptoms. These naturally selected individuals pose a different set of problems, including extreme cyanosis, polycythemia, severe ventricular hypertrophy, hypoxic cardiomyopathy, Eisenmenger complex states, collateral dependent circulations, and severe hemoptysis from profuse bronchopulmonary collaterals, to name a few. Tetralogy of Fallot, Ebstein anomaly, and VSD with pulmonary atresia are some of the common unrepaired lesions encountered in adults.

RHEUMATIC HEART DISEASE

Acute RF is caused by an immunologic reaction to antigens of the strains of the common pathogen that causes pharyngitis, group A streptococcus. An acute generalized inflammatory reaction involving the heart, joints, brain, and skin results. The heart is affected the most in RHD with long-lasting damage. Rheumatic heart disease occurs in approximately 60% of RF cases. The pericardium is inflamed and the myocardium can become dysfunctional. The endocardium that makes up the valves is the most severely affected. The pathology starts as fibrin deposits at the tip of the valve leaflets and progresses to disfiguring the valve at all levels. The mitral and aortic valves are most commonly involved and manifest as regurgitation and/or stenosis over time. The reasons for mitral regurgitation and stenosis are leaflet or chordal thickening or shortening and commissural fusion and calcification.

Rheumatic fever affects children between 5 and 15 years of age. Recurrences can occur at any age, but prevalence peaks in the third and fourth decades of life. Recurrences increase with age and each is a fresh attack on the cardiac valves. Sixty percent of all RHD cases go on to develop heart failure each year. Little is known about the rate of progression from recent onset RHD to heart failure or death.

Epidemiology

Incidence of RF is less than 1 per 100,000 per year in industrialized nations. However, incidence of acute RF ranges from 72 to 150 per 100,000 per year in sub-Saharan Africa, south-central Asia, South America, and indigenous populations of Australia and New Zealand.[12] Prevalence of RHD ranges from 21 to 62 per 1,000 school-aged children. Prevalence of clinical RHD is fewer than 5 per 1,000 in Indian cross-sectional studies. However, actual prevalence may be 10-fold when echocardiography is used for diagnosis.[13]

When approximately 5,000 schoolchildren were screened in Zimbabwe, it was found that children living in slums had a far higher incidence of RHD (22:1,000) compared with children in well-off localities (4:1,000). Risk factors identified for having RHD in this study included overcrowding in homes, malnourishment, birth during the rainy season, low birth weight, and low socioeconomic status. Multivalvular lesions are common in patients from Africa with RHD.

Diagnosis of Rheumatic Fever

The Duckett Jones diagnostic criteria consist of major manifestations of carditis, arthritis, subcutaneous nodules, erythema marginatum, and chorea. Minor criteria include fever, arthralgia, elevated erythrocyte sedimentation rate or C-reactive protein level, and prolonged P–R interval in the electrocardiogram. However, in the moderate- and high-risk population (eg, Asia, Africa), recently published guidelines[14] have changed the major criteria to add clinical or sublinical carditis or polyarthralgia or monoarthritis. The minor criteria for the moderate- and high-risk population has also been changed to add monoarthralgia to the preexisting list. Presence of 2 major, or 1 major and 2 minor, criteria, along with evidence of recent *Streptococcus* infection, are diagnostic of initial acute RF.

Prevention of Rheumatic Fever and Rheumatic Heart Disease

Primordial prevention of RF is through improved socioeconomic status and better housing and health. There is no vaccine available against this organism despite attempts to create one by working on the M protein. Primary RF prevention is through a 10-day antibiotic treatment of

Streptococcus pyogenes pharyngitis. The World Health Organization (WHO) has a subsection on RHD and policy statements for RHD prevention. Its focus is on secondary prevention, which translates into preventing colonization of the RHD patient's throat with *S pyogenes* so that repeat RF attacks are prevented. Secondary prevention is through a daily oral dose of penicillin V or a 3- to 4-week intramuscular dose of penicillin G benzathine. The duration of prophylaxis varies depending on the extent of cardiac involvement. Many patients are noncompliant despite being aware of its necessity. In addition, there is often a shortage of penicillin G benzathine.

Critical to initiating secondary prevention measures is identifying RHD. Duckett Jones criteria make diagnosing RF simple, but diagnosing RHD can be complicated—more so if the child is asymptomatic. By the time the child becomes symptomatic with heart failure, damage to the valve is irreversible. In 2006, WHO included echocardiographic criteria of Doppler evidence of mitral valve involvement in an effort to diagnosis RHD early. In 2012, the World Heart Federation published revised echocardiographic criteria that included a more comprehensive look at the valve; the 2006 WHO guideline to include echocardiography findings as a diagnostic criterion focused on Doppler assessment of the valve only.[15] It is hoped that this will help improve early and accurate diagnosis. However, there is valid concern that false-positive cases will increase.

Treatment of Rheumatic Fever

Anti-inflammatory agents such as aspirin or steroids are used to control rheumatic activity. Aspirin and steroids suppress the inflammatory response.

Treatment of Rheumatic Heart Disease With Significantly Affected Valve Function

Surgical and interventional options are available for affected valves. Rheumatic mitral stenosis responds to balloon valvuloplasty and is the treatment of choice. The Inoue balloon is a special dumbbell-shaped balloon that is positioned across the stenosed mitral valve after a tiny ASD is created and entered into the left atrium from the right atrial side. If the immediate results of the valvuloplasty are good, long-term results also continue to be good with significant relief from re-intervention for the next 6 to 8 years. The inadequate number of cardiac catheterization laboratories in Africa routinely precludes transcatheter interventions. Outcomes for surgical repair or valve replacements are good. The first option for non-balloon valves or valves with severe regurgitation is to attempt a repair, especially in younger patients. The drawbacks of

valve repair are the fact that the results depend on surgeon and valve morphology, a high rate of reoperation, and a need for tightly adhering to secondary prophylaxis. Options for valve replacements are a bioprosthetic or prosthetic valve; each has well-described advantages and disadvantages. The third less-common option is using the patient's own pulmonary valve in place of the diseased valve. In general, in a young female patient expected to bear children in the next few years, placing a tissue valve would be preferred because anticoagulation would not be required.

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is the most common cardiomyopathy in the pediatric age group. Dilated cardiomyopathy can be secondary to viral myocarditis and inherited metabolic diseases or idiopathic. Dilated cardiomyopathy is most often secondary to calcium and vitamin D deficiency in resource-limited countries where malnutrition is very prevalent. Vitamin D deficiency in resource-limited countries is common among exclusively breastfed babies born to mothers with high-risk factors such as low vitamin D stores, dark skin, and inadequate exposure to sunlight. Up to 9% of DCM cases are caused by calcium and vitamin D deficiencies in resource-limited countries.[16,17] Newborns and infants are most commonly affected. Clinical manifestations include tachycardia, poor feeding, and signs of congestive heart failure. These patients may also present with cardiogenic shock. Acute hypocalcemia causes prolongation of the QT interval, which may lead to patients presenting with hemodynamically significant ventricular dysrhythmias. Laboratory evaluation reveals severe (corrected for albumin) hypocalcemia, raised serum parathyroid hormone levels (secondary hyperparathyroidism), and depressed serum 25 hydroxy vitamin D levels. There is a quick response to calcium supplementation. Initially, calcium must be administered as intravenous infusion (dose 100–200 mg/kg/d) until the calcium level is normalized. Vitamin D (cholecalciferol) also needs to be provided.

CHAGAS DISEASE

Chagas disease was first described by Dr Carlos Chagas from Brazil in 1909. It is a major health problem in South and Central America and Mexico, with more than 12 million people affected. Historically, it was found in rural populations where there are higher chances of infected vectors inoculating humans. However, recent studies show an increasing prevalence in urban populations. The main reasons for this include migration from endemic areas and successful vector control in some

rural areas versus poor vector control in urban areas. Most endemic countries have national treatment control programs in place.

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* infecting reduviid or triatomine bugs. Humans acquire the infection when the nocturnal bug bites (usually on the face) and then defecates at the same time. Nonvector-borne disease transmission does occur through blood transfusions, maternal-fetal transmission, and ingestion of contaminated food or drinks. Initial symptoms of the acute phase occur after an incubation period of 1 to 2 weeks and are nonspecific (eg, fever, headache, myalgia, malaise). These symptoms abate without complications and are mistaken for a benign illness. Symptomatic myocarditis is rare and manifests as tachycardia, mild cardiomegaly, a mild decrease in ejection fraction, and small pericardial effusion.

Laboratory diagnosis of the acute phase of Chagas disease is done by demonstrating trypomastigote in the peripheral smear. Polymerase chain reaction assay is very sensitive and produces positive results early in the illness. Benznidazole or nifurtimox are recommended for treating acute and early congenital Chagas disease. The natural history of the acute phase is resolution in 1 to 3 months.[18,19]

About 30% of infected people who are not treated develop chronic or symptomatic Chagas disease. It may take more than 20 years from the time of the original infection to develop cardiac or gastrointestinal complications. It is recommended that all children younger than 18 years infected with *T cruzi* receive antitrypanosomal therapy. There is a similar recommendation for adults with early to mild cardiomyopathy or an indeterminate form of *T cruzi* infection.

The cardiac complications of Chagas disease are cardiomyopathy leading to cardiac failure, arrhythmias, thromboembolism, and chest pain syndrome. Chagas disease is a major cause of ischemic stroke in Latin America. Gastrointestinal complications are megacolon and megaesophagus.

Congenital Chagas disease occurs because of vertical transmission of trypomastigote from the infected pregnant mother to the fetus. The rate of maternal-fetal transmission is 4.7%, with a higher rate in endemic countries. Neonates may develop hepatosplenomegaly, meningoencephalitis, myocarditis, anasarca, or anemia, although most remain asymptomatic. Infected neonates achieve a 100% cure when treated with a 30-day course of benznidazole during the first year of life. Actively screening pregnant women in endemic areas and early screening and treatment of newborns and infants is the best approach for managing congenital Chagas disease.

KAWASAKI DISEASE

Kawasaki disease is an acute, self-limiting vasculitis that was first described by a Japanese pediatrician, Dr Tomisaku Kawasaki, in 1967. Untreated, the disease affects the coronary arteries and causes dilatation and aneurysm formation, leading to thrombosis and ischemia. It has since been found the world over with an estimated incidence of 65 to 150 per 100,000 children, with a higher incidence in Asia and the highest in Japan. Incidence in Japan is believed to be rising. The reported incidence in India and other resource-limited countries is lower, but underdiagnosis may be an important reason for the difference. Creating patient registries has been attempted. In 2013, Red de Enfermedad de Kawasaki en América Latina was formed—a Latin American Kawasaki disease network covering 20 countries in the region. There is evidence of a seasonal variation in the incidence in the extra tropics northern hemisphere, with highest incidence in late winter and early spring.

Diagnosis

Diagnosis of Kawasaki disease is based on a high index of suspicion when encountering fever for longer than 5 days in an infant or child with additional features of non-exudative conjunctivitis, strawberry tongue, cervical lymphadenopathy, polymorphic rash, indurated hands and feet, and, later, desquamation of hands and feet after 1 to 3 weeks. Due to a higher prevalence of infectious diseases in resource-limited countries, there is a natural tendency to attribute such findings to measles, RF, or other commonly encountered streptococcal or staphylococcal diseases. The diagnosis of Kawasaki disease also depends on the treating physician's awareness about this disease entity's existence. It has been reported that the clinical profile of Indian children is different from the classically described profile. Affected Indian children tend to be older, and skin peeling and thrombocytosis starts sooner.[20]

Treatment

It is vital to diagnose within the first 10 days of fever because that is when intravenous immunoglobulin (IVIG) therapy is most effective. The IVIG therapy is conclusively shown to reduce incidence of coronary artery aneurysms to less than 5%. Incidence of coronary artery disease is more than 20% in untreated patients. Intravenous immunoglobulin is costly and, hence, out of reach for most families in resource-limited countries. An aggressive attempt by hospital social workers and the family is generally made to mobilize the finances once the family understands the (costlier) repercussions of untreated Kawasaki. There is an

increasing incidence of coronary artery disease in young Asian adults and abnormal coronaries secondary to Kawasaki disease in childhood, which could be a contributing factor.[21,22]

INFECTIVE ENDOCARDITIS

There is an incidence of 1.7 to 6.2 cases of IE per 100,000 patients in the developed world. Similar data are not available for resource-limited countries. It is reasonable to assume that incidence of IE is higher in resource-limited countries because of high numbers of uncorrected CHD and RHD. There may also be a higher grade of dental caries (data show that incidence of dental caries in the general populations is similar) secondary to poor oral hygiene and poor access to dentists in resource-limited countries compared with the developed world. There is a substantial difference in the profile of a patient with IE in the developed world versus a patient in a resource-limited country. The patient in the resource-limited county is more likely to be much younger, afflicted with CHD or RHD, have a higher incidence of a negative blood culture, and have a higher chance of IE complications, including death.[23] A recent study from India reported that more than 35% of patients with IE had underlying RHD. Blood culture results were positive in more than 65% of patients with IE, and staphylococci were isolated most often.[24] American and European revised guidelines for IE prophylaxis (2007 and 2009, respectively) stress that only complex CHD and prosthetic valves require prophylaxis before specific invasive procedures. Rheumatic heart disease by itself is no longer considered a reason for IE prophylaxis unless it is associated with prosthetic valve replacement. Two primary reasons for the revision is that IE is much more commonly the result of bacteremia associated with daily activities (eg, brushing, flossing) than bacteremia from a dental, gastrointestinal tract, or genitourinary tract procedure and that prophylaxis has really not shown to prevent post-procedure bacteremia. The new guidelines stress oral hygiene and preventing gingivitis as the most important factor to decrease IE incidence. The single most important factor to reduce IE incidence in resource-limited countries is to decrease the incidence of RHD.[25]

OTHER ASPECTS OF PEDIATRIC CARDIOLOGY IN RESOURCE-LIMITED COUNTRIES

Telemedicine

Telemedicine is a means for a physician or technician who is situated in a remote center to communicate with a tertiary care center. Telemedicine has great potential in resource-limited countries. A pediatric cardiologist

could help the local field-worker diagnose CHD. A pediatric cardiac intensivist could lend expertise to a remote intensive care unit. Telemedicine is not becoming widespread because of the perceived lack of technical knowhow, setup cost, and absence of trained field workers.

Genetic Evaluation of Patients With Congenital Heart Disease

Genetic evaluation is essential and offered to affected patients in the developed world, as 50% of CHD is associated with a syndrome. Because of cost constraints, karyotype or fluorescent in situ hybridization is not offered to all eligible patients in resource-limited countries unless it is part of a research study with subsidized costs. Genetic panel tests are shipped abroad and prohibitively expensive. The neonatal screening panel, which is the norm across the developed world, is being implemented very sparingly across resource-limited countries.

Research

Basic scientific research is extremely limited due to a lack of qualified personnel, time, and infrastructure. Clinical research is improving, especially since some US and European health organizations launched multicenter data collection efforts aimed at studying postsurgical outcomes. The International Quality Improvement Collaborative initiated by Boston's Children's Hospital is a combination of CHD surgery data assessment and relevant training geared primarily toward nurses in the pediatric cardiac intensive care unit in resource-limited countries.[26] Also, scientific meetings and journals increasingly have contributions from resource-limited countries on methods by which they have saved (precious) resources by modifying equipment or techniques. A notable example is early extubation after open-heart surgeries for simple heart lesions.

Representative Regional Bodies

The Asia-Pacific Pediatric Cardiac Society (http://appcsonweb.org) is 9 years old and an effective stage to address common concerns of the region.

The SA Heart Association (http://saheart.org) is an organization catering to the South African population.

The Pediatric Cardiac Society of India (http://pedicardiacsocietyofindia.com) is 16 years old and has members from neighboring countries as well. It holds annual meetings (said to be the largest subspecialty meeting in the world) and has a quarterly journal, *Annals of Pediatric Cardiology,* which is indexed in PubMed.

KEY POINTS

- Resource-limited countries bear a greater burden of CHD. Most CHD cases in resource-limited countries remain undiagnosed and untreated. Antenatal diagnosis of CHD is rare in resource-limited countries.
- Rheumatic heart disease is the most common acquired heart disease in resource-limited countries and an important sequela of acute RF. Incidence of RHD is highest in densely populated and poor areas of the world.
- Dilated cardiomyopathy is the most common type of cardiomyopathy. Hypocalcemia and myocarditis are the most common cause of DCM in resource-limited countries.
- Chagas disease causing cardiomyopathy is common in South America. Children affected by Chagas disease manifest with myocarditis.
- Kawasaki disease is the most common cause of pediatric vasculitis globally, with the highest incidence in Japan. It is the most common cause of acquired heart disease in the developed world. It has debilitating consequences on the coronary arteries if not treated with IVIG within 10 days of onset.
- Infective endocarditis remains an important contributor to morbidity and mortality associated with CHD and RHD in resource-limited countries. Most patients in resource-limited countries receive prophylaxis for any invasive procedure, even for non–high-risk cardiac lesions.

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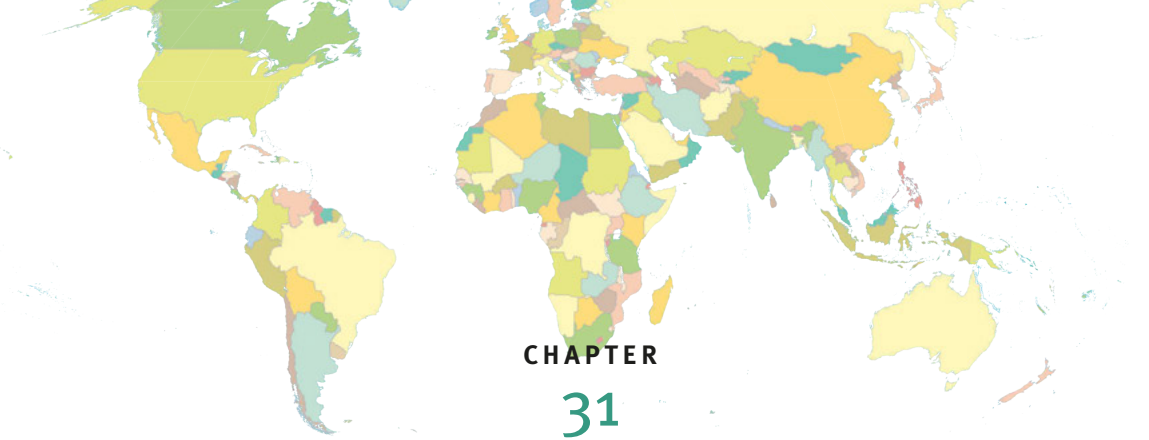

CHAPTER

31

Neurologic Disorders in Children

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INTRODUCTION

Neurologic disorders of adults and children represented 6.3% of the global burden of disease in 2005.[1] The magnitude of neurologic disorders is largely underrecognized in developing countries due to lack of disease registries, clubbing of neurologic and psychiatric disorders under the term *mental health* in epidemiologic studies, persistence of endemic infections, emergence of new infections and noncommunicable diseases, and exclusion of certain diseases and conditions from the estimates of neurologic burden, which are not primary neurologic disorders but cause substantial neurologic sequelae (eg, HIV/AIDS, tuberculosis [TB], parasitic diseases, birth trauma, malnutrition). Stumbling blocks to care of these children are numerous—scarce neurologic resources such as a lack of imaging facilities and trained neurophysiology technicians who can perform electroencephalograms (EEGs), lack of specialists and multidisciplinary treatment at most centers, striking treatment gaps, social stigma, lack of social support, and paucity of trained personnel to support daily activities of children with disabilities, to name a few.

This chapter presents an overview of neurologic disorders that may be encountered in children living in developing countries with an emphasis on clinical diagnosis, prevention, and treatment using commonly available and cost-effective options.

BURDEN OF NEUROLOGIC DISORDERS IN DEVELOPING COUNTRIES

The World Health Organization (WHO) estimates that 10% of the world's children (approximately 200 million) suffer physical disability, mental deficiencies, or developmental delay. Eighty percent of all such children reside in developing countries.[2] Death from neurologic disorders as a percentage of total death is nearly 8% in low-income countries, 17% in low- to middle-income countries, 11% in upper-middle–income countries, and 13% in high-income countries.[1] Prevalence of disability due to neurologic conditions ranges from 1.5% to 21.3% in Southeast Asia.[3]

The patterns of childhood neurologic disorders in developing countries are similar to those encountered in the West.[4] However, the relative prevalence of conditions and availability of health resources vary. Neuro-infections (9%–72%) and epilepsy (80%) are the most common and largely preventable causes of neurologic disease burden.[5,6] The median number of general neurologists per 100,000 population varies from 0.03 in Africa and 0.07 in Southeast Asia to 0.32 in the eastern Mediterranean, 0.77 in the Western Pacific, 0.89 in the Americas, and 4.84 in Europe. As expected, median numbers of pediatric neurologists or pediatricians with expertise in neurology, for a population of 100,000, is even lower at 0.12 in the Americas, 0.47 in Europe, and 0.003 in Southeast Asia.[7] The percentage of countries providing pediatric neurology services ranges from 100% in North America and 95.2% in Europe to 37.5% in Africa.[7]

COMMON NEUROLOGIC DISORDERS IN DEVELOPING COUNTRIES

Infections of the Central Nervous System

Central nervous system (CNS) infections constitute a significant health burden in several developing countries despite advances in antibiotic treatments, diagnostic facilities, and immunization practices. According to WHO, there were approximately 700,000 episodes of meningitis in 2004, and 70% of these patients lived in Africa and Southeast Asia.[8] Every year, Japanese encephalitis (JE) virus, an important cause of encephalitis in Asia, causes 50,000 cases of encephalitis, with 15,000 deaths and severe neurologic and psychiatric sequelae. The incidence of meningococcal disease in Europe is 2 to 89 per 100,000 per year in infants and 1 to 27 per 100,000 per year in 1- to 4-year-olds. On the contrary, meningococcal meningitis epidemics in certain parts of Africa, such as Niger, Chad, and Sudan, may reach an incidence of 1,000 per 100,000.[9] Global incidence of pneumococcal meningitis is estimated to be 21 cases per 100,000 per year, and global incidence of *Haemophilus*

meningitis is estimated to be 21 (16–31) per 100,000 per year in children younger than 5 years, with the highest incidence in Africa and the lowest in Europe.[10]

Acute Bacterial Meningitis

The incidence of acute bacterial meningitis is much higher in developing countries than in developed countries due to inadequate immunization of children, diagnostic delay, poverty, malnutrition, lack of health care facilities, shortage of antimicrobials, and HIV causing secondary immunodeficiency. The profile of organisms is also different. The 3 most common etiologic agents worldwide are *Neisseria meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenzae* type b (Hib). Universal immunization has significantly decreased Hib and pneumococcal meningitis in the West; however, both diseases continue in epidemic proportions in resource-poor countries. Staphylococcal meningitis is commonly seen in children in developing countries, especially after neurosurgery interventions. Neonatal sepsis or meningitis causes 5.2% of neonatal deaths globally with an estimated incidence of 0.2 to 1 per 1,000 live births in developed countries. Gram-negative organisms derived from maternal gastrointestinal or genitourinary tract, such as group B *Streptococcus* and *Escherichia coli,* are the most common. Listeria is uncommonly seen in the developing world. Children in low-income countries often present late in the course of their illness; therefore, the incidence of complications is higher.

Meningitis may be a life-threatening emergency in children. It must be considered in any child presenting with acute seizures, fever, altered mental status, headache, vomiting, and meningeal signs (nonspecific and may be absent in one-third). Cerebrospinal fluid (CSF) analysis (in the absence of brain herniation syndromes) and urinary antigen studies help in etiologic diagnosis. Treatment consists of maintenance parenteral fluids (instead of restricted fluids), use of glycerol or mannitol (to reduce cerebral edema), appropriate antimicrobials, dexamethasone, and supportive care.[11] In children beyond the neonatal age group with uncomplicated pyogenic meningitis, 5 days of parenteral ceftriaxone at a dose of 80 to 100 mg/kg of body weight is as efficacious as a traditional 10-day treatment course.[12]

Central Nervous System Tuberculosis

The majority of TB cases reported in the world are from Southeast Asia (29%), Africa (27%), and Western Pacific regions (19%). One-half million cases of TB and 74,000 TB-related deaths (6% and 8% of the global totals, respectively) in these countries were in children younger than 15

years.[13] Infection of the CNS (1% of all cases) is one of the most devastating clinical manifestations of TB. Tubercular meningitis (TBM) is a disease of young children, with 70% of cases occurring in children younger than 5 years.[14] Common neurologic manifestations of childhood TBM are meningeal irritation, raised intracranial pressure, motor paralysis, extrapyramidal movement disorders (eg, tics, chorea), brain stem dysfunction, cranial nerve palsies, and coma. Children often present with non-neurologic symptoms such as fever (67%), vomiting (53%), poor feeding (46%), and cough (32%).[14] Clinical diagnosis is supported by a history of contact with TB (53%), positive Mantoux skin test (60%), chest radiograph suggestive of primary TB (60%), and positive culture result from gastric aspirate (18.6%). The combination of hydrocephalus, basal meningeal enhancement, and infarction on neuroimaging is 100% specific and 41% sensitive for the diagnosis of childhood TBM.[15] Current WHO guidelines state that TBM should be treated with 4 antitubercular drugs (isoniazid 10–15 mg/kg, rifampicin 10–20 mg/kg, pyrazinamide 30–40 mg/kg, and ethambutol 15-25 mg/kg) for 2 months followed by 2 drugs (isoniazid, rifampicin) for 10 months. A meta-analysis of treatment regimens in TBM showed that steroid use was associated with fewer deaths in the pediatric age group.[16] Long-term sequelae include cognitive (80%) and behavioral (40%) impairments. Delayed diagnosis, drug resistance, and HIV coinfection (13% globally in 2012) affect the outcome adversely. Sub-Saharan Africa bears the brunt of this dual epidemic, accounting for approximately 75% of the estimated burden in 2007.[17]

Japanese Encephalitis

Japanese encephalitis is a leading cause of viral encephalitis in Asia, with 30,000 to 50,000 clinical cases and 20,000 deaths reported annually. It is endemic in China, India, Vietnam, Thailand, the Philippines, Malaysia, and Indonesia with an overall incidence of 1.8 per 100,000.[18] Japanese encephalitis is caused by the mosquito-borne flavivirus *Culex tritaenirhyncus*. Mosquitoes lay eggs in open water sources, pigs and aquatic birds act as the main amplifying hosts, and humans constitute the dead-end JE virus hosts. Classic presentation consists of pyrexia, seizures, and altered sensorium in young children, leading in severe cases to brain stem dysfunction and death. Serology and supportive neuroimaging establishes the diagnosis. Acute encephalitis occurs in about 0.001% to 0.05% of infections, with death in 25% of the cases and neurologic sequelae in 30%.[19] Treatment is entirely symptomatic.

Neurocysticercosis

Neurocysticercosis (NCC) is a major cause of epilepsy in Latin America, Southeast Asia, and Africa. It is caused by infection of the CNS with encysted larvae of the pork tapeworm *Taenia solium* through contaminated food, water, undercooked meat, or household carriers. The most common presenting features of parenchymal NCC are focal seizures, headache, and vomiting in a previously well child.[20] Unusual presentations include ptosis due to midbrain NCC and sudden vision loss due to occipital NCC.[21] Neuroimaging reveals a single degenerating ring-enhancing lesion (Indian subcontinent) or multiple viable and extraparenchymal lesions (Latin America).[22] Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for detecting the scolex and diagnosing extraparenchymal NCC. The treatment gap in rural India is approximately 80%.[23] Cysticidal therapy with albendazole (15 mg/kg/day for 4 weeks) is associated with a significantly increased and quicker resolution of lesions as compared with placebo,[24] but its role in improving long-term seizure control needs further study. Supportive therapy includes adjunctive steroids to reduce inflammatory edema and antiepileptic drugs. Cases with multiple lesions and those with calcifications often have frequent seizure recurrences. Cysticercus encephalitis and extraparenchymal NCC have a guarded prognosis. Preventive measures include improved personal hygiene, sanitation, animal husbandry, and meat inspection efforts. Mass population treatment programs to eliminate tapeworms with niclosamide or praziquantel and treatment of pigs with cysticidal therapy has been investigated. Owing to its varied presentation, NCC needs to be considered in the differential diagnosis for a child presenting with seizures, headache, and vomiting, especially in endemic countries.

Cerebral Malaria

Malaria is a leading cause of illness in tropical countries. Of the 109 endemic countries, 30 countries in sub-Saharan Africa and 5 in Asia account for 98% of malaria-related deaths globally. In 2010, malaria accounted for 7.4% of deaths due to infections in children (0.56 million).[25] *Plasmodium falciparum* contributes to most of the burden of cerebral malaria in developing countries. Children younger than 5 years are most severely affected. Common clinical manifestations are fever, generalized seizures, and altered sensorium. Cerebrospinal fluid studies are usually normal, but neurologic involvement seems to correlate with parasite burden in peripheral blood, which constitutes the gold standard for diagnosis. However, in the past decade, rapid diagnostic kits that

detect antigens derived from the malarial parasite in blood are available and can offer a diagnosis within 20 to 30 minutes. Mortality among children with severe malaria is highest for cerebral malaria (5%). All cases of severe malaria are treated by parenteral quinine or artemisinin derivatives irrespective of chloroquine resistance status.[26] A single dose of primaquine (0.75 mg/kg) is given for gametocytocidal action irrespective of the drug given. Neurologic sequelae, such as residual cognitive disability, epilepsy, spasticity, vision and hearing loss, chorea, tremors, and behavioral disturbances, persist in 2.5% of affected children.[27] These constitute an important hidden burden of consequences of malaria and affects vulnerable populations (especially children) by causing poor school performance and cognitive delays. The disease can be prevented by the use of insecticide-treated mosquito nets, indoor residual spraying, and sanitation measures that prevent mosquito growth and bites.

HIV

In 2011, an estimated 3.4 million children were living with HIV worldwide, with more than 90% in developing countries. The annual number of newly HIV-infected children in 2012 was 260,000 in low- and middle-income countries.[28] Neurologic complications occur in 2% to 60% of children with HIV. Manifestations include progressive encephalopathy, seizures (2%–20%), microcephaly, developmental delay, spasticity, myelopathy, vasculitis, blindness, and peripheral neuropathy. The course of CNS HIV infection in developing countries is altered due to the superimposed burden of malnutrition, opportunistic infections, TB coinfection, and child-rearing environment. Introduction of antiretroviral drugs has reduced the prevalence of HIV encephalopathy. Antiretroviral therapy tends to be less effective in CNS disease due to the low penetration of antiretroviral drugs across the blood-brain barrier and continued production of neurotoxic proteins from infected macrophages and microglia that have a longer life span. HIV treatment coverage for children (31%–39%) remains half of the coverage for adults (61%–69%), and only 3 in 10 children receive treatment for HIV in low-income countries.[29]

Poliomyelitis

Poliomyelitis (polio) is a crippling enteroviral disease caused by 1 of the 3 polioviruses in the *Picornaviridae* family. The virus is predominantly transmitted through the fecal-oral route and invades the anterior horn cells of the spinal cord or motor neurons of the brain stem to cause neurologic manifestations. Polio mainly affects children younger than 5 years. The incubation period ranges from 6 to 20 days and more than

95% of children are asymptomatic. Paralytic symptoms ensue in 1% to 2% of children. Clinical manifestations may range from the classic asymmetric flaccid paraplegia (spinal form) to a spinobulbar (with involvement of the spinal cord and brain stem) or pure bulbar form (with brain stem manifestations alone). Death is rare in children. Diagnosis is established by isolating the virus in stool or pharyngeal swabs with specific identification of wild-type and vaccine-type strains. Serologic testing of spinal fluid reveals seroconversion when repeated 3 to 6 weeks after the acute phase of the illness. Differential diagnosis includes Guillain-Barré syndrome and West Nile motor neuropathy. There is no cure for polio. It can be effectively prevented by polio vaccine given multiple times in early childhood. Cases of polio have decreased by more than 99% since 1988, when there were an estimated 350,000 cases, to 406 in 2013. In 2014, only 3 countries (Afghanistan, Nigeria, and Pakistan) remain polio endemic, which is down from more than 125 in 1988. In early 2014, WHO declared the entire Southeast Asia region polio free.[30]

Tetanus

Tetanus is caused by the exotoxin released from *Clostridium tetani* spores. The disease is endemic in developing countries. Globally, the estimated number of tetanus-related deaths in children younger than 5 years was 61,000 in 2008, of which 59,000 were attributable to neonatal tetanus. Clinical features include generalized rigidity, trismus of the jaw, and autonomic fluctuations. Treatment consists of neutralizing unbound toxin by tetanus immunoglobulin administered intramuscularly or intrathecally at a dose of 3,000 to 6,000 units; eradicating the source of toxin by wound debridement and antimicrobial penicillin; supportive respiratory measures, sedation, and hemodynamic monitoring; and controlling rigidity, spasms, and autonomic dysfunction.[31] Neonates who survive may have microcephaly and neurodevelopmental delay, possibly due to hypoxia. Tetanus is entirely preventable with tetanus toxoid immunization that induces specific antitoxin formation. Neonatal tetanus can be prevented by immunizing pregnant women and improving hygienic conditions of delivery units.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic, progressive, slow virus encephalitis caused by the wild, latent measles virus, usually 5 to 15 years after an initial infection. The current reported incidence rates are 21 cases per million in India, 11 per million in Japan, 2.4 per million in the Middle East, and 0.06 per million in Canada.[32] Clinical features include progressive personality changes, myoclonic jerks, generalized

seizures, rigidity, and decreased level of consciousness leading to coma or vegetative state. Enzyme-linked immunosorbent assay of CSF for IgG against measles virus has a sensitivity of 100% and specificity of greater than 90%.[33] Electroencephalogram and MRI can provide ancillary evidence. Treatment consists of oral Isoprinosine (an immune-modulator that possibly inhibits viral replication) and intrathecal interferon-alpha. The effect of therapy on mortality is questionable, as the disease has a high mortality rate despite treatment (95%) and progressive course. Vaccination against measles is the only definite measure to prevent SSPE.

Rabies

Rabies is a viral zoonosis transmitted by saliva of rabid animal bites, most commonly dogs, containing the rhabdovirus. The disease causes 55,000 human deaths annually, of which 56% occur in Asia and 44% in Africa.[34] Wildlife hosts, such as raccoons, skunks, foxes, mongooses, and bats, are important reservoirs in developed countries, but dogs are the single most important animal reservoir in developing countries. Reasons for poor control in these areas include lack of proper ownership and care for stray dogs, large population of abandoned dogs, low coverage of vaccination for dogs, lack of political commitment, low awareness about the magnitude of the problem due to underreporting of cases, and high cost of postexposure prophylaxis.

Neurologic features manifest after a fairly long incubation period of 1 to 2 months. The 3 classic forms of the disease are encephalitis (furious), paralysis (dumb), and nonclassical. The encephalitic form manifests as fever, altered level of consciousness, inspiratory spasms, and autonomic instability. The paralytic form presents as tetraparesis with bladder weakness. The nonclassical form has a variety of manifestations ranging from peripheral neuropathy to movement disorders. Diagnosis is established by polymerase chain reaction (PCR) and detection of viral-specific antibodies in serum, saliva, and spinal fluid. Treatment remains supportive with deep sedation, calcium channel blockers, and volume replacement (the Milwaukee protocol).[35] No effective antiviral treatments exist, and administration of immune globulin is of no benefit in established cases. There have been no reported survivors of canine rabies so far. Prevention measures include vaccinating dogs, minimizing human exposures to infected animals, controlling the population of stray dogs, and promptly caring for wounds.

Varicella Zoster

Varicella is a highly contagious disease causes by varicella-zoster virus (VZV) from the family of herpesviruses. An initial systemic infection may be followed by mild to severe meningoencephalitis, post-infectious encephalomyelitis, cerebellar ataxia, Ramsay Hunt syndrome (causing facial nerve involvement), transverse myelitis, and arterial ischemic strokes.[36] Incidence of varicella encephalitis is reported as 1 per 33,000 cases, with mortality estimates of 1.4 per 100,000 cases.[37] Diagnosis is established by detecting VZV-PCR in spinal fluid and appropriate brain imaging. Current standard of treatment for CNS infection with VZV is acyclovir or valacyclovir for 4 to 6 weeks at a dose of 10 to 20 mg/kg/day along with steroids. Ischemic strokes related to VZV infections are discussed in detail under Stroke on page 917. Prevention by varicella vaccine is highly effective.

Tropical Myelopathies

Common etiologic considerations that cause spinal cord disease in low-income countries are similar to the West. However, certain infectious myelopathies are endemic in low-income countries and are discussed in some detail in Table 31-1. Two specific toxic myeloneuropathies, lathyrism and Konzo, warrant special consideration.

Lathyrism

Lathyrism is epidemic in India, Bangladesh, and Ethiopia. It is caused by excessive consumption of chickling peas belonging to the family *Lathyrus sativus*. The legume is a hardy insect- and drought-resistant crop that is consumed individually or added as an adulterant to other foods in times of food scarcity.[38] Symptoms appear 3 to 6 months after consumption of 400 to 500 g per day. The amino acid beta-L-oxalyl amino-L-alanine is the neurotoxin responsible for clinical manifestations, which consist of an irreversible acute to subacute spastic paraparesis with very little sensory deficits. Symptomatic treatment to reduce spasticity may be of some benefit. Public health measures to reduce consumption of the specific pea variety, steeping the legume in water prior to cooking, and using metallic vessels rather than clay pots may reduce toxicity.

Konzo

Konzo is an epidemic form of paraparesis that occurs in Mozambique, Tanzania, and the Central African Republic. Children older than 2 years have a special predilection for the disease because they eat the uncooked version or short-soaked roots of cassava (*Manihot esculenta*),

Table 31-1. Endemic Infectious Myelopathies in Low-income Countries

DISEASE	AGENT	CLINICAL FEATURES	DIAGNOSIS	TREATMENT	GEOGRAPHICAL DISTRIBUTION
HSP	HTLV-1	Back pain, spasticity	ELISA Western blot reactivity to *gag, env* (gene products)	Antiretroviral treatment	Brazil Jamaica Parts of Africa
HIV myelopathy	HIV	Spasticity Loss of vibration, proprioception	Serology, imaging	Antiretroviral treatment Treatment of superimposed infections	Africa, Asia
Tuberculosis	*Mycobacterium tuberculosis*	Leg weakness, hump Pain, local mass	Isolation of organism (sputum), imaging	Rifampin, INH Pyrizanamide, ETM for 6 mo. Rifampin + INH for another 6–18 mo	Africa, Asia Latin America
Brucellosis	*Brucella melitensis* *B abortus* *B ova*	Pain Lumbar spine abscess	Serology, blood culture Imaging	Rifampin, doxycycline for 6–8 wk	Turkey Caribbean Latin America
Schistosomiasis (Bilharziasis)	*Schistosoma haematobium* *S mansoni*	Flaccid paraplegia	Serology, imaging Rectal biopsy, CSF eosinophils	Praziquantel + steroid 14 d	Africa Venezuela Brazil
Toxocariasis	*Ascaris lumbricoides* (nematode)	Prominent sensory disturbances, mild motor weakness	Eosinophilia in CSF	Albendazole for 4 wk Steroids	Worldwide
Gnathostomiasis	*Gnathostoma spinigerum* (nematode)	Transverse myelitis	Larvae in tissue samples CSF eosinophils	Albendazole for 4 wk Steroids	Southeast Asia

Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; ETM, ethambutol; HSP, hereditary spastic paraparesis; HTLV-1, human T-lymphotropic virus; INH, isoniazid.

which contains neurotoxic cyanogenic glycosides. In addition to the sudden onset of irreversible symmetric paraplegia, which starts after manual labor or a long walk, many affected children have vision and hearing loss. The WHO recommends immediate treatment with high doses of multivitamins, especially B_2, to prevent superimposed neurologic damage due to simultaneous vitamin B deficiency.[39] Public health measures include educating communities on wetting methods that detoxify cassava and introducing low-cyanide varieties of cassava in disease-prone areas.

Epilepsy

The term *epilepsy* refers to a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and is associated with cognitive, social, and psychologic consequences. The prevalence of epilepsy is much higher in developing countries (22.2 per 1,000) than in developed countries (3 per 1,000).[40] Lower-income countries contribute to 85% of the global burden of epilepsy, with Africa having the highest prevalence. Acute and chronic CNS infections are the most important cause of seizures. Malaria and HIV are much more common in Africa, whereas NCC and JE are more prevalent in Asian countries. Acute symptomatic seizures occur in nearly one-third of all CNS infections. Other important etiologic considerations for epilepsy in low-income countries include birth asphyxia, trauma, inborn errors of metabolism, genetic syndromes, and vitamin deficiencies. A carefully elicited history, detailed physical examination, developmental stages, and neurologic deficits should be noted in any child presenting with seizures. Investigations may include EEG and MRI. Phenobarbital and phenytoin represent the first-line option in most developing countries. Table 31-2 provides a list of commonly available antiepileptic agents, doses, and side effect profiles. Figure 31-1 provides a management algorithm for status epilepticus using medications widely available in low-income countries. The treatment gap in children is as high as 70% in several developing countries due to poorly trained personnel, lack of financial resources for appropriate antiepileptic drugs, and cultural beliefs.[41] Interventions to reduce mortality should include educational campaigns to dispel myths about epilepsy; availability of neurologists and pharmacologic agents at the point of care; avoiding dangerous unsupervised situations, such as cooking on an open flame, swimming, travelling into the wilderness alone, or driving on the road; and education on emergency treatment of seizures at home. Educational campaigns to dispel myths about epilepsy and availability of neurologists and pharmacologic agents at the point of care could go a long way in addressing the treatment gap.

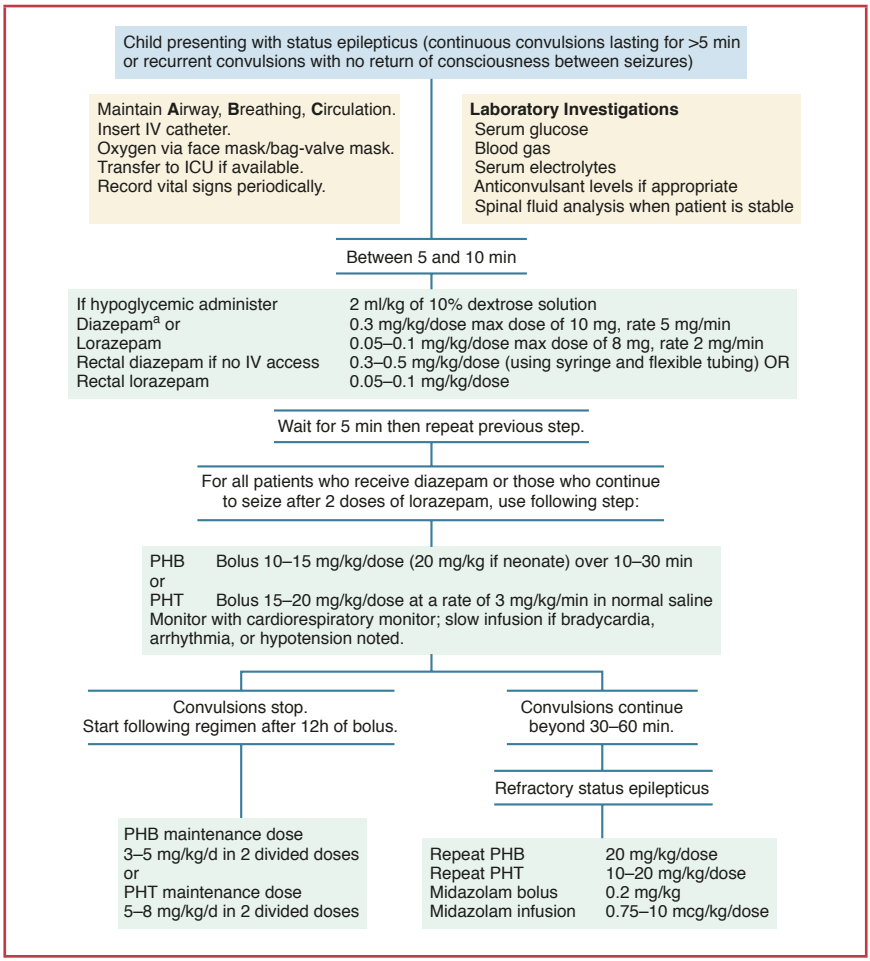
Table 31-2. Commonly Available Antiepileptic Agents, Doses, and Side Effect Profiles

DRUG	MAINTENANCE DOSE	THERAPEUTIC RANGE mcg/dL	ADVERSE EFFECTS	COST/AVAILABILITY[a]
PHB	<1 y: 3–6 mg/kg/d >1 y: 2–4 mg/kg/d	20–40	Cognitive slowing	$/+++
PHT	6–8 mg/kg/d	10–25	Gingival hyperplasia Skin rash, hepatitis Ataxia, nystagmus	$/+++
VPA	30–60 mg/kg/d	50–150	Tremor, obesity Teratogenic, hepatic failure	$$/+++
CBZ	10–30 mg/kg/d	4–12	Stevens-Johnson in HLA-B*1502	$$/++
Clonazepam	0.1–0.2 mg/kg/d	N/E	Drowsiness	$$/++
OXC	15–30 mg/kg/d	N/E	Skin rash	$$$/+
LTG	10–12 mg/kg/d	N/E	Skin rash	$$$/+
Topiramate	5–10 mg/kg/d	N/E	Cognitive slowing	$$$/+

Abbreviations: CBZ, carbamazepine; LTG, lamotrigine; N/E, not indicated or routinely available; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; VPA, sodium valproate or magnesium valproate.

[a] Availability in low-income countries: +++, widely available; +, low availability.

Figure 31-1. Algorithm for Managing Status Epilepticus Using Medications Widely Available in Low-income Countries



Abbreviations: ICU, intensive care unit; IV, intravenous; PHB, phenobarbitone; PHT, phenytoin.

[a] Diazepam is approved by the US Food and Drug Administration for treatment of status epilepticus in the United States.

The role of traditional healers and the strong effect they have, especially in certain countries of Africa, including Cameroon, Tanzania, and Kenya, cannot be discounted. In fact, epilepsy teams that include such healers and local practices, such as scarification (creating a scar on the child's forehead by scratching, etching, burning, or branding to help promote healing of seizures), have a greater effect because they offer reassurance to families that their traditional practices will not have to be completely abandoned.

NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders (NDDs) are a group of conditions characterized by impairments in motor development, learning, language, or behavior. Neurodevelopmental disorders include cerebral palsy (CP), intellectual disability, learning disabilities, attention-deficit/hyperactivity disorder, autism spectrum disorder (ASD), and developmental delay. One in 6 children (15%) between 3 and 17 years of age in the United States has an NDD. The INCLEN Trust study of 4,000 children from 5 different geographic areas of India showed that the prevalence of all NDDs was 11% in children 2 to 5 years and 15% in children 6 to 9 years.[42] Prevalence of intellectual disability alone is 16.41 per 1,000 in low-income countries (Bangladesh, Zambia), 15.9 per 1,000 in middle-income countries (China, Cuba), and 9.2 per 1,000 in high-income countries (Finland, Germany, Australia).[43] The higher prevalence rate of NDDs among children in developing countries has been attributed to perinatal problems, nervous system infections, childhood epilepsy, trauma, and a higher rate of consanguinity in these areas, which could result in a high prevalence of autosomal-recessive genetic disorders.

Cerebral Palsy

Cerebral palsy is a group of disorders of movement and posture development that cause limitation of activity due to nonprogressive disturbances of the developing brain. Although the brain injury in CP is nonprogressive, comorbidities and functional limitations change over time and affect functioning and quality of life. Prevalence rates in India and China are similar to Western figures (ie, 1.5–2.5 per 1,000 live births), whereas they vary from 2 to 10 per 1,000 in Africa.[44,45] The clinical spectrum of CP in resource-poor developing countries is different from developed countries. Overall, spastic CP is the most common type and accounts for 60% to 70% of all cases. Spastic diplegia is more common in developed countries due to increasing survival of preterm babies and advances in maternal and neonatal care. However, most children with CP in developing countries have spastic quadriplegia. Hemiplegia in low- to middle-income settings ranges from 9% to 15%, which is lower than in industrialized countries.[46,47] Perinatal asphyxia is implicated as a cause in 20% to 50% of CP cases in low-income settings compared with 7% to 10% in the developed world. Acquired preventable causes are seen in nearly one-fifth of the cases, such as CNS infections (57%) and bilirubin encephalopathy (30%).[46] Speech problems (84%), microcephaly (64%), seizures (45%), and intellectual disability (39%) are common comorbidities. Common neuroimaging findings include hypoxic-ischemic changes

and periventricular leukomalacia (ie, white matter damage). Appropriate management of a child with CP requires a comprehensive assessment to identify the motor as well as the associated deficits. Multidisciplinary care with family involvement and home-based therapies should ideally be incorporated in the individualized rehabilitation plan.

Autism Spectrum Disorder

Autism spectrum disorder is a developmental disorder that appears in the first 3 years of life and impairs normal development of social and communication skills. Prevalence of ASD in the United States is estimated to be 1 in 88, while lower incidence rates of 0.003% to 0.17% (China), 0.1% to 0.2% (Japan), and 2.6% (South Korea) have been reported from other parts of the world.[48] This may be due to inadequate epidemiologic data, lack of awareness of the disease among the general public, associated social stigma, effect of social norms, parental perceptions, and influence of community stakeholders on the parenting process.[49] Use of simplified questionnaire-based screening tools, preferably in a native language, helps early identification. Clinicians should be educated on early manifestations and encouraged to make a timely diagnosis. Earlier identification would enable children with ASD to enroll in intervention services sooner, which might result in improved outcomes.

Stroke

Pediatric stroke is an important cause of neurologic mortality and morbidity. Arterial ischemic strokes are the most common type. Incidence rates vary between 3 and 8 per 100,000 pediatric population in developed countries to 16 per 100,000 in Kenya, 8 per 100,000 in India, and 27 per 100,000 in Saudi Arabia.[50,51] Common etiologies in developed countries are genetically determined thrombotic disorders, dissection, and sickle cell disease.[52] Systemic and CNS infections (bacterial meningitis and TBM, cerebral malaria, cysticercosis, invasive fungal infections) and iron deficiency anemia predominate as etiologic considerations in low-income countries. In parts of Africa, homozygous sickle cell disease and HIV/AIDS infection are major predisposing factors. Moyamoya disease is responsible for up to 6% of strokes in Western countries but has greater incidence in Asian children, affecting 3 in 100,000 per year.[53] Infectious diseases constituted 15% and 22% of the causes of pediatric ischemic stroke in Saudi Arabia and India, respectively.[54,55] The role of VZV in predisposing arterial ischemic strokes is of particular interest because chickenpox is still common in most low-income countries and immunization can prevent this complication.

Children who present with at least one of the following clinical characteristics should undergo screening for stroke: acute onset of focal neurologic deficit of any duration; unexplained change in level of consciousness, particularly when associated with headache; seizures during the neonatal period; focal seizures in toddlers and older children; and in postoperative periods in children undergoing cardiac surgery. Lack of adequate neuroimaging facilities at all primary care centers may preclude early diagnosis. Cognitive and motor deficits are common sequelae. Efficacy and safety of low–molecular-weight or unfractionated heparin and thrombolytic agents (tissue plasminogen activator) has not yet been proven in pediatric patients. Aspirin (1–5 mg/kg/day) is recommended for secondary prevention, once dissection and cardiac embolism are excluded, although the duration of treatment remains debatable.[56]

PERINATAL/CONGENITAL DISORDERS

Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes Simplex Infections

Toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes simplex (TORCH) infections acquired in utero or during the birth process are a significant cause of fetal and neonatal mortality and morbidity. They present with variable manifestations, such as hydrops fetalis, microcephaly, seizures, cataract, hearing loss, congenital heart disease, hepatosplenomegaly, jaundice, rash, or thrombocytopenia. Seroprevalence in pregnant Indian mothers with a complicated obstetric history were 19% for toxoplasmosis, 30% for rubella, 35% for CMV, and 34% for human herpesvirus 2 infections.[57] In comparison, seroprevalence for women born in the United States is 6.7% for toxoplasmosis and greater than 90% for rubella (due to near universal immunization), resulting in decreased incidence of perinatal TORCH infections: 1% for CMV, 0.1% to 0.5% per 1,000 births for herpes simplex and syphilis, 0.1% to 0.2% per 1,000 births for toxoplasma, and approaching 0% for rubella.[58,59] Routine antenatal screening of mothers, immunization of young females, and timely treatment of affected infants are needed to reduce the burden of TORCH infections.

Neural Tube Defects

Neural tube defects (NTDs) are a group of severe congenital malformations caused by failure of neural tube closure in the first few weeks after conception. Clinical manifestations range from the most severe defects incompatible with life, such as anencephaly, to defects that cause significant morbidity and impairment of quality of life, such as spina bifida or encephalocele. Mortality rates in children younger than

5 years in low-income countries are as high as 40%, compared with 10% to 15% mortality in high-income countries. Prevalence ranges from 4.1 per 1,000 live births in India to 0.5% in China.[60,61] Low-income countries have a higher prevalence of NTDs due to a variety of genetic and environmental factors such as maternal infections, hyperthermia, folate deficiency, exposure to teratogens including antiepileptic drugs, certain genetic polymorphisms, and consanguinity. Treatment requires a multidisciplinary approach with involvement of surgeons, physical therapists, urologists, and, most importantly, pediatricians to provide coordinated care in the form of repair, rehabilitation, bladder diversion, and shunts for hydrocephalus. Prevention is possible by periconceptional folate supplementation of all women in their childbearing years at a dose of 400 to 800 mcg per day.

GENETIC/METABOLIC DISORDERS

Prevalence of inborn errors of metabolism in developing countries is estimated at 1 in 1,000 to 1 in 2,497 newborns.[62] Selective metabolic screening in patients with metabolic or neurologic features showed nonspecific generalized aminoaciduria (58%), branched chain aminoaciduria (14%), tyrosinuria (13%), methylmalonic acid (7%), mucopolysaccharidosis (4%), and phenylketonuria (2%).[63] Routine screening for inborn errors of metabolism in children with developmental delays has a diagnostic yield of approximately 1% that can increase to 5% in specific situations, such as in relatively homogenous and isolated populations, or if there are clinical indicators. The burden may be under-recognized due to a lack of routine newborn screening and genetic confirmation facilities as well as high cost of overall care of the affected children.

Infantile Tremor Syndrome

Infantile tremor syndrome is a rare, self-limiting disorder of infants and young children reported primarily from the Indian subcontinent, Southeast Asia, and, recently, war-torn Iraq. Exact incidence is not known. In India, it accounts for 0.2% to 2% of pediatric hospital admissions.[64] Infantile tremor syndrome is characterized by gradual-onset psychomotor regression, pigmentary disturbances of hair and skin, anemia, and coarse tremors that suggest structural or functional alterations of the extrapyramidal system. Etiologic considerations include malnutrition, vitamin B_{12}, zinc and magnesium deficiency, low-grade meningoencephalitis, and metabolic enzymatic defects.[65] Association with prolonged exclusive breastfeeding in vegetarian mothers has been noted. On MRI, cortical atrophy and prominence of the subarachnoid space and ventricular system are common.[66] Treatment involves nutritional rehabilitation,

parenteral vitamin B_{12}, and multivitamin supplementation. Tremors respond to oral propranolol or carbamazepine. Subnormal intelligence is a potential long-term complication. Educating mothers about nutrition with routine vitamin supplementations may help prevent infantile tremor syndrome.

Head-Nodding Syndrome

Head-nodding syndrome is an unexplained, progressive neurologic disorder in children 5 to 15 years of age that is reported from Africa, with an estimated prevalence of 12 cases per 1,000 children in certain districts of Uganda.[67] It is characterized by stereotypic head nodding or bobbing associated with seizures and stunted growth, commonly precipitated by hot food or cold weather. Winkler et al classified nodding syndrome into *head nodding only* and *head nodding plus,* in which nodding is accompanied by tonic-clonic or other seizures.[68] The cause, pathophysiology, and natural history of head-nodding syndrome remain largely unknown. Cerebrospinal fluid is normal and neuroimaging shows nonspecific cortical atrophy and focal white matter changes. An EEG shows disorganized background and generalized slowing of the background activity or frequent generalized 2.5 to 3 Hz spikes and slow waves, multifocal spikes, and polyspike and wave activity without clinical accompaniment.[69] Positive association has been observed with onchocerciasis and vitamin B_6 deficiency. The unique clinical and electrographic features and apparent geographic clustering suggest that head-nodding syndrome is an epidemic epilepsy frequently associated with encephalopathy and cognitive impairment due to epilepsy or stemming from a common unknown pathophysiology.[69] The disease is devastating, as previously healthy young children lose the ability to eat, have frequent seizures at the sight of hot food, drop out of school, and require constant supervision. World Health Organization recommendations for management include antiepileptic drugs, mass treatment for onchocerciasis in endemic areas, psychologic and social support for afflicted children, and strengthening the surveillance system for case detection.

SYSTEMIC DISEASES AND THEIR EFFECTS ON THE NERVOUS SYSTEM

Malnutrition

Malnutrition, with its 2 components of protein energy malnutrition and micronutrient deficiencies, continues to be a major health burden in developing countries. The associated prevalence of infectious diseases, poverty, and social deprivation that commonly accompany malnutrition

contribute greatly to morbidity. The most profound effects are seen in children younger than 5 years due to its effect on the developing brain, peripheral nerves, and skeletal muscles. Effects on a child's brain development may start in utero in malnourished mothers.

Protein energy malnutrition leads to impaired synaptogenesis, reduced dendritic arborization, arrest of myelination, and alterations in the composition of CNS neurotransmitters, ultimately resulting in cerebral atrophy and segmental demyelination with axonal damage in peripheral nerves. Clinically, this manifests as microcephaly, poor motor coordination, hypotonia, hyporeflexia, and impaired neuropsychologic function in the form of learning disabilities and poor academic achievement. Fine motor coordination appears to be particularly affected due to the effect of malnutrition on cerebellar neurons. Last, but not least, protein energy malnutrition affects the social competence of such children due to effects on their impulsivity, ability to form peer relationships, and motivation. Magnetic resonance imaging studies reveal thinning of the corpus callosum, poor myelination of white matter, and, in extreme cases, dilatation of the ventricles. The high mortality and developmental side effects indicate a need for a systematic approach to severely malnourished children besides an appropriate diet. The WHO has provided a 10-step scheme for severe malnutrition management.[70] Preventive interventions include amelioration of poverty, nutritional education, maternal support, food supplementation and subsidies, high immunization coverage, and early management of infectious disease, including helminthic infections. Major micronutrient deficiencies and their neurologic manifestations are outlined in Table 31-3.

ENVIRONMENT, SOCIAL DEPRIVATION, AND NEUROLOGIC DISORDERS

Chronic exposure to poverty precludes 200 million children in developing countries from achieving their full cognitive potential. Factors associated with abnormal results on developmental scales include maternal and paternal illiteracy, maternal age at birth, and low household income. Children in Peru, Vietnam, India, and Ethiopia who belong to the highest income quintile have 0.5 to 1.5 SD higher language development scores than children who belong to the lowest quintiles.[71] Socioeconomically disadvantaged children are impeded in brain development due to their predisposition to infections, nutritional deficiencies, exposure to water and food contaminated with neurotoxic chemicals, and, finally, psychosocial reasons, such as parental illiteracy, maternal depression, exposure to violence, child labor, and lack of a stimulating environment. Developmental screening and early childhood

Table 31-3. Major Micronutrient Deficiencies and Their Neurologic Manifestations

MICRONUTRIENT	NEUROLOGIC MANIFESTATIONS CAUSED BY DEFICIENCY	RECOMMENDED DAILY ALLOWANCE[a]
Thiamine (Vitamin B1)	Peripheral neuropathy Delay in language acquisition Auditory processing disorder	Infants: 0.2 mg Toddlers: 0.6 mg School age: 0.9 mg Teenagers: 1.0–1.2 mg
Cyanocobalamin (Vitamin B_{12})	Intellectual disability Myelopathy, neuropathy	Infants: 0.4 mcg Toddlers: 0.9 mcg School age: 1.2 mcg Teenagers: 1.8–2.4 mcg
Dihydroxycholecalciferol (Vitamin D)	Intellectual disability Behavior disturbances Possible schizophrenia	Infants: 400 IU Others: 600 IU
Iron[b]	Intellectual disability Behavior disturbances Stroke	Infants: 0.27–11 mg Males: 7–11 mg Females: 7–15 mg
Folate	Neural tube defects	Infants: 65–80 mcg Toddlers: 150 mcg School age: 200–300 mcg Teenagers: 400 mcg
Iodine	Intellectual disability Microcephaly Spastic diplegia Ataxia	Infants 110–130 mcg Toddlers: 90 mcg School age: 90–120 mcg Teenagers: 150 mcg
Zinc	Intellectual disability Intention tremor Emotional lability	Infants: 2–3 mg Toddlers: 3 mg School age: 5–8 mg Teenagers (male): 11 mg Teenagers (female): 9 mg

[a] Recommended Daily Allowance is the average daily level of intake sufficient to meet nutrient requirements of nearly all (97%–98%) healthy individuals.

[b] Recommended Daily Allowance for iron provided in table is for children who can consume meat. Recommended Daily Allowance for children who are vegetarians is 1.8 times higher.

interventions are needed, such as parenting interventions, center-based learning programs for toddlers, improving the content of children's educational media, educating families about the benefits of preschool education, and monitoring outcomes.[72]

MANAGEMENT

Making the Correct Diagnosis: History and Physical Examination

History is the most important part of the neurologic evaluation. The sequence of evolution of illness and onset of the symptoms, whether they are acute (minutes to hours), subacute (days to weeks), or chronic (weeks to months), and whether the illness is stable or progressive should be carefully elicited. Details on mental functions (eg, lethargy, irritability, cognitive slowing), cranial nerves (eg, vision loss, diplopia, difficulty chewing and swallowing, facial weakness, change in voice), motor (eg, weakness following a specific pattern such as paraparesis or hemiparesis, ataxia), sensory (eg, paresthesia, numbness) and autonomic system (eg, tachycardia, hypertension, sweating), and disturbances of the bowel and bladder should be noted. Details of treatments received with special emphasis on herbal, natural, and traditional remedies should be sought. Recent exanthematous illnesses, minor viral prodrome, animal bites, exposure to pesticides, trauma, swimming in bodies of fresh water, dietary habits, and social circumstances in which the child lives must be carefully elicited. A family history of consanguinity is common in several developing countries and may predispose to metabolic and neurodegenerative disorders. Birth history is of special significance in neurologic disorders, especially if onset of symptoms is temporally related to the perinatal period. Peripartum details, including maternal infections, medical coexisting illnesses, genital ulcers, prior miscarriages, and head circumference at birth, provide useful information. Specific clues toward neonatal encephalopathy, such as delayed or weak cry, poor suck or paucity of spontaneous movements, and poor sleep/wake cycles should be obtained. A detailed developmental assessment elicited from the mother or primary caregiver is relevant in most cases. If necessary, a formal developmental assessment tool may be used. The physical examination is best performed while the child is seated on the parent's lap (in case of a toddler) or with the examiner at the same level as the child. There is no clear-cut order to conducting the neurologic examination; it depends on the child's level of cooperation. Nonthreatening aspects should be performed first to gain the child's confidence; therefore, gag reflex and fundus examination are best left to the end of the examination. The head circumference should be noted and plotted using an appropriate growth chart. Details of a simplified neurologic examination are outlined in Table 31-4.

Table 31.4. Simplified Neurologic Examination

AGE	TODDLER (2–5 Y)	SCHOOL-AGED CHILD (6–18 y)
Mental Status	Observe interaction with family. Does the child explore the environment? Does the child play with toys, or is the child difficult to arouse or irritable?	Specific questions to determine orientation to time, place, and person (eg, "What is today's date, month, year?"; "Where are we now?"; "What is your name?"; "Who are these people here with you?")
Cognitive Status	Does the child talk in phrases? Does the child know body parts, colors, gender; exhibit stranger anxiety; follow simple instructions?	Assess child's ability to read and write, perform math, and draw a picture.
Cranial Nerves	Second (optic): Identify pictures on a handheld Allen chart or picture book.	Use Snellen eye chart if available. Fundus examination to look at optic disc
	Third, fourth, sixth (oculomotor, trochlear and abducens): Track a toy, check pupillary size, look for ptosis.	Check eye saccades by giving instructions (eg, "Look to the right"; "Look up") and eye pursuits by having the child follow an object; check pupillary size; look for ptosis.
	Fifth (trigeminal): Use light touch to check response to sensation on the upper and lower halves of the face.	Use light touch to check response in forehead and upper lid; cheek, upper lip, and lower lid; and chin and lower lip. Check motor function by having the child clench her teeth.
	Seventh (facial): Have the child show her teeth and shut her eyes tight.	Test upper and lower halves of the face by having the child raise her eyebrows, shut her eyes tight, blow up her cheeks, and, finally, smile and frown.
	Eighth (auditory): Rub your fingers and look at the child's response to sound.	Tuning fork if available Finger rub in front of the ear
	Ninth, 10th (glossopharyngeal, vagus): Gag response	Gag response; look for symmetry of palate movements.
	11th (accessory): Hard to test in toddler	Have the child shrug shoulders against resistance (trapezius) and push her face against your hand (sternocleidomastoid).
	12th (hypoglossal): Ask child to stick tongue out and move it side to side; look for fasciculation, atrophy.	Look for tongue motility, size, shape, and unilateral/bilateral atrophy, fasciculation.

Table 31.4. Simplified Neurologic Examination, continued		
AGE	**TODDLER (2–5 y)**	**SCHOOL-AGED CHILD (6–18 y)**
Motor Examination	Observe the child play and walk in the room, get up from a sitting posture on the ground, jump in place, and reach out for objects with one hand at a time; observe for pincer grasp and ability to use both hands equally. Test for tone when the child is quiet. Strength testing is possible in most toddlers at the knee, elbow, and shoulder.	Formal testing of strength in distal and proximal muscles in upper and lower extremities. Grade strength as 0–5 with 0 being weakest and 5 being normal. Test for tone. Look for atrophy, fasciculation, hypertrophy.
Sensory Examination	Use light touch or a wisp of cotton to test for sensation on the extremities and trunk. Note patterns of sensory loss (eg, loss in both lower extremities with presence of a sensory level is suggestive of spinal cord disease; loss of sensation in unilateral arm and leg is suggestive of stroke).	Test all modalities of sensation, including light touch, pinprick, joint position, temperature, and vibration if tuning fork is available. Note pattern of sensory loss.
Reflexes	Superficial abdominal reflexes are hard to elicit in a toddler. For deep tendon reflexes, test biceps, brachioradialis, triceps, and knee and ankle jerks. Absence may be indicative of stroke or spinal cord disease. Exaggerated reflexes are suggestive of upper motor neuron disease process (eg, old stroke, cerebral palsy). Plantar response: A Babinski reflex is physiologic until 18–24 months of age if symmetric.	Both upper and lower quadrants of the abdomen are tested for superficial abdominal reflexes. Absence may indicate spinal cord disease. In a male, cremasteric reflex may be tested. Test biceps, brachioradialis, triceps, and knee and ankle jerks. Grade from 1–4. A downgoing response is normal. Unilaterally upgoing response indicates an upper motor neuron disease process in the opposite hemisphere.
Gait and Cerebellum	Observe posture of the child in sitting position (truncal ataxia) and while walking (broad-based gait or scissoring); look for intention tremor while reaching out for an object.	Ask the child to walk a straight line, heel and toe walk, while observing for abnormalities of gait. Look for dysmetria and intention tremor and perform heel-shin test.

Neurodiagnostic Testing

Spinal Fluid Analysis by Lumbar Puncture

Spinal fluid analysis by lumbar puncture (LP) is relatively easy to perform in most clinical situations. It has a vital role in diagnosing a variety of neurologic diseases, including infections, subarachnoid hemorrhage, and demyelinating diseases. Contraindications to performing an LP include suspicion of raised intracranial pressure due to a space-occupying mass, such as a tumor or abscess. Computed tomography (brain) may not be readily available; therefore, a careful examination of optic discs to rule out papilledema is mandatory before attempting an LP.

Electroencephalogram

An EEG is a 2-dimensional surface representation of electrical activity between neuron networks. Placement of leads on the scalp and actual recording requires prior experience or availability of an EEG technician. Electroencephalogram utilization, ranging from 8% to 70% for a child presenting with a first-time seizure, is noted across developing countries. This variation is in large part determined by the facility where the child in initially evaluated. Electroencephalogram analysis may help in choosing the right anticonvulsant medication, offering prognosis for future seizure recurrence and monitoring in children with status epilepticus.

Neuroimaging

A CT scan is more widely available than an MRI in most parts of the world. Nonetheless, at a cost of US $1,150 per scan and $135,000 for a 16-slice CT scanner, it still remains an expensive test by the standards of several developing countries. Advantages are short scan times (about 5–10 minutes), which avoid the need for sedation, and relative ease of interpretation. Advantages of MRI are the detailed anatomic resolution it affords and radiation avoidance. Oral chloral hydrate (50–75 mg/kg) may be used for mild sedation in children when a MRI is being considered and anesthesia support is not available.

MULTIDISCIPLINARY CARE AND REHABILITATION

The approach to reducing the burden of neurologic disorders in children is multipronged. Improving neurologic care via availability of basic diagnostic facilities at community-level health centers, such as CSF examination, neuroimaging, and EEG; availability of specific drugs, such as acyclovir and anticonvulsants; training primary health workers; developing subspecialty care; implementing newborn screening protocols; and wider immunization coverage are all important. Additionally, promoting

multidisciplinary medical care, early child development programs, interventions directed at parents who are at socioeconomic risk, center-based programs to improve children's cognitive and social-emotional development, and, finally, strong political will to equalize, prioritize, and allocate resources for advancing neurologic facilities in individual countries are needed.

KEY POINTS

- The magnitude of neurologic disorders is largely underrecognized in developing countries with numerous stumbling blocks to the care of these children.
- Neuro-infections and epilepsy are the most common and largely preventable causes of neurologic disease burden in developing countries.
- The higher prevalence of NDDs among children in developing countries has been attributed to perinatal problems, nervous system infections, childhood epilepsy, trauma, and a higher rate of consanguinity.
- Perinatal/congenital disorders such as toxoplasmosis, rubella, cytomegalovirus, herpes simplex infection, and neural tube defects are largely preventable by improving antenatal care.
- The burden of inborn errors of metabolism is greatly under-recognized due to a lack of routine newborn screening and genetic confirmation facilities, as well as high cost of overall care of the affected children.
- The most profound effects of malnutrition are seen in children younger than 5 years due to its effect on the developing brain, peripheral nerves, and skeletal muscles.
- The approach to reducing the burden of neurologic disorders in children should aim at improving neurologic care via availability of basic diagnostic facilities at community-level health centers; availability of specific drugs, such as acyclovir and anticonvulsants; training primary health workers; developing subspecialty care; implementing newborn screening protocols; wider immunization coverage; early child development programs; and developing a strong political will to equalize, prioritize, and allocate resources.

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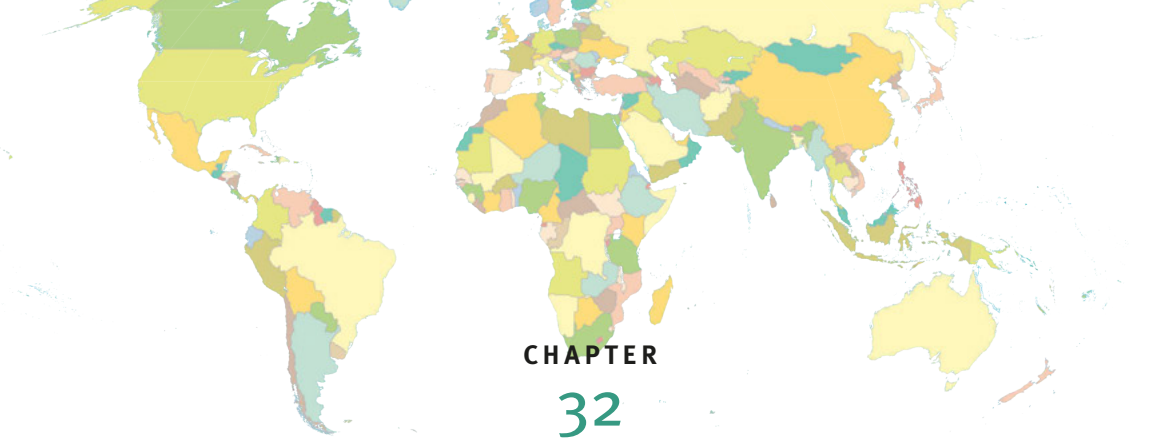

CHAPTER

32

Nephrology

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INTRODUCTION

Every nation has children; thus, every nation has health care professionals who specialize in caring for children's needs. While general pediatricians and other caregivers can be found worldwide, specialists in pediatric disease can be less easy to locate. Even in developed countries, there is a shortage of pediatric nephrology coverage. Pediatric nephrology fellowships do not always fill to capacity in the United States. Other countries have similar problems. Thus, it is to the benefit of all practitioners to have a basic understanding of how to approach diagnosis and management of common renal diseases.

IDIOPATHIC CHILDHOOD NEPHROTIC SYNDROME

Nephrotic syndrome is one of the most common pediatric renal diseases a practitioner is likely to encounter. Approximately 1 to 3 per 100,000 children will develop this condition during their lifetime.[1] In the last few decades, much cooperative work has gone into evaluating best practices for diagnosing and managing childhood nephrotic syndrome. A robust set of guidelines is available from Kidney Disease Improving Global Outcomes (KDIGO), which evaluates workup and treatment options for a wide variety of glomerular diseases.[2]

Definition

As the name implies, nephrotic syndrome is a collection of clinical findings resulting from varied underlying conditions. Clinical signs of childhood nephrotic syndrome include edema, massive proteinuria,

hypoalbuminemia, and hypercholesterolemia. Table 32-1 lists key terms and definitions for discussing childhood nephrotic syndrome. Table 32-2 lists common conversion factors for converting conventional to SI units. The most common type of nephrotic syndrome in childhood is minimal change nephrotic syndrome (MCNS).

Table 32-1. Definitions of Nephrotic Syndrome in Children

CLASSIFICATION	DEFINITION
Nephrotic syndrome	Edema, uPCR ≥2,000 mg/g (≥200 mg/mmol), or ≥300 mg/dL, or 3+ protein on urine dipstick, hypoalbuminemia <2.5 g/dL (<25 g/L)
Complete remission	uPCR <200 mg/g (<20 mg/mmol) or <1+ of protein on urine dipstick for 3 consecutive days
Partial remission	Proteinuria reduction of ≥50% from the presenting value and absolute uPCR between 200 and 2,000 mg/g (20–200 mg/mmol)
No remission	Failure to reduce urine protein excretion by 50% from baseline or persistent excretion uPCR 2,000 mg/g (200 mg/mmol)
Initial responder	Attainment of complete remission within initial 4 weeks of corticosteroid therapy
Initial nonresponder/ steroid resistance	Failure to achieve complete remission after 8 weeks of corticosteroid therapy
Relapse	uPCR ≥2,000 mg/g (≥200 mg/mmol) or ≥3 protein on urine dipstick for 3 consecutive days
Infrequent relapse	1 relapse within 6 months of initial response, or 1–3 relapses in any 12-month period
Frequent relapse	2+ relapses within 6 months of initial response, or 4+ relapses in any 12-month period
Steroid dependence	2 consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy
Late nonresponder	Persistent proteinuria during ≥4 weeks of corticosteroids following one or more remissions

Abbreviation: uPCR, urine protein-to-creatinine ratio.

From Kidney Disease Improving Global Outcomes. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2(2):164, with permission. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-GN-Guideline.pdf. Accessed July 2, 2015.

Table 32-2. Common Nephrology Conversion Factors			
ITEM	**CONVENTIONAL UNIT**	**CONVERSION FACTOR**	**SI UNIT**
Albumin	g/dL	10	g/L
Calcium	mg/dL	0.25	mmol/L
Calcium	mEq/L	0.5	mmol/L
Creatinine	mg/dL	88.4	μmol/L
Oxalate	mg/L	11.1	μmol/L
Phosphorus	mg/dL	0.323	mmol/L
Protein, Total	g/dL	10	g/L

From GlobalRPH. Conventional units to SI units—conversion factors. http://www.globalrph.com/conv_si.htm. Accessed June 11, 2015.

Symptoms

Edema

Edema in pediatric patients with nephrotic syndrome is gravity dependent. As such, it is most noticeable around the eyes in young children (who spend a lot of time lying down) and in older children on awakening from sleep. In all patients, edema is marked in the pretibial area in the afternoon or after a period of upright activity. Typically, edema is found in patients with a serum albumin of less than 2.5 g/dL. Other causes of edema that should be considered include poor nutrition, protein-losing enteropathy, and congestive heart failure.

Proteinuria

Proteinuria in active idiopathic nephrotic syndrome is massive. Therefore, it is very helpful to quantify the amount of proteinuria to help differentiate idiopathic childhood nephrotic syndrome from other conditions (eg, acute glomerulonephritis) that typically cause lower-level proteinuria. There was a time when diagnosis of idiopathic nephrotic syndrome required checking the amount of protein spilled in the urine over 24 hours. This is a complicated test to perform, primarily because collecting all of a small child's urinate over 24 hours can be difficult. Fortunately, the urine protein-to-creatinine ratio (uPCR) in a spot urine sample is the new standard. Checking the amount of protein in a urine sample and indexing that to the amount of creatinine in that same sample provides insight into how much protein spilling is occurring.

Any laboratory with the facility to do a 24-hour urine analysis can also do a uPCR by applying the same procedures but to the smaller sample.

A number of other conditions can cause proteinuria in the non-nephrotic range. The most common cause of non-nephrotic proteinuria in the pediatric age group is orthostatic proteinuria, a condition in which the patient has proteinuria after standing for some time that virtually disappears when supine. The best way to rule out orthostatic proteinuria is by obtaining a first morning urine for uPCR. Getting the first morning urine can be challenging in children; the easiest way to do so is to have the child empty the bladder completely just before bed in the evening, then collect the urine when the child wakes in the morning. If the child does not completely void before bedtime, morning urine can be contaminated with urine made during the afternoon and thus have a false-positive protein level.

While uPCR is the most common metric for evaluating the degree of proteinuria, other standards include the amount of protein on a dipstick urine test (>3) or the amount of protein in a single sample (>300 mg/dL). Because the urine dipstick can give falsely elevated levels if urine is concentrated (specific gravity >1.015, common on first morning urine samples), indexing the amount of protein to the amount of creatinine in the sample is preferred.

Other

A small percentage of patients will also present with hypertension (10%–15%) or microscopic hematuria (about 30%–40%). If both are present, the chance of the patient having a cause of nephrotic syndrome other than MCNS increases.

Workup

Certain laboratory tests are required prior to beginning therapy when a child presents with edema and massive proteinuria (Box 32-1). Documenting a child's weight and blood pressure is important when starting treatment. Weight decrease as interstitial fluid is mobilized and excreted can be a helpful parameter in assessing response to standard therapy for idiopathic nephrotic syndrome: corticosteroids. Urinalysis and uPCR are extremely helpful to provide a quantitative framework for disease activity. In addition, checking a complete blood cell count (CBC) to evaluate for anemia (a useful measure of chronicity in renal disease) and measuring renal function are useful baseline tests.

Other causes of nephrotic syndrome need to be considered in any child with nephrotic syndrome. Clinical signs and laboratory tests can help distinguish among various causes of nephrotic syndrome in

Box 32-1. Workup of Patient With New-Onset Nephrotic Syndrome
Weight/height
Blood pressure
Urinalysis
uPCR
CBC
Serum electrolytes
Renal function
Complement C3 level
HBV, HCV, and/or HIV serology

Abbreviations: CBC, complete blood cell count; HBV, hepatitis B virus; HCV, hepatitis C virus; uPCR, urine protein-to-creatinine ratio.

children. Membranoproliferative glomerulonephritis, systemic lupus erythematosus, and postinfectious glomerulonephritis can all consume complement C3; documenting a low C3 level can suggest these etiologies. Membranous nephropathy, while it can be idiopathic, is frequently seen in the presence of chronic infection such as HIV or hepatitis B; depending on the local epidemiologic situation, checking can be helpful.

STEROID-SENSITIVE NEPHROTIC SYNDROME

First Episode

Steroids are the foundation of all treatment for childhood nephrotic syndrome. Evidence suggests that proper dosing and duration of steroid treatment during the initial nephrotic event can reduce the number of relapses and thus reduce the chronic steroid burden.[3] International guidelines for treating the initial episode of nephrotic syndrome are freely available. The KDIGO provides the following evidence-based guidelines:

> *3.1: Treatment of the initial episode of [steroid-sensitive nephrotic syndrome]*
>
> *3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone) be given for at least 12 weeks.*

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose starting at 60 mg/m²/d or 2 mg/kg/d to a maximum 60 mg/d.

3.1.1.2: We recommend that daily oral prednisone be given for 4 to 6 weeks followed by alternate-day medication as a single daily dose starting at 40 mg/m² or 1.5 mg/kg (maximum 40 mg on alternate days) and continued for 2 to 5 months with tapering of the dose.[2]

Corticosteroid Therapy

Daily oral prednisone is the standard therapy for treating the initial nephrotic syndrome episode, longer duration being better than shorter. Oral and intravenous (IV) prednisone is widely available in the developing world. The oral route is preferred, and single daily dosing is the norm for treating childhood nephrotic syndrome. While there are no randomized, controlled trials looking at dosing regimens, the normal morning cortisol spike has led most experts to recommend that the single dose be given in the morning to limit side effects.

About 80% of children with idiopathic nephrotic syndrome will respond within 2 weeks of instituting therapy; more than 90% will respond by 3 weeks. In some cultures, there will be a strong tendency to stop medication at this point; the practitioner should guard against this with close follow-up and patient education.

Side Effects and Monitoring

Side effects of steroid therapy are well known. Hypertension, weight gain, skin and mood changes, and cataracts are all well-documented risks of steroid therapy. Patients on induction therapy for a first episode of nephrotic syndrome should be monitored. Typical practice would include a follow-up visit 2 to 3 days after initiating therapy to check blood pressure and then again after 2 weeks of therapy to check for remission of proteinuria and review the importance of completing the therapy course. The next follow-up visit would typically occur after 6 weeks of therapy when the steroid dose begins to taper. The practitioner should review steroid side effects, check blood pressure and weight, and discuss skin or mood changes at each visit. In children who require continued or repeated steroid therapy, the possibility of cataract formation exists and should be monitored.

For the initial treatment of a child with nephrotic syndrome, steroids are given in a relatively large dose over a long period. Side effects can be expected with this level of steroid therapy. For the most part,

steroid-associated hypertension and mood changes will resolve with therapy cessation. Patients and families should always be cautioned that weight gained while taking steroids can be difficult to lose once medication is discontinued, so prevention is the best approach. Skin changes can be permanent and should be monitored accordingly. Eye changes, such as cataracts, rarely occur with the first treatment course but may be permanent should they occur.

Relapse Therapy

Idiopathic nephrotic syndrome is a chronic disease in about 70% of cases; in these cases, relapse will occur with edema and protein spilling.[3] A relapse of nephrotic syndrome is defined by a return of proteinuria (uPCR ≥2,000 mg/g or 3+ on urine dipstick for 3 consecutive days). It is not unusual for an ill child with a history of nephrotic syndrome to have an increase in urine protein to trace or 1+ on dipstick, which will generally resolve in 1 or 2 days and does not meet the criteria for a nephrotic relapse. In such cases, urinalysis or uPCR can be used to determine if a relapse is occurring.

Relapse treatment is quite similar to treating the initial event; the major difference is the total time of treatment. When a relapse is identified, the child is started back on oral corticosteroid therapy at 2 mg/kg/d (max of 60 mg/d) given as a single dose daily, ideally in the morning. The main difference between relapse therapy and initial episode therapy is how long this induction therapy is continued. In a relapse, the urine should be monitored and steroids tapered when the urine protein becomes trace or undetectable for 3 days.[2] At this point, corticosteroid tapering can begin with a goal to completely taper off steroids over the next 4 weeks. Tapering schemes vary from an immediate decrease to dosing every other day to gradually decreasing total daily corticosteroid dosing; with all, total time of steroid therapy should be at least 4 weeks beyond the induction therapy.

Frequent Relapse and Steroid Dependence

Corticosteroids

While most children with nephrotic syndrome will have at least one relapse, some will have many. Frequently relapsing nephrotic syndrome (FRNS) is defined as more than 3 relapses in a 12-month period or more than 2 relapses within the first 6 months after initial response. Nephrotic syndrome is said to be steroid dependent if a relapse occurs during steroid therapy or shortly after discontinuing steroids. Table 32-1 provides

definitions of these conditions. Frequently relapsing nephrotic syndrome and steroid-dependent nephrotic syndrome (SDNS) are treated similarly.

Some studies have shown a benefit in using longer term, low-dose corticosteroids to decrease the incidence of relapses. Doses from 0.25 mg/kg/d for as long as 18 months have shown some efficacy in decreasing relapses.[4] While such approaches are inexpensive and corticosteroids are widely available even in resource-limited settings, this does not solve the problem of decreasing the patient's overall lifetime exposure to steroids. Children with nephrotic syndrome who are followed into adulthood are seen to have long-term complications of steroid use, primarily obesity and osteoporosis.[5] While each relapse is treated as previously discussed, when a patient is having frequent relapses, effort should be made to decrease overall steroid exposure by instituting treatment with steroid-sparing agents.

Alkylating Agents

Alkylating agents cyclophosphamide or chlorambucil are the first line of therapy (or perhaps after a trial of long-term, low-dose oral corticosteroids) for a child having frequent relapses.[6] A normal cyclophosphamide regimen would be 2 mg/kg/d given orally for 8 to 12 weeks. Chlorambucil can serve as an alternative to cyclophosphamide and can be given for a shorter duration of 8 weeks. These agents do not typically stop relapses but can decrease the number of relapses per year, thereby decreasing overall corticosteroid dose and toxicity. While not always possible, it is best to have the patient achieve remission of nephrotic syndrome before instituting alkylating agents. These agents are myelosuppressive, so CBCs should be routinely evaluated for leukopenia in patients undergoing therapy with them.

Calcineurin Inhibitors

Third-line drugs are introduced when a patient continues to frequently relapse despite a course of an alkylating agent. At this point, there is a choice in therapy: calcineurin inhibitors or mycophenolate mofetil (MMF). Calcineurin inhibitors have a longer history of use and are more widely studied than the newer agent, MMF.

Early calcineurin inhibitor therapy relied on cyclosporine A (CSA). While effective, CSA had side effects of hypertrichosis and gingival hyperplasia, which made it unpopular with patients and families. Cyclosporine A is also known to cause renal toxicity that can be irreversible. Tacrolimus, the next generation of calcineurin inhibitor, is more widely used now. Tacrolimus causes less hypertrichosis and gingival hyperplasia and appears to control steroid-sensitive nephrotic syndrome,

as does cyclosporine. Tacrolimus has been associated with an increased risk of diabetes mellitus (probably higher than that with CSA) but has much less incidence of nephrotoxicity when compared with CSA.[7,8]

Calcineurin inhibitors can be expensive and require serum drug-level monitoring, which can be a problem in some resource-limited settings. In general, treatment with calcineurin inhibitors should continue for a minimum of 12 months. It should be noted that relapse is common after discontinuing calcineurin inhibitors. Table 32-3 shows doses and target drug levels for calcineurin inhibitors. The lowest level that maintains remission is preferred to avoid nephrotoxicity.

Mycophenolate Mofetil

Mycophenolate mofetil has emerged as an alternative to calcineurin inhibitors for treating FRNS and SDNS.[9] Small studies have shown that MMF may not be as efficacious as CSA in reducing relapses in a patient with FRNS, but that effect appears to be short-lived, and MMF did show significantly less nephrotoxicity.[10]

While MMF may not completely stop all relapses, it does appear to decrease relapse frequency and overall steroid dose required in frequently relapsing and steroid-dependent patients.[11] In studies of MMF use for FRNS and SDNS, doses varied from 300 mg/m^2/d to 1,200 mg/m^2/d. The KDIGO guidelines recommend 1,200 mg/m^2/d in 2 divided doses.[2] Studies have not shown the benefit of drug-level monitoring with MMF use, so routinely monitoring blood levels (done with area under the curve measurements) is no longer required in the clinical setting.

The most common side effects of MMF therapy relate to the gastrointestinal system. Diarrhea and abdominal pain are often alleviated by a decrease in dose. Bone marrow suppression, infection, and lymphoproliferative disorders have been reported with use of MMF as well.

Rituximab

Rituximab is a recently developed anti-CD20 monoclonal antibody that is being researched as a potential treatment for refractory nephrotic

Table 32-3. Drug Doses and Blood Levels for Calcineurin Inhibitors

DRUG	DOSE	TARGET LEVEL
Cyclosporine A	4–5 mg/kg/d in 2 divided doses	12-h trough of 80–150 ng/mL (67–125 nmol/L)
Tacrolimus	0.1 mg/kg/d starting dose	12-h trough of 5–10 ng/mL (6–12 nmol/L)

syndrome. Most research indicates that it may have a role in treating SDNS in establishing remission or decreasing total steroid exposure.[12,13] Ideal protocols for using rituximab are still being evaluated with regard to dosing intervals,[14] number of doses, and post-rituximab adjunct immunosuppressive therapy.[15] Current protocols call for 1 to 4 weekly doses of 375 mg/m^2/dose. Trials in other aspects of this drug's use (eg, post-rituximab immunosuppression, CD20 level monitoring) are ongoing.

STEROID-RESISTANT NEPHROTIC SYNDROME

A patient with steroid-resistant nephrotic syndrome (SRNS) is one of the most difficult types of patients whom a pediatric nephrologist can see. Research has not revealed the key to solving this problem. The recommendation is to refer these patients to an experienced nephrologist for care; however, this may not be possible in resource-limited contexts.[16] In addition to typical SRNS, a form of late SRNS, in which the patient is initially responsive to corticosteroid therapy but develops non-responsiveness, has been described for decades, with few studies looking at reasons and treatment.[17,18] In the last few years, renewed interest in this form of SRNS has led to looking at treatment options and demonstrating usefulness of further immunosuppressive therapy.[19,20]

The KDIGO guidelines for SRNS treatment are similar to the guidelines for FRNS or SDNS, with a few adjusments.[2]

1. Treatment with corticosteroids should continue for a minimum of 8 weeks to define steroid resistance.
2. Calcineurin inhibitors (along with lower-dose corticosteroids) are the preferred initial therapy once steroid resistance is established (see Table 32-3 for doses) and are continued for a minimum of 6 months (up to 12 months if partial or complete remission is seen while on therapy).
3. Should the patient fail corticosteroid or calcineurin inhibitor therapy, MMF with or without high-dose corticosteroids is recommended.
4. Cyclophosphamide is not recommended in SRNS.

In addition to these therapy changes, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers may have a role. The ACE inhibitor dose required for controlling proteinuria is often not as high as that required to control hypertension. Usual practice is to start at a low dose of ACE inhibitor and titrate up as blood pressure allows.

Renal Biopsy

Renal biopsy plays a role in the management of steroid-sensitive nephrotic syndrome, but the underlying pathology in the kidney is not the primary concern in treatment—steroid sensitivity is. Renal biopsy may not be possible in many resource-limited areas; however, good evidence-based treatment of childhood nephrotic syndrome will be. Biopsy should be considered whenever there is a high index of suspicion that the underlying pathology may be different from MCNS (ie, indicators of systemic lupus). Elucidating the underlying pathology can help explain why a patient is not responding to steroids, as some pathologies are more associated with a frequently relapsing or steroid-dependent course than others. Despite this, the best judge of prognosis for the nephrotic child is still response to steroids in initial and subsequent episodes.

Adjunct Therapy for Nephrotic Episodes

Edema/Ascites

Edema is a frequent concern of nephrotic patients. Often the presenting sign of nephrotic syndrome, it can be quite distressing to parents. It is not uncommon for children to initially see an allergist or other specialist due to periorbital edema that is thought to be from other etiologies.

Edema of nephrotic syndrome is not the same as edema from other etiologies. Although the child appears to be volume overloaded, it is important to keep in mind that the child may actually be intravascularly volume depleted, euvolemic, or volume overloaded. A careful evaluation of the child's volume status should be conducted to guide interventions for edema. The child with intravascular volume depletion may well have hypertension, as the kidneys struggle to maintain blood pressure in the face of an apparent volume depletion.

Edema can appear in many places; the most common places include the periorbital and pretibial areas. Some patients are so disfigured by facial edema that the tendency is to want to treat the edema directly by administering diuretics. Given that the edematous nephrotic patient may be intravascularly volume depleted, using diuretics alone prior to a considered assessment of volume status is obviously ill advised. Such a move would be safe in a child with volume overload; however, it may increase the volume depletion and could increase the risk of clotting in one with intravascular volume depletion.

A dose of albumin (total dose 0.5–1 g/kg), along with a diuretic such as furosemide (0.5–1 mg/kg/dose), may be helpful if a patient

has concerning edema (eg, pleural or pericardial effusions, pulmonary edema). Intravenous albumin can increase intravascular volume, as fluid is mobilized from the interstitial spaces, thus dramatically increasing blood pressure, making diuretics necessary. One useful method (sometimes referred to as the albumin-furosemide sandwich) is to give half the dose of albumin, then a full dose of furosemide, and then the second half of the albumin dose. Careful monitoring of the child during albumin infusion can be a helpful guide for the need to interrupt the dose to give diuretics.

As long as the patient continues to spill protein, IV albumin is only a stopgap measure, employed when edema is threatening the function of vital systems. The focus of therapy is on treating the protein leak, while albumin is an adjunct to assist with symptoms in the early phases.

Infection

Nephrotic patients are at increased risk of infection because the protein being spilled through the kidneys includes immunoglobulins. In the past, this has led some experts to give prophylactic antibiotics to all patients while they are nephrotic, which is still a common practice in some parts of Asia. The KDIGO guidelines do not recommend this practice. Infection is generally of less concern if the protein leak can be stopped with the judicious use of steroids and other therapies.

Practitioners should keep in mind the infection risk when faced with a child with ascites as a result of nephrotic syndrome. The temptation is to do a paracentesis to drain fluid from the abdomen. However, this is an ill-advised intervention given the rich culture medium in the abdominal ascites fluid and the lower resistance to disease of the patient with active nephrotic syndrome.

The most common infectious complication of active nephrotic syndrome is spontaneous bacterial peritonitis, which typically manifests as fever and abdominal pain. It is difficult to predict which patients will experience this complication, although some have suggested that lower-serum albumin (<1.5 mg/dL) at the time of disease onset may be a useful risk indicator.[21] The organisms associated with this sort of complication originate in the patient's normal flora (eg, *Streptococcus* species, gut flora); thus, antibiotic therapy should be instituted accordingly. Occasionally, signs are subtle, and there are times when a paracentesis is required to make a diagnosis and get a causative organism. Such decisions should be weighed with the risk of the procedure introducing new organisms and making the problem worse. However, if diagnosis is obvious, the practitioner can forego paracentesis and treat according to likely organisms.

Nutrition

Nutrition is always a concern in children. There are a few special issues that must be considered when a child has nephrotic syndrome.

Total body sodium may well be high in a child who is actively nephrotic. Given this and the propensity for such children to develop hypertension, sodium restriction is advised. Keeping a child to a 2-g sodium diet is ideal; this may require some creativity in certain cultures in which salt is an important part of cooking and food preservation.

Children need protein to grow. Certain adult renal diseases require protein restriction; however, in children, it is better to allow protein intake and monitor growth and renal function.

As previously mentioned, obesity is a common result of long-term steroid therapy. When a child is placed on corticosteroids for nephrotic syndrome, the family should be counseled on good nutrition habits to help prevent excessive weight gain.

GEOGRAPHIC VARIATIONS IN NEPHROTIC SYNDROME PATHOLOGY

While steroid sensitivity is the most important indicator of prognosis in idiopathic childhood nephrotic syndrome, different pathologies of the disease are more or less likely to be steroid sensitive. Due to limited resources, not every country has the ability to perform extensive pathologic studies, but some studies do exist that look globally at the different types of biopsy results (Table 32-4).[22–25]

Table 32-4. Geographic Variation of Nephrotic Syndrome Pathology

STUDY	REGION	MCNS	FSGS	Memb	MPGN	IgA	OTHER
Narasimhan et al[22]	India	11.6%	17%	9.8%	3.7%	8.6%	20.2%
Bhimma et al[23]	South Africa Indian children African children	46.8% 13.5%	20.6% 28.4%				
Alwahaibi et al[24]	Oman	17%	21.2%	12.3%		8.3%	
Wang et al[25]	China	10.5%	1.4%	8.6%	1.6%	28.2%	49.7%[a]

Abbreviations: FSGS, focal segmental glomerulosclerosis; IgA, IgA nephropathy; MCNS, minimal change nephrotic syndrome; Memb, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.

[a] In Wang et al,[25] the largest percentage of patients showed mesangial proliferative glomerulonephritis: 38.9%.

HENOCH-SCHÖNLEIN PURPURA

Epidemiology

Henoch-Schönlein purpura (HSP) is the most common small-vessel vasculitis in children. Normally, HSP presents with purpuric rash and joint and abdominal pain; however, up to 50% of patients may have renal manifestations, with 25% having significant renal disease as a consequence of the vasculitis. Annual incidence of vasculitis is between 3 and 26.7 cases per 100,000 children.[26]

Global differences in incidence are difficult to determine given the lack of long-term follow-up and comparative studies. The percentage of vasculitis in patients with HSP was 26.1%. in a Malaysian study.[27] A study in central China looked at 15 years of renal biopsy data for patients with all-cause renal disease and found that as many as 35.8% of the biopsy specimens had evidence of HSP disease, making HSP the second most common cause of secondary glomerulonephritis in this sample. Other studies found slightly lower numbers in East Asia.[25] Although a small series of patients are reported from Africa, similar large-number, population-based studies are lacking.[28,29]

A number of experts have suggested a genetic link to explain variations in incidence between nationalities. Mediterranean fever mutation,[30] cytotoxic T lymphocyte–associated antigen 4 exon-1 +49A/G polymorphism,[31] Ras gene polymorphism,[32] and Th17/regulatory T cell 21,[33] among others, have been investigated as possible indicators to aid in determining which patients are at most risk for developing long-term renal disease. Thus far, there is no consensus on immunologic markers that are useful for prognostic prediction.

Presentation

Henoch-Schönlein purpura is a disease diagnosed clinically. The mean age of onset is 5 years, and there tends to be a slight male predominance and seasonal variation (autumn and winter onset more frequent). There may also be an association with preceding infectious illness. Several diagnostic methods have been suggested. The American College of Rheumatology provides one of the oldest diagnostic criteria but may lend itself to overdiagnosis.[34] The European League Against Rheumatism has suggested a slight variation to add specificity, which allows for older patients and includes signs of renal disease.[35] Both criteria are summarized in Table 32-5.

Table 32-5. Diagnostic Criteria for Henoch-Schönlein Purpura

AMERICAN COLLEGE OF RHEUMATOLOGY[34]	EUROPEAN LEAGUE AGAINST RHEUMATISM[35]
Two or more of the following criteria:	Major: Palpable purpura or petechia
Age <20 y at onset	Minor (at least one):
Palpable purpura	Diffuse abdominal pain
Acute abdominal pain	Biopsy showing IgA deposition
Biopsy evidence showing granulocytes around arterioles or venules	Arthritis/arthralgia

Skin

Rash is typically the presenting sign of HSP. It typically appears on the extensor surfaces as petechia that may coalesce into palpable purpura. There is no accompanying thrombocytopenia or pruritus. While the rash is typically on the lower extremities, it may also be seen on the buttocks, scrotum, upper extremities, and even the face. The rash may be accompanied by edema of the extensor surfaces of the hands and feet.

Joints

The majority of patients have joint involvement (60%–86%), most commonly of the ankles and knees, which may be in the form of arthralgia or frank arthritis with swelling and tenderness. Joint symptoms are temporary and do not progress to erosive disease.

Gastrointestinal

Abdominal pain is a common feature (up to 76% of cases) and is occasionally accompanied by intestinal bleeding and vomiting. It is important to note that abdominal pain may precede the rash in up to one-third of patients.[36] In some studies, the presence of occult blood has been quite common (from 18%–50%).[37,38] Intussusception, pancreatitis, bowel ischemia and infarction, and late ileal stricture have also been reported.[36,39]

Renal

The problem with any disease like HSP that causes acute symptoms but may well lead to chronic problems is deciding which patients are likely to progress to chronic illness. Most HSP is self-limited, resolving without any residual renal disease. While not common, renal lesions may lead

to chronic illness and even end-stage renal disease (ESRD). Determining which patients are at risk for such progression is difficult and a frequent focus of study in this field.

Acute renal disease can present with a gamut of symptoms[40]: microscopic hematuria, gross hematuria, hypertension, renal insufficiency, and non-nephrotic and even nephrotic range proteinuria. Box 32-2 lists Meadows classes,[41] which is a framework for clinically thinking about these renal manifestations. Patients with a more severe disease at outset (nephrotic syndrome, nephritic syndrome, or mixed) may benefit from renal disease staging via renal biopsy. Biopsy results can be staged using the International Study of Kidney Disease in Children criteria listed in Table 32-6.

Determining the prognosis of HSP is still difficult and, thus, expectant follow-up is required. Studies suggest that the older the patient is at disease onset, the more likely he is to have renal disease.[37] This is supported by the significantly worse course in adults diagnosed with HSP.[38] Progression to chronic renal disease is fairly slow, so expectant monitoring of the patient's blood pressure, symptoms, and renal function (including chemistries and uPCR) every 3 to 6 months is generally adequate.

Treatment

Nonrenal manifestations of disease will generally resolve without consequence, although patients with marked abdominal complains may get relief from a brief course of corticosteroids. Patients will occasionally have a relapse of skin or abdominal complaints over the 6 months after the first episode, but they rarely require treatment.

One of the most frustrating aspects of HSP is that few treatment options have been identified to prevent renal progression despite it being recognized since the late 1800s. The best evidence available suggests

Box 32-2. Classes of Renal Involvement
Microscopic hematuria
Non-nephrotic proteinuria and/or hematuria
Nephritic syndrome (hematuria, renal insufficiency, hypertension, edema)
Nephrotic syndrome (with or without hematuria)
Mixed nephritic/nephrotic picture

Table 32-6. International Study of Kidney Disease in Children Henoch-Schönlein Purpura Pathologic Classification

CLASS	PATHOLOGY
I	Minimal glomerular alterations
II	Mesangial proliferation only
III	<50% glomeruli containing crescents, segmental lesions of thrombosis necrosis, or sclerosis
IIIa	Focal mesangial proliferation
IIIb	Diffuse mesangial proliferation
IV	Similar mesangial proliferation to III but with 50%–75% crescents
V	>75% crescents
VI	Pseudo-membranoproliferative pattern

using ACE inhibitors or angiotensin receptor blockers in patients with renal disease and persistent, low-grade proteinuria (0.5–1 g/d per 1.73 m^2 body surface area) may be beneficial.[2]

Using steroids to prevent renal disease is not recommended; however, if proteinuria is persistent and higher grade (1 g/d per 1.73 m^2), a 6-month trial of oral corticosteroids is warranted.[42] Two regimens of steroids have been suggested: 1 g/d for 3 days each in months 1, 3, and 5, followed by 0.5 mg/kg prednisone orally on alternate days, to treat for a total of 6 months,[43] or 0.8 to 1 mg/kg/d for 2 months, followed by 0.2 mg/kg/d for 4 more months, for a total of 6 months.[44] The benefit of steroid therapy for HSP nephritis in children has only been seen in uncontrolled trials; randomized, controlled clinical trials have not demonstrated a benefit of steroids alone.

Other immunosuppressive regimens, including azathioprine, cyclophosphamide, cyclosporine, plasma apheresis, and IV immunoglobulin, have been investigated, but large, randomized trials have not been done to evaluate the efficacy of such treatments. Adjunct therapeutic approaches have been tried, including traditional medicines,[45] anticoagulants, and tonsillectomy, but again, the evidence for benefit is insufficient thus far.[36]

Prognosis

Prognosis for HSP, even for those with renal involvement, is generally good. The more severe the renal involvement, the more likely the patient is to progress to long-term complications such as hypertension or renal insufficiency. However, prognosis is excellent for younger patients with less-severe renal involvement.[46]

HEMATURIA/GLOMERULONEPHRITIS

Gross and microscopic hematuria are common presenting symptoms in the pediatric nephrology clinic. Gross hematuria is distressing to parents in many cultures even though the problems associated with it are often of less concern than proteinuria. Microscopic hematuria is a common presenting complaint in areas where routine urinalysis is performed for well-child checks or preparticipation physical examinations.

Workup of Hematuria

Hematuria workup starts with determining the extent of the disease and attempting to determine the source of the bleeding. Simple observation of the urine can be suggestive, if not perfectly reliable. Red urine generally implies a source lower down in the urinary tract, while dark brown or tea-colored (red tea) urine implies a source higher up. Microscopic analysis of the urine can also be helpful (eg, are there cellular casts?). Red cell casts are usually a result of bleeding in the renal parenchyma, as the cells are packed together to form the cellular cast. Lack of red cell casts does not rule out upper tract bleeding; thus, all data should be taken in aggregate with the clinical situation to assess the cause of hematuria and develop treatment plans.

Blood tests should include evaluating CBCs, checking compliment levels (especially compliment C3), and evaluating renal function, including albumin. In some cases, urine cultures or antibody screens (see Acute Postinfectious Glomerulonephritis on page 952), family urinalysis (see Benign Familial Hematuria on page 956), or further testing of the patient's mineral metabolism may be warranted. Imaging the kidney can also be helpful, especially if hypercalciuria or renal stones are suspected. Physical examination should focus on looking for signs of nephritis: hypertension, swelling, and rashes.

Idiopathic Hypercalciuria

When too much calcium is in the urine, this can cause irritation and microscopic bleeding. Idiopathic hypercalciuria is the most common cause (other causes are listed in Box 32-3). While idiopathic

Box 32-3. Differential Diagnosis of Hypercalciuria
High dietary calcium
Calcineurin inhibitor (cyclosporine or tacrolimus) nephrotoxicity
Hypercalcemia
Renal tubular acidosis
Bartter syndrome
Pseudohypoaldosteronism type 2 (Gordon syndrome)
Primary hyperparathyroidism
Excess vitamin D
Sarcoidosis
Autosomal-dominant hypoparathyroidism
Hypophosphatemia
Hereditary hypophosphatemic rickets with hypercalciuria

hypercalciuria is a very common cause of microscopic hematuria, it is fortunately not difficult to treat.

Evaluation

Evaluation requires quantifying the amount of calcium in the urine, which is done by indexing calcium in a spot urine sample to the amount of creatinine and calculating a urine calcium-to-creatinine ratio (uCaCr). In a child, a uCaCr greater than 0.2 mg calcium/mg creatinine is considered elevated and merits monitoring or intervention (higher ratios may be quite normal in infants). If a uCaCr is not possible, a 24-hour urine is required to look for elevated calcium excretion. Further testing the patient's mineral metabolism by looking at phosphorus levels, parathyroid hormone, and vitamin D levels may be warranted.

Symptoms

Symptoms of hypercalciuria range from painless microscopic hematuria to painless gross hematuria, chronic abdominal pain, or even recurrent renal stone formation. Renal stones are a problem that persist throughout the world, although they are not as common in children as they are in adults. Patients (children and adults) with recurrent stone formation

from various countries have been studied, with the percentage having hypercalciuria ranging from 5.6% in Iran[47] to 47% in Croatia,[48] although most studies report percentages in the mid-teens to 20s.[49–53]

Treatment

First-stage treatment of hypercalciuria is simply diluting the urine. This is often most easily and inexpensively accomplished by increasing water intake of the patient to 3,000 mL/m^2/d. Many mild cases will require no further treatment if the patient can keep up the water intake. Should this not be possible or the patient continues to have symptoms or an elevated uCaCr, diuretics can be used to further dilute the urine. Hydrochlorothiazide is inexpensive and readily available in many countries and is the first drug of choice for hypercalciuria. A typical starting dose of hydrochlorothiazide would be 0.5 to 1 mg/kg/d divided into 2 daily doses and adjusted upward if blood pressure permits and hypercalciuria persists.

Diet can be adjusted in conjunction with increasing water intake to assist in controlling hypercalciuria. Achieving a low-sodium diet is difficult in much of the world, but the benefits for ameliorating the effects of hypercalciuria are clear. A low-salt diet is important, as it seems to help decrease hypercalciuria as well as possible stone formation.[54] Considering a diet low in oxalate may be beneficial as well because patients with hypercalciuria appear to be at increased risk for stone formation later in life. When a Dietary Approaches to Stop Hypertension (DASH) diet (a diet low in sodium and high in vegetables and dairy products) was studied versus a diet low in oxalate, the findings suggested (results were not statistically significant) that the DASH diet may decrease calcium oxalate supersaturation despite increasing urinary oxalate. This decreased calcium oxalate supersaturation may lead to less stone formation. Further study in dietary manipulations is warranted.[55]

Acute Postinfectious Glomerulonephritis

Acute postinfectious glomerulonephritis (APIGN) is one of the most frightening renal-related diseases to deal with. The patient arrives with gross hematuria, very high blood pressure, possibly edema, rash, or even altered mental status. Fortunately, most pediatric patients recover quickly, as this condition is usually self-limited with an excellent prognosis.

Epidemiology

Acute postinfectious glomerulonephritis affects males slightly more than females and is most common in the 2- to 6-year age group. Most

of these cases occur after infection with *Streptococcus pyogenes*. In recent years, awareness is growing of other bacterial[56,57] and even viral[58,59] and parasitic causes of the disease.[60] Streptococci species may account for as few as 28% to 47% of these cases, with staphylococci and gram-negative bacteria making up the diffirence.[61]

For the most part, children continue to develop APIGN after an infection from nephritogenic *Streptococcus* species. In the past, most nephritogenic strains infected skin, leading to the adage that impetigo can lead to glomerulonephritis and streptococcal pharyngitis leads to rheumatic disease. While this is no longer as clear cut, anything that increases the chance of streptococcal skin infection (eg, eczema, scabies infestation, burns) will increase the risk of glomerulonephritis. However, adults are more likely to develop glomerulonephritis after other infections and often have a more troublesome course.[62] As such, the global epidemiology of this condition follows the epidemiology of the underlying infectious agents.

Symptoms

Typically patients present after the infectious insult, 10 to 14 days after a streptococcal throat infection or 4 to 6 weeks after the resolution of impetigo (other infectious agents are not as well characterized as to course). This is a disease of immune-complex deposition: the infection that started the problem occurred in the past, as it takes time for immune complexes to form and cause damage.

Gross hematuria is the most common presenting complaint, with urine described as brown, red, or tea colored (in countries where red or black tea is commonly consumed). On examination, there may be evidence of recent skin infection and edema. There is often marked hypertension and occasionally mental status changes.

Evaluation

Measuring blood pressure and checking urinalysis and a compliment C3 level are essential to make the diagnosis. Urinalysis typically shows hematuria, possibly with casts if a careful microscopic examination is done. Patients with APIGN may also have non-nephrotic range proteinuria.

Looking for evidence of prior infection with an antistreptolysin titer or anti-deoxyribonuclease B can be helpful. There is a temptation to perform a throat culture, but because this is a postinfectious condition, throat cultures are rarely helpful. Checking renal function and CBCs also helps to guide therapy.

Treatment

Treatment is primarily supportive. Addressing blood pressure and maintaining fluid balance without allowing fluid overload are the primary goals. If blood pressure is only mildly elevated, watchful waiting is the best course of action. In a situation in which blood pressure is markedly elevated and renal function is diminished, intervention may be necessary. Hypertension is due to volume expansion, so loop diuretics are a good first choice for treatment. Furosemide can be started at 2 mg/kg/dose orally and increased as needed for appropriate control. If diuretics don't adequately control hypertension, ACE inhibitors may be useful. Angiotensin-converting enzyme inhibitors do carry the risk of decreasing renal blood flow and worsening hyperkalemia and should be used with caution. In patients with mental status changes, nitroprusside (via continuous infusion of 0.5–2 mcg/kg/min) or diazoxide is frequently useful.

Parents should be counseled that recovery is generally quite good for children with APIGN but that microscopic hematuria may well persist for up to 2 years. Most practitioners will monitor children after recovery from glomerulonephritis until urine is consistently clear of blood. Monitoring of such children primarily consists of checking growth, renal function, and blood pressure.

IgA Nephropathy

Also known as Berger nephropathy, IgA nephropathy (IgAN) is one of the most common types of glomerulonephritis. It is typically a disease of adults but does occur in children. On biopsy, IgAN looks much like HSP, but clinically, they can be distinguished by the lack of rash, joint symptoms, and other systemic involvement in IgAN.

Epidemiology

IgA nephropathy shows a marked geographic variation; as a percentage of biopsy findings, it varies from region to region. This was thought to be the result of some regions doing fewer biopsies than others, but as numbers of biopsies increase, percentages hold true. With percentages as high as 30% in Asia and Pacific Rim countries and as low as 20% in Europe and even lower in Africa, there is quite a variation in effect of disease. Table 32-7 shows some of the specific percentages from various biopsy results surveys.[25,63–68]

Presentation

Most children with IgAN present with painless hematuria (microscopic or gross) and few to no other symptoms. There may be a history of recurrent gross hematuria, particularly with concurrent infections. Of note,

Table 32-7. IgA Nephropathy Geographic Variation	
REGION	**PERCENTAGE**
South Africa	5.8%[63]
Kingdom of Saudi Arabia	5.8%–13.6%[64]
Morocco	12%[65]
Midland Rural China	18%[25]
Croatia	19.3%[66]
Italy	22%[67]
Hong Kong	35%[68]

gross hematuria of IgAN generally occurs 1 to 2 days after any concurrent infection, helping to differentiate it from APIGN. Also differentiating it from APIGN is the fact that compliment C3 levels are normal. If there is proteinuria, it is typically less than 1 g/d but can occasionally be in nephrotic range. Hypertension, if present, is usually mild to moderate. Diagnosis is based on symptom pattern and, when necessary, renal biopsy. Serum IgA levels do not help make this diagnosis.

Treatment

The most important aspect of treatment of IgAN is blood pressure control. Risk of progression of IgAN is associated with proteinuria, hypertension, and renal function at time of diagnosis. Rate of decline of renal function increases with the level of proteinuria; thus, protecting the kidney by treating even mild proteinuria is advised.[2] Angiotensin-converting enzyme inhibitors can be helpful in controlling blood pressure, preserving renal function, and decreasing low-level proteinuria sometimes seen in IgAN. The goal of ACE inhibitor treatment is to get the proteinuria below 1 g/d/1.73 m^2.

If the patient continues with proteinuria greater than 1 g/d after 3 to 6 months of ACE inhibition, KDIGO guidelines suggest corticosteroid use as previously described for treating persistent proteinuria in patients with HSP.

Fish oil supplementation has been shown to be beneficial in adult patients with IgAN and many experts recommend its use in children as well. Data are not strong for this intervention, but side effects of fish oil therapy are minimal. The dose of fish oil should be 3.3 g/d and added to a supportive regimen that includes ACE inhibition.[2]

Many other interventions have been suggested, but current data do not support their use: calcineurin inhibitors, alkylating agents, antiplatelet agents, and tonsillectomy.

Prognosis

Up to 30% of IgAN patients progress to renal insufficiency and ESRD. Prognostic indicators of risk of progression are of keen interest, but studies in children are lacking. Children rarely progress to ESRD from IgAN in the childhood period; generally, such progression takes 15 to 20 years. In adults, it is quite clear that hypertension, proteinuria (>1 g/d/1.73 m^2), and renal insufficiency at diagnosis all affect long-term prognosis. Others have suggested that a family history of hypertension and histologic grade of initial biopsy may also help predict risk of progression to ESRD.[69]

Benign Familial Hematuria

The line distinguishing Alport syndrome (hereditary nephritis with sensorineural hearing loss and ocular changes) from benign familial hematuria is hard to determine. Renal disease will never progress in some patients presenting early in life with isolated microscopic hematuria. If biopsy is performed, many of these patients will have thin basement membranes and be classified as benign familial hematuria or thin basement membrane disease.

Epidemiology

A survey of biopsies of kidneys donated for transplant (ie, from healthy individuals) has shown an incidence of thin basement membranes in 5% to 9% of the samples.[70] If looking at a population of patients with isolated hematuria, no proteinuria, no hypertension, and normal renal function, the percentage with thin basement membranes is more like 28% to 36%.[71,72]

Kindred of Alport syndrome have been reported for many years. Early in the course of disease, patients with Alport syndrome may have only isolated hematuria and basement membranes may be thin on renal biopsy. About one-fourth of Alport syndrome patients have sensorineural hearing loss, and ocular lesions (eg, lenticonus, keratoconus, spherophakia) are even less common. Practitioners should be careful to follow patients with isolated hematuria (microscopic and/or episodically macroscopic) and a family history of the same to watch for disease progression. Patients with benign familial hematuria do not typically progress but are easily confused with having Alport syndrome.

Presentation

Patients typically present with isolated microscopic hematuria; occasionally, a history of episodic gross hematuria associated with illness may be elicited. Patients do not typically have proteinuria, and if they do, it should be less than 500 mg/1.73 m^2/d. Hypertension and impaired renal function should prompt a workup for other causes.

Treatment

Treatment is not required for true benign familial hematuria, but follow-up to distinguish between this and Alport syndrome is indicated.

Prognosis

Some of these patients may be early in the course of Alport syndrome. As such, follow-up is needed to monitor for worsening renal function. Most patients with thin basement membrane nephropathy in the absence of Alport syndrome will have a benign course.

HYPERTENSION IN CHILDREN

In the past, the vast majority of high blood pressure in children was due to secondary disease, most often renal disease. With increasing rates of obesity and more sedentary lifestyles in the West (and other parts of the world), essential hypertension is becoming a bigger part of pediatric practice.

Evaluation

Normal blood pressure in children is dependent on gender, age, and height. Normal values are shown in Table 32-8; diagnostic and therapeutic decisions can be guided by staging hypertension according to the criteria.[75]

Prehypertension

Children with blood pressure between the 90th and 95th percentiles should be considered prehypertensive. Closely monitor these children for progression and encourage lifestyle changes.

White Coat Hypertension

Some children's blood pressure will be elevated in the clinic and change rapidly during the visit. Ambulatory blood pressure monitoring can be done (if resources allow) if the blood pressure shows an average above the 95th percentile for gender, age, and height on recheck in the clinic, but diagnosis is still in question. Blood pressure checks can also be done at school or home if a trained person is available to do the testing.

Table 32-8. Diagnostic Criteria for Hypertension in Children

CATEGORY	CRITERIA
Normal BP	SBP, DBP <90th percentile for gender, age, and height
Prehypertension	SBP or DBP ≥90th percentile (≤95th percentile in children); BP >120/80 in adolescents
White coat hypertension	BP >95th percentile in clinic but less outside clinic setting; ambulatory BP monitoring may be required for diagnosis.
Hypertension	SBP and/or DBP >95th percentile for gender, age, and height on 3 separate occasions
Stage 1 hypertension	SBP and/or DBP >95th percentile but ≤99th percentile for gender, age, and height
Stage 2 hypertension	SBP and/or DBP 5 mm Hg >99th percentile for gender, age, and height

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Hypertension

Because children's blood pressure varies, diagnosis of hypertension is not usually made until the child demonstrates high blood pressure on 3 occasions: in the clinic, with ambulatory monitoring, or during school blood pressure checks. Hypertension in children can be divided into 2 stages. Children in stage 1 are evaluated for underlying causes, end-organ damage, and comorbidities such as obesity and dyslipidemia. Children with stage 2 hypertension should undergo a more extensive evaluation for possible treatable causes for the hypertension as well as evaluation of comorbidities.

Once diagnosis and staging are established, treatment decisions can be informed by checking for end-organ damage. If possible, an echocardiogram can be very helpful for evaluating for left ventricular hypertrophy, particularly in patients with questionable blood pressure. Retinal damage is less common but would indicate the need for more aggressive treatment.

Differential diagnosis of secondary hypertension is extensive; Table 32-9 gives a few possible diagnoses that should be considered.

Table 32-9. Differential Diagnosis of Hypertension	
CATEGORY	**DIAGNOSES**
Endocrine	Hyperthyroid, Cushing syndrome, aldosteronism, adrenal hyperplasia
Tumor	Wilms tumor, neuroblastoma, pheochromocytoma
Cardiovascular system	Coarctation of aorta
Renal	Chronic renal failure, tuberous sclerosis, renal artery stenosis, polycystic kidney, multicystic renal dysplastic
Exogenous	Anabolic steroids or drugs of abuse
Rheumatologic	Systemic lupus erythematosus
Infectious	Postinfectious glomerulonephritis
Other	Liddle syndrome, Turner syndrome, Williams syndrome, sleep apnea

Treatment

Diet and Exercise

Children at all stages, from prehypertension to stage 2 hypertension, will benefit from dietary manipulation to improve health. Fat and salt restriction have proven helpful in decreasing blood pressure, but these guidelines can be difficult to follow in areas where food labeling is rare. The DASH diet has also proven helpful in managing hypertension and decreasing blood pressure and need for medication and is easier to follow when food labeling is not common. The DASH diet is high in fresh fruits and vegetables and low-fat dairy products and low in salt. Such approaches have been well studied in the West,[74] and studies are happening with global populations as well[75]; all show a benefit to controlling blood pressure.

Exercise benefits children by lowering blood pressure and decreasing weight. A dose response has been noted between amount of exercise and lowering of blood pressure.[76] This has led to the recommendation of 1 hour per day of moderate physical activity and at least 3 hours per week of vigorous physical activity.[77]

Drug Therapy

Patients with symptoms of hypertension (eg, headache, dizziness, seizure) and stage 2 hypertension should begin drug treatment immediately. Patients with stage 1 hypertension and no end-organ damage can be given a trial of diet and exercise management; should their hypertension persist, drug treatment may be necessary. Additionally, patients with stage 1 hypertension and comorbid conditions should be considered for treatment.

Several classes of drugs are available for use in hypertensive children. Thiazide diuretics, ACE inhibitors, calcium channel blockers, and beta-blockers are all available. The goal of antihypertension therapy is to maintain the patient's blood pressure on the lowest possible dose of the fewest number of medications. As such, it is advised to start with lower doses and increase until control is achieved. In general, a child is started on one class of drug for a trial period. If the child fails to respond to the first class after an appropriate period at maximal doses, then another class is added. Hydrochlorothiazide is widely available and inexpensive in most parts of the world. A good progression for pharmacologic treatment of hypertension is to start with thiazide diuretics and add ACE inhibitors; while combination medications may not be available in resource-limited settings, giving these drugs as 2 separate pills can be just as effective. Calcium channel blockers and beta-blockers can be reserved for third-line use. Commonly available antihypertension drugs are listed in Table 32-10.

RENAL COMPLICATIONS OF INFECTIOUS DISEASE

Many parts of the world experience burdens of infectious diseases not seen in more developed countries. As a result, practitioners educated in the more developed world may not be familiar with these infections and their renal implications.

Table 32-10. Commonly Available Antihypertensive Drugs

DRUG	DOSE
Hydrochlorothiazide	0.5–1 mg/kg/d, 3 mg/kg/d maximum
Lisinopril	0.07 mg/kg/dose every day (6–16 y)
Amlodipine	0.1 mg/kg/dose given every day or divided into 2 daily doses
Metoprolol	1–2 mg/kg/d divided into 2 daily doses, maximum 6 mg/kg/d (>1 y)

Malaria

In spite of decades of work and significant successes in control, malaria continues to be a problem worldwide, with more than 200 million cases in 2012.[78] It is important for practitioners in malaria-endemic areas to be aware of the renal aspects of the disease.

Plasmodium falciparum, the most deadly form of the disease, can cause an immune-complex mediated glomerulonephritis. Patients with this condition may have mild proteinuria and generally resolve with treatment of malaria. Severely ill patients may progress to acute kidney insufficiency (AKI), which should be addressed. Acute kidney insufficiency in a patient with malaria is an ominous sign, indicating the severity of the disease. Practitioners should keep kidney function in mind when treating *P falciparum* malaria and reduce doses of antimalarial drugs appropriately.[2]

Quartan malaria is the result of chronic infection with *P malariae*. Children may present with transient proteinuria and hematuria, which often resolve with treatment of malaria. In some cases, proteinuria progresses to full blown nephrotic syndrome and should be treated as such. It should be noted that nephrotic syndrome secondary to quartan malaria is often steroid resistant and progression to chronic kidney disease is not uncommon. In the past, quartan malaria presented a significant problem and still occasionally can be at the root of new-onset nephrotic syndrome cases.[79] Since the mid-1970s, however, idiopathic nephrotic syndrome has become a more common cause of nephrotic syndrome in malaria-endemic areas.[80]

P vivax and *P ovale* can cause a transient mesangial proliferative glomerulonephritis, which generally resolves with treatment of malaria. Recent studies suggest that the renal pathology in malaria due to *P vivax* may, in fact, become more of a problem.[81–83] More data are needed in this area. Finally, any disease that causes intravascular hemolysis can lead to AKI, and malaria is no exception.

Schistosomiasis

Schistosomiasis was originally identified as a result of research into the cause of endemic hematuria. Gross hematuria remains the main renal symptom of infection with *Schistosoma* trematodes, but some forms of the infection can present with glomerular disease as well.

There are 3 primary types of *Schistosoma* flukes: *S japonicum* (in East Asia), *S haematobium* (in Africa), and *S mansoni* (in Africa and South America). Each causes slightly different disease with respect to the kidney.

Schistosoma japonicum causes little to no renal disease but primarily hepatic fibrosis instead. While in some animal studies, *S japonicum* has been seen to be associated with renal disease (especially with high infection burden and portal hypertension),[84] this has not been shown in humans.[85]

S haematobium is a prominent cause of disease in Africa. *S haematobium* eggs cause granuloma formation in the bladder wall and along the ureters. When the granuloma bleed, especially when stressed by bladder contraction, hematuria results, often at the end of urination. The granuloma can also cause post-obstructive disease, leading to dilation of the urinary system and increased risk of infection. Genitourinary system cancer (squamous cell carcinoma) is a possibility after long-term infection.

S mansoni, found in Africa and South America, does appear to cause an immune-complex mediated glomerulopathy. Five types of glomerulonephritis have been seen in *Schistosoma* infection: mesangioproliferative, exudative (typically with *Salmonella* coinfection), membranoproliferative, focal segmental glomerulosclerosis, and amyloid,[86] with membranoproliferative glomerulonephritis being the most common. Patients without proteinuria, hypertension, or renal insufficiency who undergo incidental renal biopsy during splenectomy have had subclinical glomerular lesions.[87]

Treating the parasite infection is the best way to affect renal disease in schistosomiasis. Experts advise against using steroids or other immune modulators to treat glomerulopathy in the face of trematode infection. Given the more severe course of patients coinfected with *Salmonella,* it is recommended that an investigation be done in any patient with hepatosplenic schistosomiasis to rule out *Salmonella* infection.[2]

Practitioners in regions with high endemicity of schistosomiasis should keep in mind that the parasitic infection may be coincidental in patients with nephrotic syndrome. An effort should be made to rule out causality on a case-by-case basis.

HIV

Problems of chronic HIV infection are becoming more important with patients living longer. Renal disease is one of the most common complications of chronic HIV infection.

In the 1980s, most HIV renal disease was seen to be sclerosing glomerulopathy, which got labeled HIV-associated nephropathy (HIVAN). Development of this glomerulopathy was seen as ominous because patients typically progressed to ESRD rapidly. Presentation is primarily proteinuria (generally in the nephrotic range) and renal insufficiency.

Some series report other findings typical for nephrotic syndrome, but others do not. In US studies, there seems to be a racial disparity between HIVAN patients and other HIV patients, with blacks overrepresented when compared with whites by a ratio of 12:1.[88]

Development of HIVAN is an indication for treatment with highly active antiretroviral therapy (HAART).[2] Antiretroviral treatment of HIV patients with HIVAN has demonstrated improvement in kidney function and delay of progression to ESRD. Early studies suggested benefit of ACE inhibitors in HIVAN, but the sample sizes were small and the studies were done before HAART use was common. It is unclear whether ACE inhibition adds to the reno-protective benefit of HAART in treating patients with HIVAN.

While kidney disease is a frequent complication in adult patients with HIV, children who acquire the disease perinatally seem to be another matter. When evaluating all forms of noninfectious disease in perinatally acquired HIV, renal disease was seen to have an incidence of 0.26 per 100 person years.[89] Renal manifestations of HIV infection in children with perinatally acquired disease include focal segmental glomerulosclerosis, IgAN, membranous nephropathy, a lupus-like syndrome, and collapsing crescentic glomerulonephritis.[90]

Hepatitis B Virus

Hepatitis B virus (HBV) is one of the most common human infections; it is estimated that one-third of the world's population has evidence of this infection. Most pediatric forms of HBV-induced renal disease are caused by maternal-child transmission. The clinician should be aware of this as a possible underlying cause for kidney disease in areas with a high endemicity of HBV.

Patients with glomerular disease secondary to HBV infection generally present with proteinuria and sometimes with nephrotic-range proteinuria. Several pathologic patterns occur in these patients, including focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and IgAN, but membranous nephropathy is the most common in children.[91,92] Patients with glomerulonephritis in conjunction with HBV infection should be treated with antiviral drugs to alleviate the underlying infection. Kidney disease improves in children with membranous nephropathy secondary to HBV when the HBV-DNA burden decreases.[93,94] Antiviral drug doses should be adjusted based on the patient's renal function.

Some recent work was done that looked into possible serologic markers that may help distinguish primary membranous nephropathy from secondary disease. It seems clear that elevated anti-phospholipase

A_2-receptor antibody is only present in cases of primary membranous nephropathy.[95,96] Future work in this area will be very helpful in distinguishing primary from secondary disease.

ACUTE KIDNEY INJURY

Acute kidney injury is a common problem, primarily or secondarily, in intensive care units. When a child's renal function is declining, practitioners need to focus on the underlying cause of the illness as well as fluid, electrolyte, and blood pressure management. The most common causes of AKI in children include multiorgan failure, intravascular hemolysis (eg, hemolytic uremic syndrome, malaria), and nephrotoxic drugs. Some of these initiating causes of AKI respond well to treatment (eg, some types of glomerulonephritis, shock, and malaria) and others resolve spontaneously (eg, hemolytic uremic syndrome, recovery after withdrawal of nephrotoxic drugs); as such, the decision to perform dialysis should not be entered into lightly.

When kidneys are failing and course of the illness appears to be prolonged, dialysis may be considered. Many such patients are too ill for the fluid shifts of acute dialysis, which, in resource-rich locations, would be an indication for the use of continuous renal replacement therapy (CRRT). The equipment and disposables for CRRT make such a therapy cost prohibitive in many areas of the world. Fortunately, peritoneal dialysis is relatively simple and effective, even in patients who are hemodynamically unstable. In some countries, efforts have begun to expand the provider base by training nurses, medical students, and postgraduate medical students on the use of peritoneal dialysis in the acute setting.[97,98]

When Not to Initiate Dialysis

The normal course of many renal insults is to improve over time. It is important that the practitioner keeps in mind the natural history of the current illness when deciding whether to initiate dialysis. A child with hemolytic uremic syndrome, for example, will often recover, and good management of fluids and electrolytes can help avoid dialysis prematurely. Malnutrition and dehydration may lead to AKI. While peritoneal dialysis may help these patients, it is far better to recognize the problem early and avoid progressing to the point where peritoneal dialysis is needed.

When to Initiate Dialysis

Dialysis is intended to replace kidney function to assist in management of patients with renal injury. Dialysis is indicated when volume overload or hyperkalemia threaten the patient's life. Although the patient may

not be volume overloaded, dialysis can assist with volume management, allowing for more room in the daily ins and outs to give nutrition.

Hyperkalemia

Patients with elevated potassium and changes on electrocardiogram should be immediately treated to redistribute potassium. Calcium gluconate will protect cellular membranes from hyperkalemia. Sodium bicarbonate and insulin (given in conjunction with glucose) can drive potassium intracellularly and thus lower serum potassium. To lower total body potassium, a potassium-binding agent such as sodium polystyrene can be used. Table 32-11 gives dosage and administration information for these measures. If hyperkalemia does not respond, dialysis may be required to reverse it.

Practitioners who use potassium-shifting strategies (eg, sodium bicarbonate, insulin) to deal with hyperkalemia and then follow with renal replacement therapy should monitor for potassium levels after dialysis is instituted. Renal replacement therapy is effective in removing extracellular potassium from the body. However, if all the potassium was driven into the cells by the maneuvers listed previously, effectiveness of renal replacement therapy at lowering total body potassium will be limited initially but will improve as the intracellular shift of potassium resolves.

Acidemia

Sodium bicarbonate can be useful in controlling the acidemia of renal insufficiency. The metabolic acidosis associated with AKI can be from the renal insufficiency itself or from offending toxins. There is usually no reason to institute dialysis to control acidosis, as this can be handled with infusions of bicarbonate, but if acidosis and AKI are caused by a

Table 32-11. Drugs for Managing Hyperkalemia

DRUG	ADMINISTRATION
Calcium gluconate (10% solution)	100 mg/kg/dose over 3–5 min; may repeat every 10 min; do not exceed 100 mg/min.
Sodium bicarbonate	1–2 mEq/kg/dose over 5–10 min (not compatible with calcium gluconate)
Insulin	0.1 U/kg given with 2 mL/kg of D25W; infuse over 30 min.
Sodium polystyrene resin	1 g/kg/dose every 6 h orally or every 2–6 h rectally

Abbreviation: D25W, dextrose 25% in water.

toxin, use of dialysis to help control acidosis and remove the toxin may be indicated.

Volume Control

Patients with AKI and volume overload can benefit from furosemide. Children with lower amounts of fluid accumulation and overload seem to do better in recovering from multiorgan failure and AKI[99] than those with greater fluid overload. Preventing fluid overload through careful fluid management (eg, matching outputs plus insensible losses with inputs, judicious use of bolus fluids) is beneficial. Nutrition is always a concern in pediatric patients. Diuretics can help allow volume to be given to the patient to facilitate nutrition. Loop diuretics, such as furosemide, can help manage volume overload as well as hyperkalemia but have not helped treat AKI itself.[100] As such, their use early in the course of illness to prevent progression of fluid overload is indicated, while their use to directly treat AKI is not.

Peritoneal Dialysis

Peritoneal dialysis allows nephrologists to care for patients with extremely poor renal function while awaiting transplant. The bridge that dialysis provides can also be useful in the case of a patient with an acute injury who is expected to improve but needs some extra support in the interim. In resource-rich countries, use of CRRT is becoming more common as an acute dialysis modality, particularly in situations in which fluid shifts and other stresses acute hemodialysis places on the body may be dangerous. Continuous renal replacement therapy requires specialized machinery, water sources, and disposables that may not be available in a resource-limited setting. Recent studies suggest that acute peritoneal dialysis may offer some benefit to patients in need of acute dialysis, benefits which may be comparable to CRRT modalities[101] while also useful for patients who are hemodynamically unstable. Countries in resource-limited areas are increasing training in peritoneal dialysis to increase access to renal replacement therapy.[98,102–105] There are even case studies in which peritoneal dialysis was done with improvised equipment, resulting in good outcomes.[106] Box 32-4 lists indications for peritoneal dialysis.

Peritoneal Dialysis Access

There are 3 main ways to place peritoneal dialysis catheters: surgical, laparoscopic, and percutaneous. If placed surgically, a double-cuffed catheter is used. The peritoneum can be closed with a purse string suture with the proximal cuff just proximal to the suture. The catheter is tunneled so

Box 32-4. Indications for Acute Dialysis
Fluid overload (with hypertension or congestive heart failure)
Hyperkalemia
Acidosis
Uremic pericarditis
Uremic encephalopathy

that the distal cuff is 2 cm from the outlet. The outlet is placed such that the catheter exits inferolaterally to decrease infection risk.

There are situations in which surgical placement of a peritoneal dialysis catheter is impossible. In such circumstances, a bedside temporary peritoneal dialysis catheter can be placed percutaneously.[106,107] The following steps are for performing a modified Seldinger technique for percutaneous peritoneal dialysis catheter placement:

- Make an incision above the midline with blunt dissection to the abdominal rectus sheath.
- Insert an 18-gauge finder needle into the peritoneal cavity.
- Advance a 0.035" guide wire through the finder needle.
- Place the dilator and sheath over the guide wire.
- Remove the dilator and wire.
- Using the stylet, advance the peritoneal dialysis catheter through the sheath.
- Advance the peritoneal catheter until the proximal cuff is in the preperitoneal space.
- Remove the sheath and stylet.
- Check catheter placement.
- Tunnel the distal end of the catheter to the exit site; place the distal cuff subcutaneously 2 cm from the exit site.

Catheter placement is often checked fluoroscopically but can be accomplished by inflating the peritoneum with air or running saline into the space.

Some centers have begun using a laparoscopic technique to achieve access.[108] When compared in small studies, percutaneous and laparoscopic placement appear to be similar in terms of complications and efficacy for dialysis.[109,110]

Fluids and Prescription

Principles of dialysis are rather simple, but the way they get worked out in the clinical setting can be confusing. Essentially, dialysis allows for exchange of water and solute across a membrane. Dialysate, low in concentration of the solute targeted for removal, is placed on one side of the membrane, while the blood, high in the solute targeted for removal, is on the other side. The high-concentration solute on the blood side will move to the dialysate to balance concentrations on the 2 sides. The dialysate is then removed and exchanged for fresh fluid to allow the cycle to start again.

With this understanding, it is clear why dialysate is made the way it is made. Concentrations of electrolytes are set close to the physiological levels so that not much will be removed. Urea, high in concentration in the blood, moves easily to the dialysate and equilibrates early in the cycle; as such, decreasing dwells and increasing cycles allow for increased urea clearance. Table 32-12 gives a typical recipe for dialysate used in pediatric peritoneal dialysis.

Glucose is the typical osmotic agent used to draw water from the blood into the dialysate for removal. Glucose concentration can be varied to assist in volume control, with higher concentrations leading to greater water removal. Euvolemic patients would typically be started using 1.5% glucose (lower concentrations, down to 1.37%, are available in some countries); 2.5% is used for fluid overload, and 4.25% can be used if even more ultrafiltration is needed.

Table 32-12. Typical Components for Peritoneal Dialysis Fluid

COMPONENT	AMOUNT
Sodium	132–134 mmol/L
Calcium	1.75 mmol/L
Magnesium	0.25–0.75 mmol/L
Chloride	96–104 mmol/L
Lactate	35–40 mmol/L
Glucose	1.5%–4.25%
Osmolarity	340–512 mOsm/kg
pH	5.5

When first starting a patient on peritoneal dialysis, the infused volume should be small, 5 to 10 mL/kg. After 2 good cycles, the dialysate volume can be increased to the target volume. Box 32-5 gives a typical peritoneal dialysis prescription.

Complications

While peritoneal dialysis is easy to perform, it is not without its complications. Box 32-6 lists the most common complications. Dialysate leaking can be decreased by using properly cuffed dialysis catheters and a purse string closure around the peritoneum end (if using a surgically placed catheter).

Should the patient develop a fever, abdominal tenderness, and cloudy fluids, peritonitis should be considered. The ultrafiltrate can easily be cultured and antibiotics put in the dialysate to counter peritonitis.

SPINA BIFIDA: THE RENAL ISSUES

In certain areas of the world (eg, northwest China), the diet is deficient in folate. As a result, the number of children born with spinal defects is greater. Physicians practicing in such areas should be prepared to care for such children at a greater frequency than they may be used to in their home country.

While dealing with the neurologic aspect of spina bifida care is outside the scope of this chapter, the practitioner will do well to remember that children with spinal defects often have neurogenic bladders.

Box 32-5. Typical Dialysis Prescription
Volume: 25–50 mL/kg
Cycle time: 30–60 min
Dwell time: 25–50 min
Drain time: 5–15 min

Box 32-6. Peritoneal Dialysis Complications
Dialysate leak
Infection (catheter site, tunnel, or peritonitis)
Catheter site hernia
Catheter blockage

Micturition is relaxation; if enervation to the bladder is interrupted for some reason, relaxation cannot occur and urine accumulates in the bladder and puts the whole urinary system under pressure. Many of these children will urinate and be thought to be incontinent when in fact the urine is the product of simple overflow. Ultrasound will reveal a large, urine-filled bladder even after the child has urinated. If left untreated, this increased urinary system pressure can lead to poor renal development and ultimately chronic kidney disease.

Treatment for this problem is quite simple: keep the bladder drained. This can be accomplished with intermittent catheterization every 2 to 3 hours during the day. These children often do not have sensation in the perineum, so catheterization is a simple matter.

HEMOLYTIC UREMIC SYNDROME

Epidemiology

The most common type of hemolytic uremic syndrome is secondary to bacteria producing Shiga-like toxin. In Asia and Africa, *Shigella dysenteriae* type 1 is more likely; in the United States and Europe, the more common etiology is Shiga-like toxin (also called verotoxin)–producing *Escherichia coli*, particularly the O157:H7 serotype.

Disease occurs in epidemics and sporadically. Clusters have been traced to food sources, petting zoos, and swimming and water sources. Sporadic cases occur during the summer at a rate of 3 per 100,000 population. Age of onset is generally young (6 months–4 years).

Presentation

Most cases occur after an episode of acute gastroenteritis with fever, vomiting, abdominal pain, and diarrhea. Diarrhea is usually bloody but not necessarily. Gastroenteritis may be severe or mild, but after onset of gastrointestinal symptoms, the patient develops pallor and possibly oliguria. Oliguria can be difficult to detect in small children, as it may coincide with diarrhea.

Testing will reveal azotemia, thrombocytopenia, and anemia. Schistocytes are often evident in peripheral blood smear. It is not unusual for the patient to have hematuria, proteinuria, or a mix of both at some point during the illness.

Treatment

Severity of renal insufficiency ranges from quite mild to severe, requiring dialysis. Careful management of fluids and electrolytes is called for, reserving dialysis for anuric or severely oliguric patients.

Controversy continues concerning treatment of bloody diarrhea.[111–115] Some have pointed out that most *E coli* isolates are beta-lactamase producers and if treatment with non–beta-lactamase antibiotics is instituted, an increase in hemolytic uremic syndrome risk is not seen,[112] while others have not seen this effect. Study numbers and relative effects on risk remain small.

Prognosis

Prognosis of hemolytic uremic syndrome is quite good. Mortality is low, but 20% to 30% of patients may require continued dialysis after resolution of other symptoms. Prognosis is better with diarrhea-associated disease as opposed to genetic or other causes of hemolytic uremic syndrome.

KEY POINTS

- Pediatric renal disease is an important source of morbidity and mortality worldwide.
- Many of the common causes of pediatric renal disease can be evaluated and treated even in resource-limited settings. Evidence-based guidelines like KDIGO and expert opinion can be helpful in guiding care internationally.
- While many of the diseases are quite similar globally (nephrotic syndrome), the practitioner needs to be aware of special circumstances inherent in international medicine, such as renal complications of tropical infections (eg, malaria, schistosomiasis) and differing epidemiology of certain diseases (eg, HSP).

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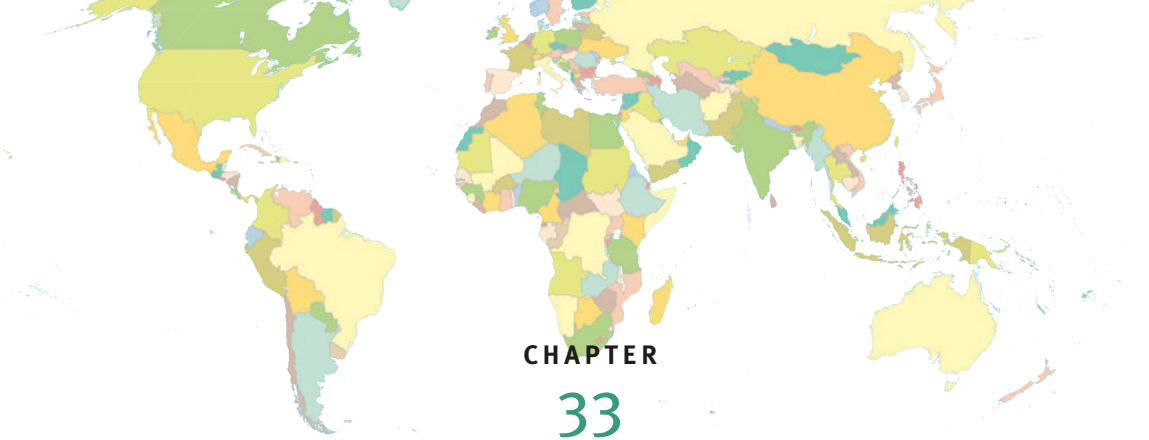

CHAPTER

33

Emergency Medicine and Critical Care

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INTRODUCTION

One of the proposed United Nations Sustainable Development Goals is to end preventable newborn, infant, and younger-than-5-years deaths by 2030. Pneumonia, diarrhea, malaria, measles, and malnutrition remain leading contributors to child mortality in developing countries. Pneumonia and diarrhea each kill 2 million children worldwide every year.[1] Appropriate emergency management of diarrhea with severe dehydration and severe bacterial pneumonia is very important. Traffic accidents and trauma also result in significant mortality.[2] Trauma is predicted to become one of the leading causes of death globally by 2020.[3] However, childhood trauma has been neglected in resource-constrained countries.[4] The need for good trauma management has been obscured by the huge burden of medical problems.

Emergency and critical care can be defined as all care given in a hospital to patients with sudden, serious, reversible disease. The World Federation of Pediatric Intensive and Critical Care Societies adopted the definition of critical care as "the treatment of the child with a life-threatening illness or injury in its broadest sense, without regard for the location and including pre-hospital and emergency and intensive care." This includes interventions such as early antibiotic therapy for neonatal infections, increased availability of oxygen monitoring and therapy

for children with pneumonia, improved care for sick children at district hospitals, improved structure and organization of acute care services for children, development of triage and management systems, and innovative training programs in prehospital trauma care.[5]

The priorities of developing countries are public health focused and not traditionally aimed at emergency medical care needs, nor have they been traditionally part of health sector reform.[6] Emergency and critical care services are considered one of the weakest parts of the health system. This was demonstrated in a World Health Organization (WHO) survey of hospital care in developing countries that showed numerous, significant deficiencies in triage and emergency care, including absence of standardized assessment and treatment guidelines, understaffing (especially at night), poorly trained staff, little appreciation of the need for urgent treatment, inadequate facility organization for triage, and inadequate medication and supplies. The study estimated that improving triage and emergency care would contribute substantially to reducing morbidity and mortality in infants and young children brought to the hospital.[7]

Managing critically ill children requires rapid identification, prioritization, and urgent treatment. However, there is usually little prioritization of patients and no formal triage system and clinicians see the patients in the order they arrive. There is often no emergency department, and patients are first seen on a ward or as outpatients.[8] Some patients arrive too late; however, some will benefit from more rapid institution of appropriate care. There can be delays in accessing emergency drugs and providing essential treatment once a critically ill patient is identified. Many deaths occur in the first 24 hours after arriving at the hospital. Critically ill patients are often admitted to general wards because many hospitals do not have intensive care units.[9] The consequences of poor-quality care are most serious for the hospitalized critically ill patients. This can partially be explained by limited resources. Critical care services have additional challenges. Working in hospitals with limited resources can lead to a sense of fatalism whereby very sick children are presumed to be beyond saving and left to take their chances. While some of these children are too ill to be saved, others have reversible diseases and may respond to quick resuscitative therapies.[10]

Treating critically ill patients in developing countries requires optimal use of available resources, and families may be entirely responsible for the cost; therefore, judicious use of available testing is warranted. Effective use of relatively low-cost therapies, such as intravenous (IV)

fluids, oxygen, antibiotics, thermal control, and nutrition, can decrease mortality. When the younger-than-5 mortality rate is less than 20 per 1,000 live births, few deaths are caused by infections, and intensive care can make an important contribution to reduce mortality from noninfectious causes such as congenital heart disease and trauma. In the growing number of communities with intermediate mortality rates (younger-than-5 mortality of approximately 20 to 30 per 1,000), there is a place for the use of continuous positive airway pressure (CPAP) or intubation and ventilation for carefully selected patients using basic equipment. In a resource-limited setting, it is important to selectively manage children who have a good chance of long-term survival.[11]

Well-organized emergency services that provide seamless triage and timely and effective management for children will lead to decreased mortality, which will lead to better individual care, quicker admissions, reduced secondary complications, shorter inpatient stays, fewer nosocomial infections, and, ultimately, lesser workloads for already overburdened services.[12] Effective teamwork is essential for optimal care of the critically ill child in the limited resource setting. Communication and collaboration among members of the health care team improve the quality and efficiency of patient care.[9]

Steps, such as introducing effective triage and emergency treatment, improving inpatient care, introducing hospital systems for prioritizing the very sick, and ensuring a reliable oxygen delivery system, need not be resource intensive. Emergency Triage Assessment and Treatment (ETAT) guidelines were developed to improve initial hospital care for sick children.[13]

Care of patients with trauma can be improved with training, triage, and a systematic team approach.[14] Also training health staff in fundamentals of critical care, concentrating on airway, breathing, and circulation, and developing guidelines for managing common medical emergencies could improve quality of inpatient pediatric care.[10] Use of clinical pathways has been shown to improve efficiency of care and decrease resource utilization.[15] These measures can have a significant effect in reducing mortality in resource-limited settings.

The following sections will summarize ETAT guidelines and resuscitation and trauma management and review emergency and critical care management of pneumonia, gastroenteritis, dehydration, and sepsis in resource-limited settings.

TRIAGE

The WHO and United Nations Children's Fund developed a strategy, Integrated Management of Childhood Illness (IMCI), of simplified guidelines to improve the triage and rapid initiation of appropriate emergency treatments for children presenting to hospitals in developing countries. In resource-limited settings, it is important to address emergency management of diarrhea with severe dehydration, severe malaria, severe malnutrition, and severe bacterial pneumonia and to focus attention on sick infants younger than 2 months.[13]

The ETAT guidelines have many similarities to the initial approach to pediatric medical emergencies that is taught in Advanced Pediatric Life Support (APLS) and other pediatric emergency courses. The ETAT guidelines are based on standardized emergency management by health workers involved in initial triage and emergency treatment. These guidelines rely on a few clinical signs, which can be readily taught to and used by health workers with a limited clinical background (Table 33-1).[13]

Airway and Breathing

Assess for breathing—look for chest movement, listen for breath sounds, and feel for breath. This assessment is skipped if the child is alert, active, talking, or crying. Cyanosis is based on examining the lips and, if they are blue, examining the tongue and inside of the mouth. Airway management and oxygen treatment are immediately implemented if any of these emergency signs are positive.

Circulation

For most children, only a rapid check that their hand is warm is required. Check the capillary refill if it feels cold. Treat the child for shock if this is prolonged or the pulse is fast and weak. These guidelines define prolonged capillary refill as 3 seconds or longer.

Coma and Convulsions

If the child is not awake and alert, the health worker tries to rouse him by talking and then shaking his arm. If the child does not respond, ask the mother if he has been abnormally sleepy or difficult to wake. Treat the child emergently for coma if the mother confirms that the child is not just sound asleep. Emergency treatment for convulsions is limited to those characterized by loss of consciousness and obvious "uncontrolled, jerky movements."

Table 33-1. Pediatric Emergency Triage Assessment and Treatment

ASSESSMENT **Emergency Signs**	**MANAGEMENT** **If any sign is positive, give treatment(s), call for help, and draw emergency laboratory tests (glucose, malaria smear, hemoglobin).**
Airway and Breathing ● Is the airway obstructed? ● Is the child breathing? ● Is the child cyanosed? ● Are there signs of severe respiratory distress?	Manage airway. If the patient is not breathing ● Open the airway. ● Remove any foreign body. ● Ventilate with a bag and mask. In all cases of airway or breathing problems ● Provide oxygen.
Circulation ● Does child have warm hands? ● Is the capillary refill time >3 seconds? ● Is the pulse fast and weak? ● Check for severe malnutrition.	● Stop any bleeding. ● Give oxygen. ● Make sure the child is warm. If *no* severe malnutrition ● Insert IV line and begin giving fluids rapidly. ● If not able to insert peripheral IV line, insert an external jugular or intraosseous line. If severe malnutrition ● Assess if child can drink oral or NGT fluids. ● Give IV glucose and fluids if child unable to tolerate oral or NGT fluids.
Coma **Convulsing (now)**	● Manage airway. ● If convulsing, give diazepam rectally. ● Position child (stabilize neck first if neck or head trauma is suspected). ● Check blood sugar and give IV glucose.
Severe Dehydration (with diarrhea) Diarrhea and any 2 of ● Lethargy ● Sunken eyes ● Very slow skin pinch	● Make sure the child is warm. Severe dehydration *without* severe malnutrition ● Treat shock if present. ● Give IV or NGT fluids. ● Start oral fluids as soon as possible. Severe dehydration *with* severe malnutrition ● Treat shock if present. ● Give oral or NGT fluids.

Abbreviations: IV, intravenous; NGT, nasogastric tube.

Adapted from Gove S, Tamburlini G, Molyneux E, Whitesell P, Campbell H. Development and technical basis of simplified guidelines for emergency triage assessment and treatment in developing countries. WHO Integrated Management of Childhood Illness (IMCI) Referral Care Project. *Arch Dis Child.* 1999;81(6):473–477 with permission from BMJ Publishing Group Limited.

Diarrhea

Only 3 signs are assessed for diarrhea: sunken eyes, very slow skin pinch, and lethargy; only 2 of these signs are required for treating severe dehydration.

Cardiopulmonary Arrest

Most younger-than-5 mortality occurs in developing countries. Timely recognition of and attention to life support for critically ill children will significantly reduce mortality. Continued and improved efforts at preventing and treating life-threatening disorders is needed to secure real progress toward globally reducing mortality in children younger than 5 years. Although important advances in prevention are being made, APLS management is often incomplete in developing countries because of limited resources and poor health care systems.[16]

Prompt and skillful response can make the difference between life and death and intact survival and debilitation when cardiac arrest or life-threatening emergencies occur. Cardiopulmonary arrest among children is more commonly a result of progressive respiratory failure or shock leading to severe hypoxia. Early recognition and treatment of sudden cardiac arrest improves survival for children and adults. Survival rates among children with pulseless arrest can be improved by quickly beginning cardiopulmonary resuscitation (Figure 33-1).[17]

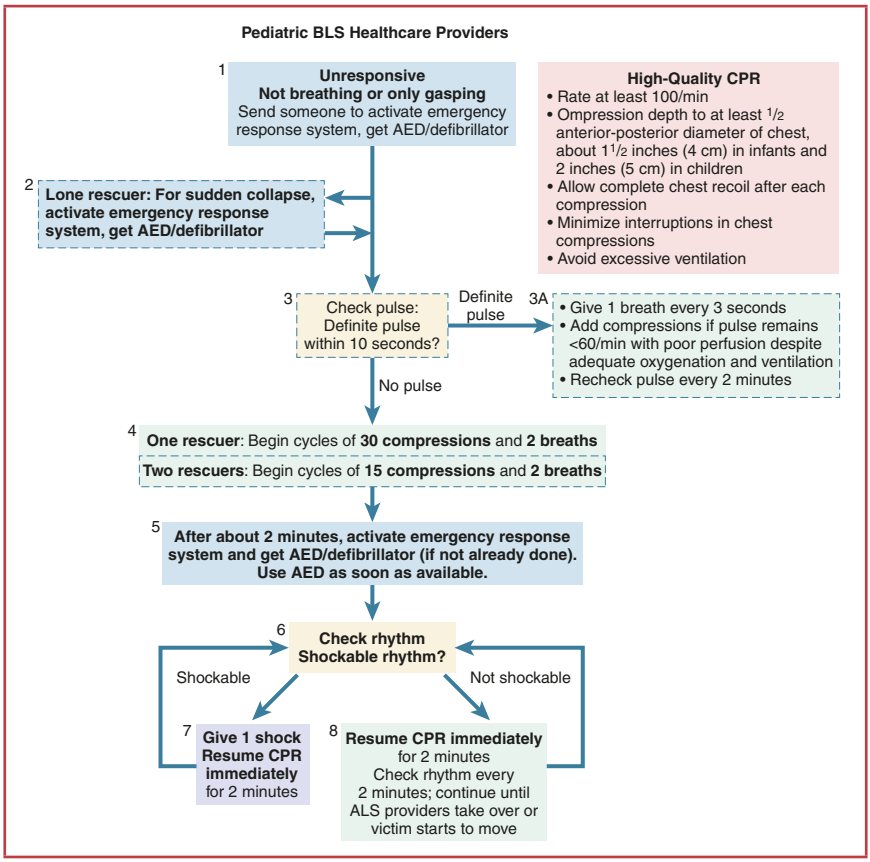
Pneumonia

Pneumonia kills about 2 million children each year. It is the most common cause of death in children in developing countries. It is also an important contributory factor in deaths from neonatal sepsis, HIV, pertussis, and measles. Eleven to 20 million pediatric episodes (of an estimated 156 million/year) of acute lower respiratory tract infections are severe enough to require hospital admission.[18] Most cases of bacterial pneumonia in children are caused by aspiration of bacteria from the nasopharynx; mixed infections with *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus,* and *Moraxella catarrhalis* are also common. Fatal pneumonia in children is usually caused by *S pneumoniae* or *H influenzae*.[19] Other causes of pneumonia include HIV infection (often with pneumocystis), chlamydia, mycoplasma, and tuberculosis.[11]

Oxygen Therapy and Pulse Oximetry

Oxygen therapy may be lifesaving in patients with severe pneumonia. Pulse oximetry is recommended to determine the presence of hypoxemia and guide administration of oxygen therapy in infants and children with hypoxemia. When available, pulse oximetry should be used for detecting

Figure 33-1. Pediatric Basic Life Support



Note: The boxes bordered with dashed lines are performed by healthcare providers and not by lay rescuers.

From Berg MD, Schexnayder SM, Chameides L, et al. Part 13: Pediatric Basic Life Support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2010;122(18 Suppl 3):S862–S875, with permission.

hypoxemia in children with severe lower respiratory infections. If oximetry is not available, the following clinical signs could be used to guide the need for oxygen therapy: central cyanosis, nasal flaring, increased work of breathing (tachypnea, chest in-drawing), head nodding, inability to drink or feed (due to respiratory distress), grunting with each breath, or depressed mental state (ie, drowsy, lethargic).

Indications for oxygen therapy include an Spo_2 of 90% or less (≤2,500 m above sea level) and an Spo_2 of 87% or less (>2,500 m above sea level). Nasal prongs are the preferred method for delivering oxygen to infants and children younger than 5 years with hypoxemia who require oxygen therapy. Nasal or nasopharyngeal catheters can be used

as an alternative delivery method when nasal prongs are not available. Face masks or head boxes are not recommended.[20]

Using mask or nasopharyngeal CPAP up to 12 cm H_2O pressure can improve oxygenation and ventilation in cases of severe respiratory distress or failure. If endotracheal intubation and mechanical ventilation are available, start with low tidal volumes of 6 to 8 mL/kg, positive end-expiratory pressure of 8 to 10 cm, inspiratory time of 1 second with a rate of 20 to 30 per minute in an infant (assuming no bronchiolitis or asthma is present), and peak pressure less than 30 cm to minimize ventilator-associated lung injury.[11]

Antibiotic Treatment

Antibiotic treatment varies based on drug availability, local epidemiology, and ministries of health recommendations. Children with severe pneumonia should be treated with ampicillin 50 mg/kg per dose or benzylpenicillin 50,000 units/kg per dose intravenously or intramuscularly every 6 hours, in addition to gentamicin 5 mg/kg per dose intravenously or intramuscularly every 24 hours for at least 5 days. If this treatment fails, treat with ceftriaxone sodium intravenously or intramuscularly (Table 33-2).[20] The combination of benzylpenicillin and gentamicin has synergistic activity against many strains of *S pneumoniae* and *H influenzae*.[11]

Staphylococcal pneumonia is suggested by a poor response to penicillin and gentamicin, presence of pneumatoceles, pneumothorax, empyema, or associated soft tissue or joint infection. Cloxacillin (or oxacillin, flucloxacillin, or dicloxacillin) and gentamicin given intravenously are appropriate treatments.[11]

Fluid Therapy

Children with pneumonia can present with hyponatremia, which is usually caused by excess water rather than sodium deficiency and should be treated by fluid restriction. Fluid requirements are often only 30% to 40% of normal maintenance after the initial fluid resuscitation to restore the intravascular volume because the child may have high antidiuretic hormone concentrations.[11]

Feeding

Monitor the blood glucose level closely. It is important to prevent hypoglycemia by adjusting the glucose infusion rate. Start continuous small nasogastric feedings at admission as long as no cardiovascular compromise is evident. Full enteral feedings can usually be achieved within 24

Table 33-2. Severity of Pneumonia and Management

PNEUMONIA SEVERITY	SIGNS		TREATMENT
Non-severe	Fast breathing No chest in-drawing No danger signs	No wheeze	Low HIV prevalence ● Amoxicillin 40 mg/kg/dose twice daily for 3 d High HIV prevalence ● Amoxicillin 40 mg/kg/dose twice daily for 5 d
		Wheezing and no fever	● Antibiotics are not routinely recommended because the cause is most likely to be viral.
Severe	Fast breathing Chest in-drawing No danger signs		Children aged 2–59 mo ● Oral amoxicillin 40 mg/kg/dose twice a day for 5 d
Very severe	Chest in-drawing Danger signs ● Lethargy ● Unconsciousness ● Inability to drink/breastfeed ● Persistent vomiting ● Central cyanosis ● Severe respiratory distress ● Convulsions		Children aged 2–59 mo: First line ● Ampicillin 50 mg/kg or benzylpenicillin 50,000 units/kg IM/IV every 6 h for at least 5 d **and** Gentamicin: 7.5 mg/kg IM/IV once daily for at least 5 d ● Ceftriaxone should be used as a second-line treatment in children with severe pneumonia with failure on the first-line treatment.

Abbreviations: IM, intramuscular; IV, intravenous.

Adapted from World Health Organization. *Evidence for Technical Update of Pocket Book Recommendations: Recommendations for Management of Common Childhood Conditions. Newborn Conditions, Dysentery, Pneumonia, Oxygen Use and Delivery, Common Causes of Fever, Severe Acute Malnutrition and Supportive Care.* Geneva, Switzerland: World Health Organization; 2012. http://apps.who.int/medicinedocs/documents/s19652en/s19652en.pdf. Accessed June 11, 2015.

to 48 hours. A nasojejunal tube can be placed and nasojejunal feedings may be initiated if gastric feedings are not tolerated.[11]

Gastroenteritis and Dehydration

Gastroenteritis is the second most common cause of child mortality. It also causes about 2 million child deaths every year. During diarrhea, there is an increased loss of water and electrolytes in the liquid stool. Dehydration occurs when these losses are not replaced adequately. Particular problems include shock, acid-base abnormalities, electrolyte abnormalities, and secondary bacterial infection.[21] The most common

causes of dehydration include rotavirus, enterotoxigenic *Escherichia coli,* and, during epidemics, *Vibrio cholerae* O1 or O139.[22]

Consequences of fluid loss depend on the rate and amount of loss. The volume of fluid lost through stools in 24 hours can vary from 5 mL/kg (near normal) to 200 mL/kg or more. The degree of dehydration is graded according to signs and symptoms that reflect the amount of fluid lost. There are no signs or symptoms in the early stages of dehydration. Signs and symptoms develop as dehydration increases; initially, these include thirst, restless or irritable behavior, decreased skin turgor, sunken eyes, and sunken fontanel (in infants). In severe dehydration, these effects become more pronounced and the patient may develop evidence of hypovolemic shock, including diminished consciousness, lack of urine output, cool moist extremities, a rapid and feeble pulse (radial pulse may be undetectable), low or undetectable blood pressure, and peripheral cyanosis. Death soon follows if rehydration is not started quickly.[23]

Signs of dehydration overestimate the degree of dehydration in the severely malnourished child. Malnourished children may appear lethargic and have sunken eyes and a very slow skin pinch. To check for severe malnutrition, look rapidly at the child's arms and legs and pull up her shirt to look at the chest. A child with visible severe wasting has a form of malnutrition called marasmus. Pitting edema of the feet may suggest kwashiorkor, which is another form of severe protein-energy malnutrition. In these cases, when possible, provide fluids orally or use a nasogastric tube. If the child cannot swallow or tolerate a nasogastric tube (eg, vomiting), use half-strength normal saline with 5% glucose at 15 mL/kg in 1 hour. Closely monitor the patient during IV hydration. The IV infusion should be discontinued if there is an increase of pulse rate by 15 or respiratory rate by 5 per minute.

Emergency assessment for dehydration has been simplified based on substantial experience with the WHO diarrheal disease control and IMCI guidelines (Table 33-3).[22,23]

Treatment Plan A: Therapy to Prevent Dehydration and Malnutrition

Give the child more fluids than usual to prevent dehydration. Many countries have designated recommended home fluids. Wherever possible, these should include at least 1 fluid that normally contains salt, such as oral rehydration solution (ORS). The general rule is to give as much fluid as the child wants until the diarrhea stops. Give 50 to 100 mL of fluids after each loose stool for children younger than 2 years and 100 to 200 mL of fluids for children 2 to 10 years of age. Give supplemental zinc (10–20 mg) to the child every morning for 14 days. Continue to

Table 33-3. Dehydration Classification and Management

DEHYDRATION CLASSIFICATION	SIGNS OF DEHYDRATION	FLUID DEFICIT	MANAGEMENT
No dehydration	Not enough signs to classify as some or severe dehydration Well, alert, drinks normally, not thirsty	<5%	Give fluids, zinc supplements, and food to treat diarrhea at home (treatment plan A).
Some dehydration	2 of the following signs: Restless, irritable, sunken eyes.[a] Drinks eagerly; thirsty. Skin pinch[b] goes back slowly.	5%–10%	Weigh the patient and use treatment plan B.
Severe dehydration	2 of the following signs: Lethargic[c] or unconscious. Sunken eyes. Not able to drink or drinking poorly. Skin pinch goes back very slowly.	>10%	Weigh the patient and use treatment plan C URGENTLY. If child is ≥2 years and there is cholera in the area, give antibiotic for cholera.

[a] In some infants and children, the eyes normally appear somewhat sunken. It is helpful to ask the mother if the child's eyes are normal or more sunken than usual.

[b] The skin pinch is less useful in infants or children with marasmus or kwashiorkor or obese children.

[c] Being lethargic and sleepy are not the same. A lethargic child is not simply asleep; the child's mental state is dull and the child cannot be fully awakened and may appear to be drifting into unconsciousness.

Adapted from World Health Organization. *Integrated Management of Childhood Illness: Distance Learning Course Module 4: Diarrhoea.* Geneva, Switzerland: World Health Organization; 2014. http://apps.who.int/iris/bitsteam/10665/104772/6/9789241506823_Module-4_eng.pdf?ua=1. Accessed June 11, 2015.

feed the child, offering food every 3 or 4 hours (6 times a day). Frequent small feedings are better tolerated than less frequent large feedings.[22]

Treatment Plan B: Oral Rehydration Therapy for Children With Some Dehydration

The amount of oral rehydration therapy (ORT) may be estimated by multiplying the child's weight in kilograms by 75 mL. Teach a family member how to prepare and give ORS. The solution should be given to infants and young children using a clean spoon or cup. The child's normal daily fluid requirements must also be met. Breastfed infants must continue to breastfeed as often and as long as they want, even during

oral rehydration. Give 100 to 200 mL of plain water by mouth to non-breastfed infants younger than 6 months. Offer older children and adults as much plain water as they wish to drink, in addition to ORS.

Begin giving supplemental zinc (as outlined in treatment plan A) as soon as the child is able to eat following the initial 4-hour rehydration period. Except for human milk, food should not be given during the initial 4-hour rehydration period. However, children who are on treatment plan B longer than 4 hours should be given some food every 3 to 4 hours. Children older than 6 months should be given some food before being sent home; this helps emphasize to mothers the importance of continued feeding during diarrhea.

Signs of dehydration may persist or reappear during ORT. Such children should be given ORS by nasogastric tube or lactated Ringer solution intravenously (75 mL/kg in 4 hours), usually in the hospital. It is usually possible to resume ORT successfully after confirming that signs of dehydration have improved. Check the child from time to time during rehydration to ensure that the ORS is being taken satisfactorily and that signs of dehydration are not worsening. Shift to treatment plan C if, at any time, the child develops signs of severe dehydration.[22]

Treatment Plan C: For Patients With Severe Dehydration

Start IV fluids immediately. If the patient can drink, give ORS by mouth until the drip is set up. Give 100 mL/kg lactated Ringer or normal saline solution (Table 33-4). If IV therapy is not available nearby, trained health workers can give ORS solution by a nasogastric tube at a rate of 20 mL/kg of body weight per hour for 6 hours (total of 120 mL/kg body weight).

Antibiotics should be considered for bloody diarrhea. Recommended regimens include ciprofloxacin 15 mg/kg dose orally, twice daily for 3 days. If treatment failure, give ceftriaxone sodium 50 to 80 mg/kg per dose intravenously or intramuscularly daily for 3 days; follow guidelines according to local sensitivities. Cholera should be suspected when a child older than 5 years or an adult develops severe dehydration from acute watery diarrhea (usually with vomiting) or any patient older than 2 years has acute watery diarrhea when cholera is known to be occurring in the area.[22]

Sepsis/Septic Shock

Infection and sepsis are among the leading causes of death worldwide. This high morbidity and mortality in resource-limited countries can be attributed to the high incidence of bacterial, parasitic, and HIV infection combined with low hygienic standards and vaccination rates, widespread malnutrition, and a lack of resources.[24]

Table 33-4. Guidelines for Intravenous Treatment of Children and Adults With Severe Dehydration

AGE	FIRST GIVE 30 mL/kg IN	THEN GIVE 70 mL/kg IN
Infants (<12 mo)	1 h	5 h
Older	30 min	150 min (2.5 h)
Reassess the patient every 1 to 2 hours. Give the intravenous drip more rapidly if hydration is not improving. Repeat once if radial pulse is still very weak or not detectable. After 6 hours (infants) or 3 hours (older patients), evaluate patient using the assessment chart and choose the appropriate treatment plan (A, B, or C) to continue treatment.		

From World Health Organization. *The Treatment of Diarrhoea: A Manual for Physicians and Other Senior Health Workers*. Geneva, Switzerland: World Health Organization; 2005. http://whqlibdoc.who.int/publications/2005/9241593180.pdf. Accessed June 11, 2015.

In 2008, the Surviving Sepsis Campaign released international guidelines for severe sepsis and septic shock management.[25] Implementation of these guidelines, together with timely administration of essential therapies (eg, fluid resuscitation, antibiotics, source control measures), improved management and outcomes.[26] However, these guidelines cannot be implemented universally in most middle- or low-income countries due to a lack of resources.[27] The Global Intensive Care working group of the European Society of Intensive Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies developed recommendations for sepsis management in resource-limited settings.

The purpose of these recommendations is to provide clinicians practicing in resource-limited settings with a framework to improve management of pediatric and adult septic patients. Recommendations are specifically based on resources affordable and commonly available in middle- and low-income countries and systematically weigh the available scientific evidence for its applicability in resource-limited settings. However, they are not meant to replace the Surviving Sepsis Campaign but can be considered if the latter guidelines are impossible to implement due to resource constraints.[28] Refer to Table 33-5 for definitions of suggested sepsis diagnosis with limited resources.

Management of Sepsis

Circulation

Infuse crystalloids or colloids to achieve adequate tissue perfusion. Add an epinephrine or dopamine drip along with steroids if signs of tissue hypoperfusion persist (Figure 33-2).[28] The Fluid Expansion as Supportive

Table 33-5. Definition of Suggested Sepsis Diagnosis With Limited Resources

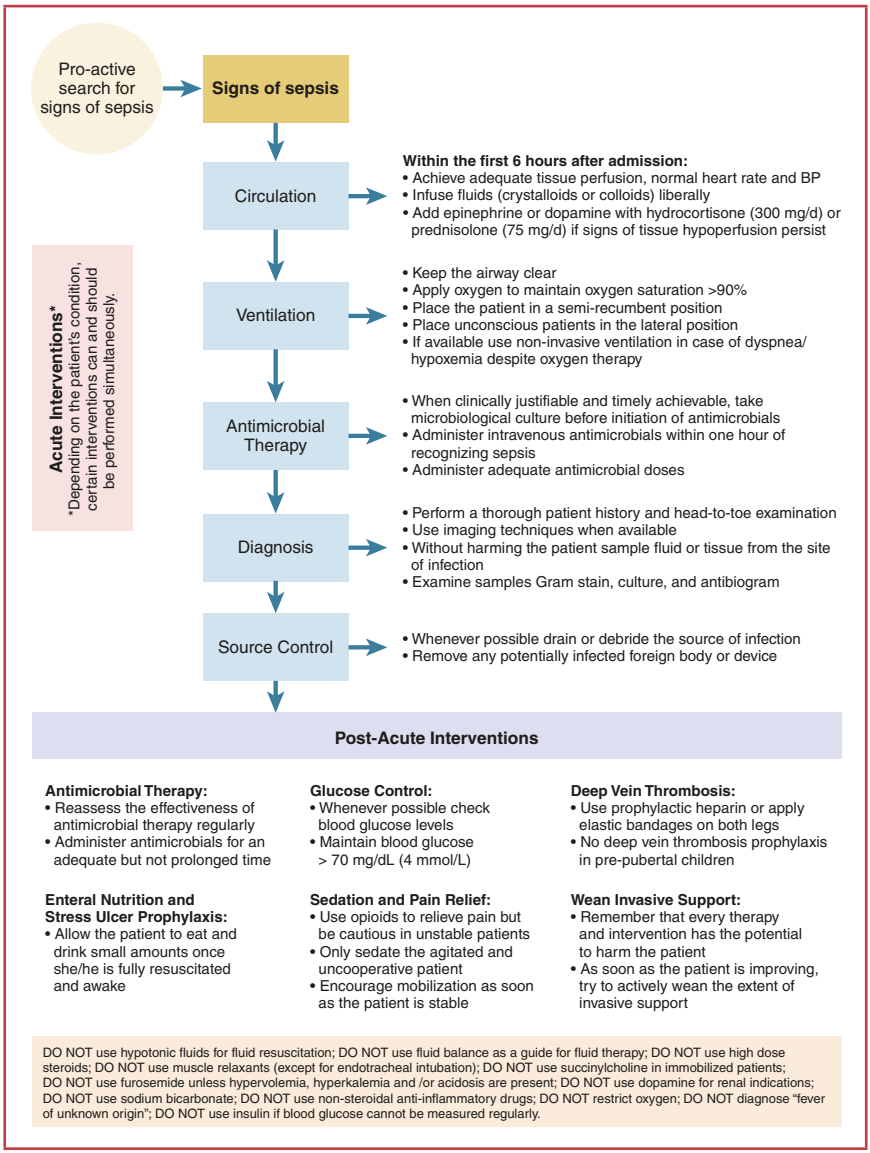
Sepsis	Proven or highly suspected infection plus presence of ≥2 of ● Heart rate >90 bpm ● Respiratory rate >20 bpm ● Temperature <36°C or >38°C ● Malaise and/or apathy
Severe sepsis	Sepsis-induced tissue hypoperfusion or organ dysfunction Tissue hypoperfusion ● Decreased capillary refill or skin mottling ● Peripheral cyanosis ● Arterial hypotension: systolic arterial BP <90 mm Hg or systolic arterial blood pressure decrease >40 mm Hg Pulmonary dysfunction ● Spo_2 <90% with or without oxygen ● Central cyanosis ● Signs of respiratory distress (eg, dyspnea, wheezing, crepitations) Renal dysfunction ● Acute oliguria (urine output <0.5 mL/kg/h) Hepatic dysfunction ● Jaundice Coagulation dysfunction ● Petechiae or ecchymoses ● Bleeding/oozing from puncture sites Gastrointestinal dysfunction ● Ileus (absent bowel sounds)
Septic shock	Sepsis-induced arterial hypotension despite adequate fluid resuscitation and signs of tissue hypoperfusion

Abbreviation: BP, blood pressure.

Adapted from Dünser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. *Intensive Care Med*. 2012;38(4):557–574. http://link.springer.com/article/10.1007/s00134-012-2468-5. Accessed July 15, 2015.

Therapy trial was designed to investigate the practice of early resuscitation with a saline bolus compared with no bolus (control) and with an albumin bolus compared with a saline bolus. It was noted that fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in resource-limited settings in Africa. Results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who do not have hypotension.[29]

Figure 33-2. Recommendations for Sepsis Management in Resource-Limited Settings



Adapted from Dünser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. *Intensive Care Med.* 2012;38(4):557–574. http://link.springer.com/article/10.1007/s00134-012-2468-5. Accessed July 15, 2015.

Antibiotics

Empiric antimicrobial therapy should be adjusted to local infectious disease patterns, including HIV/AIDS prevalence, pathogen spectrum, and antimicrobial resistance. Antibiotics for suspected bacterial sepsis in patients with severe acute malnutrition (with complications) include benzylpenicillin 50,000 units/kg per dose or ampicillin 50 mg/kg per dose, intramuscularly or intravenously every 6 hours for 2 days, and then amoxicillin 15 mg/kg per dose orally every 8 hours for 5 days, in addition to gentamicin 5 mg/kg per dose intramuscularly or intravenously every 24 hours for 7 days.[20]

Malaria

Promptly start IV artesunate in adults and children (2.4 mg/kg) followed by the same dose at 12 hours, 24 hours, and then daily until oral medication can be taken. Intramuscular artemether (3.2 mg/kg on admission followed by 1.6 mg/kg daily) may be used if IV artesunate preparation is unavailable. Alternatively, artesunate by suppositories (8–16 mg/kg at 0 and 12 hours and then daily) or IV quinine (20 mg/kg loading dose over 4 hours followed by 10 mg/kg administered over 4 hours and repeated every 8 hours until patient is stable enough to be started on oral medication) can be used.

Parenteral antibiotics, in addition to antimalarial treatment, should be given to children. Empiric antibiotic therapy needs to cover gram-positive, gram-negative, and anaerobic bacteria. Seizures should be treated with rectal or IV diazepam, IV lorazepam, intramuscular paraldehyde, or other standard anticonvulsants. Fluid management should be performed judiciously and more restrictively in the absence of shock than in patients with bacterial sepsis. A blood transfusion should be considered in cases of severe anemia (eg, hemoglobin level ≤6 g/dL).[28]

Sepsis in Patients With HIV/AIDS

Patients with active mycobacterial infections require isolation or cohorting. In *Pneumocystis jiroveci* pneumonia, therapy of choice is trimethoprim (10 mg/kg/d)/sulfamethoxazole administered for 3 weeks. For patients with hypoxemia, prednisolone (40 mg twice a day for 5 days followed by 40 mg/day for 5 days and then 20 mg/day for 11 days) should be added. In malnourished patients, energy supply should be restarted slowly with a stepwise increase of daily caloric intake and avoidance of large amounts of carbohydrates to prevent refeeding syndrome.[28]

Post-acute interventions to treat septic patients with limited resources include[28]

- *Antimicrobial therapy:* Regularly reassess effectiveness of the antimicrobial regimen. Adjust antibiotics according to sensitivity results. Administer antimicrobials for an adequate but not a prolonged time.
- *Glucose control:* Check blood sugar levels in every septic patient whenever possible. Provide a glucose calorie source to keep blood glucose above 70 mg/dL (>4 mmol/L).
- *Deep vein thrombosis prophylaxis:* Use prophylactic heparin or apply elastic bandages on both legs in postpubertal children and adults. Deep vein thrombosis prophylaxis is not required in prepubertal children.
- *Enteral nutrition:* Allow the patient to eat and drink small amounts once she is fully resuscitated and awake.
- *Sedation and pain relief:* Use opioids to relieve pain. Titrate opioids cautiously in unstable patients. Only sedate the agitated and uncooperative patient. Encourage mobilization as soon as the patient is stable.
- *Wean invasive support:* Try to actively wean the extent of invasive support as soon as the patient is improving

It is challenging to effectively implement guidelines into clinical practice. Summarizing different recommendations in care bundles has been shown to facilitate implementation of the Surviving Sepsis Campaign guidelines.[26]

Suggested care bundles for sepsis management in resource-poor settings include[28]

- *Acute care bundle:* Oxygen therapy, fluid resuscitation, early and adequate antimicrobial therapy, and surgical source control
- *Post-acute care bundle:* Reevaluation of antimicrobial therapy, deep venous thrombosis prophylaxis, glucose control, and weaning of invasive support

Trauma

Trauma continues to be a major health problem worldwide with high mortality and morbidity, particularly in the developing world. Trauma is predicted to become the leading causes of death globally by 2020.[3] However, childhood trauma has been neglected in resource-constrained countries and many developing countries lack an organized trauma system.[4] The need for good trauma management has been obscured by the huge burden of medical problems and lack of financial support. Prompt surgical intervention for life-threatening injuries may not be available in most low-resource settings.

Trauma outcome has shown to improve following the advanced trauma life support program in developing countries.[30,31] The philosophy of pediatric trauma care is essentially the same as for adults. However, children are not small adults; they are anatomically and physiologically different than adults, which creates specific challenges while assessing and managing any ill or injured child. Specific considerations include skills to handle injured children, equipment in pediatric sizes, and adjusting medication doses. Securing and maintaining the airway is more difficult in children due to their relatively large tongue and occiput, small oral cavity, cephalad and anteriorly placed larynx, floppy U-shaped epiglottis, and narrow short trachea. Children's flexible neck makes them more prone to spinal cord injury without radiographic abnormality. Their pliable chest wall makes them more likely to develop tension pneumothorax and pulmonary contusion following trauma. A child's liver and spleen are also less protected due to a thin abdominal wall. Children's pliable bones put them at a higher risk for fractures and growth abnormalities.[30]

Children can quickly become hypoxemic because of their high metabolic rates and low functional residual capacity. A child's relatively large body surface creates a higher possibility of hypothermia and insensible fluid losses. Children can keep up their blood pressure despite a 30% to 45% loss of total blood volume. Initial signs of circulatory failure include tachycardia and poor skin perfusion while maintaining blood pressure. However, children can suddenly decompensate, leading to severe and sudden hypotension. Difficult vascular access makes fluid resuscitation another challenge.[30]

Management

Traumatic injuries in children vary from minor to major and may be limb or life threatening. Trauma may involve a particular part of the body or multiple organs or organ systems. Management requires urgently identifying the limb- and life-threatening injuries in a systematic manner. The first hour of the injury, called the *golden hour,* is the most critical time to save the child's life. Basic triage methods are simple and easy to assess the child's health care needs.

Managing a child who has multiple traumas or who is unstable requires efficient teamwork. Severe multiple injuries or major trauma are life-threatening problems with which children may present at the hospital. Multiple organs and limbs may be affected, and the cumulative effects of these injuries may cause rapid deterioration of the child's condition. Management requires urgent recognition of the life-threatening injuries.[32]

Primary Survey[32]

The purpose of the primary survey is to identify life-threatening injuries, such as airway obstruction, chest injuries with breathing difficulty, severe external or internal hemorrhage, head and cervical spine injuries, and abdominal injuries (Table 33-6). The primary survey should be systematic. During the primary survey, any deterioration in the patient's clinical condition should be managed by reassessment, as a previously

Table 33-6. Emergency Management of Pediatric Trauma

EVALUATION	IDENTIFICATION	MANAGEMENT
PRIMARY SURVEY		
Airway	Obstruction	• Open airway, use airway adjuncts, suction secretions, and administer oxygen.
	Cervical spine injury	• Stabilize cervical spine.
Breathing	Inadequate oxygenation and ventilation	• Deliver high oxygen concentration. • Secure airway (intubation) when appropriate.
	Tension pneumothorax	• Needle decompression followed by chest tube.
	Open pneumothorax	• Apply 3-sided occlusive dressing.
	Massive hemothorax	• Insert chest tube.
Circulation	Absent central pulses	• Start cardiopulmonary resuscitation.
	Shock	• Vascular access, blood sample for Hb and grouping, fluid resuscitation (isotonic fluids 20 mL/kg boluses) • 20 mL/kg whole blood or 10 mL/kg of packed red cells
	External bleeding	• Try to control with manual direct compression.
	Cardiac tamponade	• Pericardiocentesis
	Pelvic fracture	• Pelvic wrap or bind
Disability	Level of consciousness	• Elective intubation if GCS ≤8.
	Signs of raised ICP	• Elevate head end of bed to 30 degrees. • Urgent surgical consultation.
Exposure	Hypothermia	• Prevent and manage hypothermia. • Use warm fluids during resuscitation.

Table 33-6. Severity of Pneumonia and Management, continued

EVALUATION	IDENTIFICATION	MANAGEMENT
Primary Survey Adjuncts	Laboratory investigations	• Blood group, Hb, glucose, prevent hypoglycemia.
	FAST	• To detect hemorrhage: abdomen, thorax, or pericardium
	Urinary catheter	• To monitor urine output, avoid if urethral injury.
	Gastric tube	• To prevent aspiration
SECONDARY SURVEY		
Head-to-Toe Examination and Management	Continue to reassess and manage airway, breathing, circulation, and disability.	
	Head-to-toe examination	• Manage accordingly.
	Investigation (as per clinical indications)	• Laboratory studies • Imaging
	Wounds and fractures	• Dressing and splinting
	Medications	• Provide analgesia: morphine 0.05–0.1 mg/kg IV. • Provide tetanus prophylaxis as per immunization status. • Antibiotics: open fracture, bowel perforation, wound. • IV fluids. • Blood product transfusions as per need.
DEFINITIVE CARE		
		• Ongoing definite care as per organ and system injury.

Abbreviations: FAST, facial drooping, arm weakness, speech difficulties, and time; GCS, Glasgow coma scale; Hb, hemoglobin; ICP, intracranial pressure; IV, intravenous.

From American College of Surgeons. *Advanced Trauma Life Support: Student Course Manual.* 9th ed. Chicago, IL: American College of Surgeons: 2012.

undiagnosed injury may become apparent. Start with assessing and stabilizing the airway while maintaining cervical spine immobilization; assess breathing, circulation, and level of consciousness; and stop any hemorrhage. Expose the child's whole body to look for injuries. The systematic approach should comprise an assessment of

- Airway patency
- Breathing adequacy
- Circulation and control of hemorrhage
- Central nervous system (assess coma scale), cervical spine immobilization
- Exposing the whole body and looking for injuries

Resuscitate measures include providing oxygen by bag or mask, if necessary; stopping any external hemorrhage; and obtaining circulatory access to support circulation by infusing crystalloids or blood, if necessary. Draw blood for hemoglobin and group and crossmatching as IV access is set up. Document all procedures undertaken.

Secondary Survey[32]

Perform a secondary survey after stabilizing the patient's airway patency, breathing, circulation, and consciousness (see Table 33-6). Undertake a head-to-toe examination, particularly noting

- *Head:* Scalp and ocular abnormalities, external ears, and periorbital soft tissue injuries.
- *Neck:* Penetrating wounds, subcutaneous emphysema, and tracheal deviation.
- *Neurologic:* Assess brain function. Use the alert, voice, pain, unresponsive (AVPU) scale to assess level of consciousness. Check motor activity, sensation, and reflexes.
- *Chest:* Clavicles and all ribs and breath and heart sounds.
- *Abdominal:* Evaluate for penetrating and blunt abdominal trauma.
- *Pelvis and limbs:* Fractures, peripheral pulses, cuts, bruises, and other minor injuries.

Investigations[32]

Investigations can be performed after the child is stabilized and when indicated. In general, the following investigations may be useful, depending on the type of injury:

- *Radiographs:* Depending on the suspected injury (may include chest, lateral neck, pelvis, cervical spine [all 7 vertebrae], long bones, and skull).
- *Ultrasound scan:* A scan of the abdomen may be useful in diagnosing internal hemorrhage or organ injury.

Head Trauma

It is important to prevent secondary brain damage from hypoxia, hypotension, or hypoglycemia. Children more frequently suffer from acute brain swelling after a severe head injury. Evaluate for lacerations,

bleeding, and bruising and palpate for fractures or deformity. Assess for signs of fractured skull base: periorbital bruising, blood behind the eardrum, cerebral spinal fluid leak, or bleeding from the nose or ears. Obtain a radiograph if available.

Ensure that the airway remains open and that breathing is adequate, correct shock, and prevent hypotension. Seek urgent help from an anesthetist to secure the child's airway if the child does not respond to pain or is unconscious (P or U on the AVPU scale). In a young child, check for hypoglycemia and correct as appropriate. Give nothing orally and limit fluid intake to two-thirds of maintenance fluid requirements. Place an orogastric tube. Elevate the head of the bed to 30 degrees, but keep it in recovery position if consciousness level is reduced. Diagnose and treat other injuries. Seek an urgent surgical consultation.[32]

Pneumothorax

Clinical signs of tension pneumothorax include severe shortness of breath, cyanosis (hypoxemia), decreased chest movement, and no air entry on the pneumothorax side but with hyperresonance on percussion. Give oxygen as near to 100% as possible (mask with reservoir). Insert a large bore needle in the second intercoastal space above the rib on the side of the tension pneumothorax; this should be followed by placing an intercostal drain. Seek urgent surgical advice.[32]

Hemothorax

Hypovolemic shock will occur, as well as respiratory distress due to lung compression on the involved side, if the hemorrhage is severe. The child may be in respiratory distress with cyanosis, decreased chest movement, and air entry on the affected side but with dullness on percussion. Insert a large chest tube for drainage. Seek urgent surgical advice, as continued bleeding may require thoracotomy. Give IV fluids (10–20 mL/kg of normal saline) initially and transfuse with fresh whole blood (20 mL/kg) as soon as possible. Provide oxygen as near to 100% as possible.[32]

Pulmonary Contusion

Pulmonary contusion (bruising) is common after chest trauma. It is a potentially life-threatening condition. Onset of symptoms may be slow and progress over 24 hours after the injury. Symptoms and signs may include shortness of breath, hypoxemia, and rib fractures. Provide oxygen as near to 100% as possible. Seek urgent surgical advice.[32]

Abdominal Injuries

Any child involved in a serious accident should be considered to have an abdominal injury until proven otherwise. Abdominal injuries can be life threatening, as they result in severe internal blood loss. Look for signs of bruising and penetrating trauma, listen for bowel sounds, check renal angles, and examine urine for blood. Penetrating wounds may result in injuries to the intra-abdominal organs. Any penetration of the bowel wall will lead to peritonitis. Ultrasound is useful, if available, to investigate intra-abdominal bleeding and injury to internal organs.

Assess the patient for airway patency and breathing, provide oxygen, assess circulation, set up IV access, and take blood for hemoglobin, blood crossmatching, and amylase activity (if available). Transfuse as necessary. Seek urgent surgical advice.[32]

KEY POINTS

- Appropriate emergency management of diarrhea with severe dehydration and severe bacterial pneumonia is very important to reduce mortality and morbidity.
- Trauma is predicted to become one of the leading causes of death globally.
- Emergency Triage Assessment and Treatment guidelines were designed to be carried out quickly for triaging children in resource-limited settings.
- Simple inexpensive APLS management can improve child survival when integrated into existing primary care programs.
- Oxygen therapy may be lifesaving in patients with severe pneumonia.
- Hypovolemic shock should be corrected rapidly with fluid resuscitation and frequent response assessment.
- Effectively implementing sepsis guidelines into clinical practice improves outcomes.
- Trauma management requires urgently identifying the limb- and life-threatening injuries in a systematic manner.

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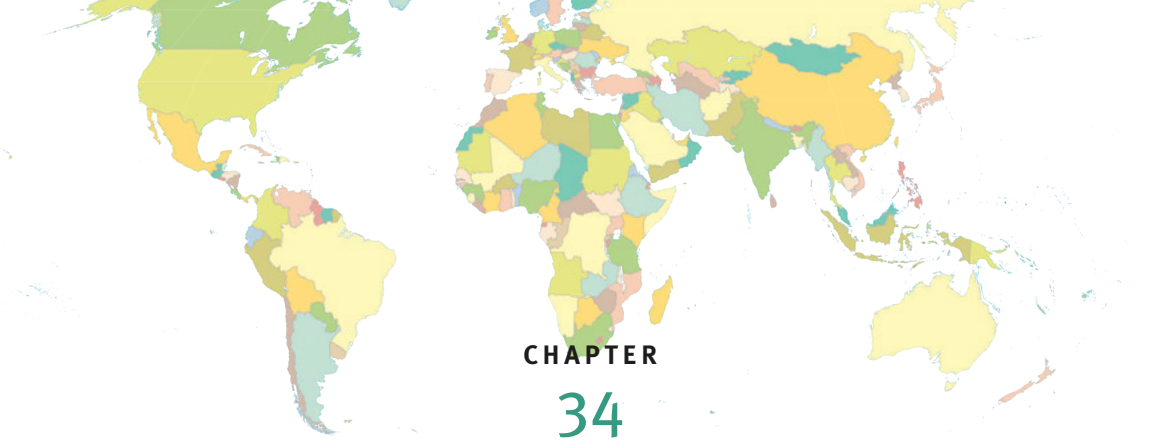

CHAPTER

34

Pediatric Hematology/Oncology

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INTRODUCTION

Pediatric hematologic and oncologic diseases are a global problem. However, due to discrepancy in health care resources, outcomes of these diseases differ vastly between developed and underdeveloped countries. Globally, anemia is prevalent in most developing countries and is considered to be of public health significance. In 2008, the World Health Organization (WHO) estimated worldwide prevalence of anemia by regions and population groups. Women and young children are most vulnerable to anemia.[1] The proportion of women and children was highest in the African region, where 57% of pregnant women (17 million), 48% of nonpregnant women (70 million), and 68% of preschool-aged children (84 million) were anemic. Although the proportion of people with anemia is lower in Southeast Asia, the sheer number of people with anemia is higher than those in the African region due to the large population size. In Southeast Asia, 48% of pregnant women (18 million), 46% of nonpregnant women (182 million), and 66% of preschool-aged children (115 million) are known to suffer from anemia.[1] Although iron deficiency is the leading cause of anemia worldwide, it is seldom isolated. More frequently, it coexists with a number of other causes, such as malaria, parasitic infection, nutritional deficiencies, and hemoglobinopathies. Hemoglobinopathies also contribute to the health burden, as they are the most common monogenic disorders throughout the world. Recent estimates suggest that approximately 7% of the world's

population are carriers and approximately 300,000 to 400,000 children are born with a hemoglobinopathy every year—most with sickle cell disease (SCD).

Bleeding disorders constitute another health care challenge on a global level. Hemophilia A and B, characterized by deficiency of clotting factor VIII (FVIII) and IX (FIX), are the most significant inherited bleeding disorders. Although incidence of hemophilia A is the same across nations, prevalence varies considerably between developed and developing nations. This is likely due to a discrepancy in reporting, lack of access to care, inaccurate diagnosis, or the high mortality associated with these disorders. The number of people with hemophilia worldwide is estimated to be approximately 400,000, but only 75% of these people may have access to clotting factors.[2–4] Several acquired bleeding disorders also affect health in the developing world. Vitamin K–deficiency bleeding (VKDB) in infants, liver disease, hemorrhagic fevers (eg, dengue, Ebola), and disseminated intravascular coagulation are also very common in the developing world. Late VKDB in infants is commonly found in breastfed infants 2 weeks to 2 months of age. There is a strikingly high (80%–90%) incidence of intracranial bleeding, which results in a high mortality rate (25%) and a high level of permanent sequelae (50%); prevalence is 80 per 100,000 births and even higher in developing countries where breastfeeding is common.[5] A surge in VKDB was recently reported in developed countries due to parental refusal of vitamin K injections during the neonatal period.[6]

Approximately 250,000 children and adolescents are diagnosed with cancer every year worldwide; 80% live in low- and middle-income countries.[7] Overall, reported annual pediatric cancer incidence rates are generally lower in low- and middle-income countries than in high-income countries. This is most likely attributed to underdiagnosis and underreporting. There are very few and inconsistent population-based cancer registries in developing countries, making it more challenging to gather accurate data. Nonetheless, there are some striking differences in the pattern of childhood cancer between developing and developed worlds that are likely to be secondary to socioeconomic status, environmental factors, geographic and ethnic variations, dietary habits, hygienic conditions, infections, and exposure to toxins.[8]

ANEMIA

Anemia is defined as a reduction in red blood cell (RBC) mass or a hemoglobin concentration 2 SDs below the mean for the healthy population (adjusted for age and sex).[9]

Iron Deficiency Anemia

Iron deficiency accounts for approximately half of the world's anemia burden. According to WHO estimates, iron deficiency anemia resulted in 273,000 deaths in 2004; 97% of these deaths occurred in low- and middle-income countries.[10]

Factors Affecting Iron Balance

Iron exists in 2 major forms in the body: functional and stored. Most of the functional iron is in the form of heme iron (hemoglobin and myoglobin), while a small portion (<1%) is bound in critical enzyme systems (ie, catalase and cytochromes). Stored iron is in the form of ferritin and hemosiderin and can be mobilized to meet functional iron requirements when intake is low. Most iron is recycled from the breakdown of old RBCs by macrophages of the reticuloendothelial system. Normally, only a small amount of iron is lost from the body as a part of normal turnover of the intestinal mucosa. Menstrual blood loss accounts for an additional physiologic loss of iron in adolescent girls and women of childbearing age.[11] Approximately 5% of daily iron needs in adults comes from dietary sources and equals the physiologic iron loss. However, in infants and children, 30% of daily iron needs must come from diet because of growth spurts and increase in body mass. Most of the iron from digested food or supplements is absorbed by enterocytes in the duodenum and jejunum. In general, nonheme (vegetable) sources have poor iron bioavailability (10%) compared with heme sources, such as fish, poultry, and meat (30%). In addition, co-consumption of certain dietary factors, such as tannates (teas), phytates (plant fiber), polyphenols, zinc, and calcium, inhibit iron absorption, while ascorbic acid enhances the absorption of nonanimal iron sources, such as cereal, breads, fruits, and vegetables.[10]

Dietary Recommendations for Infants and Children

For breastfed full-term infants, the American Academy of Pediatrics recommends 1 mg/kg/day of elemental iron starting at 4 to 6 months of age and continuing until the infant is taking sufficient quantities of iron-rich complementary foods (eg, at least 2 servings of 15 g each of iron-fortified infant cereal). Premature breastfed infants need 2 to 4 mg/kg (maximum 15 mg) of elemental iron starting at 1 month of age. Children 1 to 3 years of age need 7 mg/day of elemental iron; 4 to 8 years, 10 mg/day; and 9 to 13 years, 8 mg/day. Adolescent boys need 11 mg/day of elemental iron and adolescent girls, 15 mg/day.[11]

Etiology of Iron Deficiency Anemia

Iron deficiency may result from inadequate iron intake and absorption, increased iron requirements, and excessive iron losses. Although multifactorial, poor nutrition and low socioeconomic status are associated with most iron deficiency anemia cases in developing countries.[10]

Nutritional Factors

Nutritional iron deficiency arises when physiological requirements cannot be met by diet alone. Inadequately consuming foods rich in a highly bioavailable form of iron and co-consuming foods that inhibit iron absorption are important causes of nutritional iron deficiency. Introducing unmodified cow's milk (non-formula cow's milk) before 12 months of age, as well as drinking more than 720 mL (24 oz) of milk daily, increases the risk for iron deficiency among preschool-aged children because of the low concentration and bioavailability of iron in cow's milk and possibly because of the increased intestinal blood loss.[11]

Increased Iron Requirements

Rapid expansion in red cell mass in infants results in very high dietary iron requirements, especially in low birth weight and premature infants who are born with lower iron stores and who are at increased risk for iron deficiency anemia. Similarly, iron requirements escalate rapidly during adolescence because of an expansion in hemoglobin and muscle mass. Maternal iron status may influence a fetus' iron accumulation, and maternal hemoglobin and receipt of iron supplementation may influence infant iron stores.[10]

Excessive Iron Losses

Menstruating adolescent girls and women of reproductive age are at particular risk for iron deficiency. Pregnancy and childbirth result in a net iron loss of approximately 600 mg because of fetal and placental requirements and bleeding during delivery.[10]

Infections

Hookworm infestation and schistosomiasis can cause chronic gastrointestinal blood loss and thus lead to iron deficiency. *Helicobacter pylori* causes peptic ulcers and may cause resistance to iron therapy. Chronic giardiasis is also associated with iron deficiency anemia secondary to poor absorption. Iron absorption and incorporation into erythrocytes is impaired during malaria and other infections, predominantly mediated by hepcidin.[10]

Malabsorption

Gastrointestinal malabsorption of iron occurs in conditions such as celiac disease and inflammatory bowel disease and in patients with resection of the proximal small intestine.[12]

Clinical Manifestations

Many children with mild to moderate anemia are asymptomatic; their anemia may get detected incidentally when a complete blood cell count (CBC) is done for some other reason or as part of routine screening. Children with severe anemia may present with lethargy, irritability, poor feeding, pallor, tachypnea, tachycardia, flow murmur, and cardiomegaly. Pallor can be appreciated in conjunctiva, gums, creases of the palms, and nail beds.[13]

Although anemia is a common manifestation of iron deficiency, impaired brain development and cognitive, behavioral, and psychomotor impairment are some of the serious manifestations of iron deficiency; some of these changes occur during a brain growth spurt (<2 years of age) and may be irreversible. Impaired cell-mediated immunity and bactericidal function may be noted in iron-deficient persons; however, findings are inconsistent. Association of iron deficiency and thrombotic complications, including stroke, is increasingly recognized. Although the mechanism is not entirely clear, an iron deficiency state is associated with other conditions, such as restless legs syndrome and breath-holding spells.[14,15] Many studies report low iron status as a possible risk factor for a first febrile seizure. These studies postulate that low plasma ferritin levels may lower the seizure threshold, as iron is important for function of various enzymes and neurotransmitters in the central nervous system. In addition, various forms of pica have been described in association with iron deficiency anemia, including geophagia (eating clay or dirt), pagophagia (ice), amylophagia (starch), and ryzophagia (raw rice).[14]

Diagnosis

Iron deficiency anemia develops as the result of a series of steps, beginning with depletion of iron stores in the body. First, iron disappears from the bone marrow, leading to increased red-cell distribution width (RDW). Next, there is a loss of transport iron, which is reflected by a reduced serum iron level. Erythropoiesis then becomes iron deficient, as indicated by a reduced mean corpuscular volume (MCV), which ultimately results in overt anemia.[16]

A focused dietary history is the most important screening test for iron deficiency; some red flags in the history include

- *Infants:* Use of low-iron formula or non-formula cow's milk, goat's milk, or soy milk for the milk-based part of the diet before 12 months of age, or fewer than 2 servings/day of iron-rich foods (meats or fortified infant cereal) after 6 months of age[11]
- *Preschool-aged children:* Milk intake of more than 720 mL (24 oz)/day or fewer than 3 servings daily of iron-rich foods[11]

Other relevant history, such as acute or chronic blood loss, including gastrointestinal bleeding and menstrual blood loss in adolescent females, is important. In addition, history suggesting infections, particularly parasites (eg, hookworm, giardiasis), should be obtained.

Laboratory Investigations

Complete blood cell count shows low hemoglobin and hematocrit, low RBC count, low MCV, low reticulocyte count, and high RDW. Table 34-1 shows normal hemoglobin, hematocrit, and MCV values in children. A review of the peripheral blood smear of a patient with iron deficiency anemia shows microcytic and hypochromic RBCs with anisocytosis (variation in size) and poikilocytosis (variation in shape) with pencil-shaped cells. Basophilic stippling could be noted in the presence of concomitant lead toxicity or thalassemia trait. The iron panel is characterized by reduced serum ferritin level, serum iron level, and transferrin saturation and increased total iron binding capacity. These biochemical parameters may be altered by physiological states unrelated to iron stores and must be carefully interpreted. For example, ferritin is an acute phase reactant and thus may be falsely normal or even elevated in the setting of acute inflammation.

It is important to acknowledge that an entire panel of diagnostic testing may not be necessary when history and CBC (especially a low MCV with an elevated RDW) are consistent with iron deficiency anemia. Response to treatment may serve as a "diagnosis test." However, in such cases, it is important to follow patients to document response to treatment. Additionally, as mentioned previously, iron deficiency is always secondary to an underlying cause and care should be taken to evaluate and treat the underlying condition leading to iron deficiency.

Differential Diagnosis

Thalassemia Trait

Thalassemia trait (α- or β-thalassemia) is one of the major differential diagnoses of microcytic anemia. The index score by Mentzer is a useful

Table 34-1. Normal Hemoglobin, Hematocrit, and Mean Corpuscular Volume Values in Children

	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		MCV (fL)	
AGE	MEAN	-2 SD	MEAN	-2 SD	MEAN	-2 SD
Birth	16.5	13.5	51	42	108	98
2 mo	11.5	9	35	28	96	77
3–6 mo	11.5	9.5	35	29	91	74
0.5–2 y	12	10.5	36	33	78	70
2–6 y	12.5	11.5	37	34	81	75
6–12 y	13.5	11.5	40	35	86	77
12–18 y Female Male	 14 14.5	 12 13	 41 43	 36 37	 90 88	 78 78

Abbreviation: MCV, mean corpuscular volume.

Derived from Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux S. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia, PA: Saunders/Elsevier; 2015.

tool; it is calculated as the ratio of MCV to RBC count in millions. Scores above 13 are consistent with a diagnosis of iron deficiency anemia, and scores 13 or below are consistent with thalassemia. However, scores should be confirmed by further testing.[13]

Lead Poisoning

Microcytosis associated with lead poisoning is mainly due to iron deficiency caused by 2 mechanisms: interference with iron absorption and inhibition of enzymes required for heme synthesis. There is also contribution from nutritional iron deficiency as a result of pica.[13] A blood lead level should be done to confirm lead toxicity.

Anemia of Chronic Disease

Normocytic to mildly microcytic anemia occurs in chronic inflammatory conditions such as cancers, chronic infections, and autoimmune disorders such as inflammatory bowel disease, juvenile idiopathic arthritis, and connective tissue diseases. Cytokines, produced secondary to chronic inflammation in these conditions, cause iron accumulation in storage sites and inhibit RBC proliferation and differentiation, affecting iron hemostasis.[13]

Table 34-2 summarizes laboratory findings in iron deficiency anemia, thalassemia, and anemia of inflammation.[17]

Management

After iron deficiency anemia in confirmed, it is important to determine the underlying cause and correct the abnormality. The patient may be started on oral iron (eg, ferrous sulfate) at 3 to 6 mg/kg/day of elemental iron 1 to 2 times per day. Iron should be administered 30 to 45 minutes before meals or 2 hours after meals, preferably with a small amount of citrus juice (eg, orange juice) to ensure optimum absorption. Iron should not be given with milk, as it inhibits iron absorption. Limiting milk intake to a maximum of 720 mL (24 oz) should be implemented in patients with iron deficiency anemia secondary to excessive milk consumption. An adequate response to iron therapy is evaluated by an increase of more than 1 g/dL of the hemoglobin concentration or more than 3% of the hematocrit concentration after 4 weeks of oral iron treatment. Once the response is confirmed, iron supplementation and monitoring should be continued for an additional 2 months after the hemoglobin reaches the age-adjusted normal range. If the hemoglobin or hematocrit concentration does not increase after 4 weeks of iron treatment, further laboratory evaluation to look for an underlying etiology of iron deficiency is indicated, given that the patient is compliant with the medication.

Table 34-2. Laboratory Findings in Differential Diagnosis of Iron Deficiency Anemia

TEST	IRON DEFICIENCY ANEMIA	ALPHA/BETA THALASSEMIA	ANEMIA OF INFLAMMATION
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
Red cell distribution width	Increased	Normal	Normal-increased
Total iron-binding capacity	Increased	Normal	Normal-decreased
Transferrin saturation	Decreased	Normal	Normal-decreased
Serum ferritin	Decreased	Normal	Normal-Increased
Serum iron	Decreased	Normal	Decreased

Abbreviation: MCV, mean corpuscular volume.

Derived from Van Vranken M. Evaluation of microcytosis. *Am Fam Physician.* 2010;82(9):1117–1122; and Wallach J. *Interpretation of Diagnostic Tests*. 8th ed. Boston, MA: Little Brown and Compnay; 2006.

American Academy of Pediatrics Guidelines for Preventing Iron Deficiency in Infants[11]

1. Provide human milk for at least 4 to 6 months when possible. If an infant remains exclusively breastfed beyond 6 months of age, iron supplement should be given to provide 1 mg/kg/day of elemental iron.
2. Provide the non-breastfed infant with an iron-fortified formula (containing 12 mg of iron per L) for the first 12 months of life.
3. Provide an iron-enriched cereal when solid foods are introduced into the diet. An average of 2 servings (15 g of dry cereal per serving) is needed to meet the daily iron requirement.
4. Avoid feeding of whole cow's milk during the first year of life, as it may cause occult gastrointestinal bleeding. The modification of cow's milk protein when preparing commercial infant formula or evaporated milk appears to sufficiently alter the protein, preventing it from causing bleeding.

Megaloblastic Anemia

Megaloblastic anemia is characterized by macrocytic RBCs and typical morphologic changes in RBC precursors. The RBC precursors are larger than the same-stage cells and exhibit disparity in nuclear-cytoplasmic maturation.[18]

The basic underlying pathogenic mechanism in megaloblastic anemia is deficiency of folate (vitamin B_{10}) or cobalamin (vitamin B_{12}) at the cellular level with resulting DNA synthesis impairment. Most cases of megaloblastic anemia in developing countries result from nutritional deficiency of these micronutrients.[18] Rarely, inborn errors of vitamin B_{12} metabolism may result in megaloblastic anemia. Prevalence of vitamin B_{10} or B_{12}, as reported by various studies from India and other developing countries, ranges from 6% to 70%.[18]

Folate (Vitamin B_{10}) Deficiency

Folate carries hydroxymethyl and formyl groups necessary for the synthesis of purines and thymine, which are required for DNA formation. This is necessary for the maturation of RBCs and promotes cellular growth in general. Natural sources of folate include fresh green vegetables, fruits, cereals, grains, nuts, meat, liver, and yeast. Folate in natural sources occurs in the pteroylpolyglutamate form, which must be hydrolyzed by conjugase in the brush border of the intestine to folate monoglutamates. These are absorbed in the duodenum and proximal jejunum and transported to the liver.[11,19]

Normal daily folate requirements are about 200 to 400 mcg per day; this increases to 500 to 800 mcg per day in pregnancy and lactation. Total body stores of folate are relatively low at 5 to 10 mg; hence, the effects of folate deficiency can occur relatively sooner (ie, 4–5 months) in a diet that is deficient in folic acid.[20]

Causes of Folate Deficiency

Lack of dietary intake, malabsorption, increased demand, or medications that interfere with folate metabolism are the main causes of folate deficiency. Next to iron deficiency, folate deficiency is one of the most common micronutrient deficiencies worldwide. Folate deficiency is common in areas where poverty and malnutrition are prevalent and dietary supplements are not a standard practice. Adolescent girls and women of childbearing age are particularly vulnerable, as the daily requirement almost doubles during pregnancy and lactation. Similarly, individuals with hemolytic anemia or exfoliative skin diseases have increased folate requirements. Malabsorption of folate can occur with Crohn disease, celiac disease, and small bowel resection. Medications such as methotrexate, pyrimethamine, and trimethoprim disrupt folic acid metabolism, and phenytoin blocks folate absorption, potentially leading to folate deficiency. Folate concentration in goat's milk is markedly less than in cow's milk; as a result, infants who are fed goat's milk as a primary source of nutrition are at risk for developing folate deficiency.[20] Rarely, inborn errors of folate metabolism, including congenital folate malabsorption, severe methylenetetrahydrofolate reductase deficiency, and formiminotransferase deficiency, contribute to folate deficiency.[19]

Cobalamin (Vitamin B_{12}) Deficiency

Cobalamin functions as a coenzyme to a number of enzymes involved in RBC maturation and development of the central nervous system. Cobalamin and folate are necessary for the re-methylation of homocysteine to methionine synthase.

Natural sources of cobalamin are only animal foods, including meat, fish, poultry, dairy, and eggs. Once ingested, vitamin B_{12} is bound to R protein in saliva and gastric juice. Pancreatic proteases release vitamin B_{12} from R proteins in the small intestine, where it binds to intrinsic factor (IF) produced by gastric parietal cells. Vitamin B_{12} bound to IF is then transported to the terminal ileum. Enterocytes in the terminal ileum absorb vitamin B_{12}, break the vitamin B_{12}-IF complex, and release vitamin B_{12} into the portal circulation bound to transcobalamin II. Vitamin B_{12} is then transported to different tissues throughout the body. Humans

recycle vitamin B_{12} via enterohepatic circulation; it is excreted in bile and reabsorbed in the terminal ileum.[11,20]

The normal daily requirement of vitamin B_{12} for children is only 0.4 to 2.4 mcg. The liver stores 2 to 3 mg of vitamin B_{12}; because of this large store and active enterohepatic circulation, it takes several years of a deficient diet for a person to become vitamin B_{12} deficient.[20]

The primary role of vitamin B_{12} is to serve as a cofactor for 2 major metabolic reactions. Vitamin B_{12} is required for methylation of homocysteine to methionine. During this reaction, 5-methyltetrahydrofolate is demethylated to tetrahydrofolate, which is important in DNA synthesis. Vitamin B_{12} is also necessary for converting methylmalonyl coenzyme A to succinyl coenzyme A.[20]

Causes of Cobalamin Deficiency

Vitamin B_{12} deficiency in children and adolescents is the result of 3 pathophysiologic mechanisms: inadequate intake, decreased absorption, or inborn errors of transport and metabolism.

Inadequate Intake

Dietary vitamin B_{12} deficiency rarely occurs in children who adhere to a normal Western diet. However, individuals on a strict vegan diet, avoiding all animal products including dairy, can become deficient over time. The most common scenario for infants who become vitamin B_{12} deficient are those who are exclusively breastfed by mothers who are vitamin B_{12} deficient. Rarely, vitamin B_{12} deficiency occurs in children who are on restricted diets, such as in poorly controlled phenylketonuria, or in children with glycogen storage disease type 1B.[20]

Decreased Absorption

Abnormal absorption can occur for multiple reasons. Gastric resection and autoimmune pernicious anemia, as part of autoimmune polyglandular syndrome, result in decreased IF. Long-term gastric acid suppression, as with proton pump inhibitors, results in decreased release of vitamin B_{12} from dietary proteins. Pancreatic insufficiency can result in malabsorption secondary to decreased proteases that degrade R proteins. Intestinal parasitic infections, such as giardiasis, infestation with the fish tapeworm, and *Diphyllobothrium latum,* are associated with vitamin B_{12} deficiency. Decreased absorption in the ileum can occur in Crohn disease, celiac disease, and surgical resection of the ileum.[20]

Inborn Errors of Transport and Metabolism

Rarely, inborn errors of cobalamin metabolism affect its absorption (IF deficiency, Imerslund-Graesbeck syndrome) and transport (transcobalamin deficiency), as well as its intracellular metabolism, affecting adenosylcobalamin synthesis, methionine synthase function, or both. Imerslund-Graesbeck disease is an autosomal-recessive syndrome in which there are abnormal ileal receptors for vitamin B_{12}, leading to malabsorption of vitamin B_{12}.[19,20]

Clinical Manifestations

Apart from general signs and symptoms of anemia (easy fatigability, tiredness, poor feeding, pallor, tachypnea, tachycardia, flow murmur, and cardiomegaly), patients with vitamin B_{12} deficiency may have neurologic abnormalities, including developmental delay or regression, paresthesia, impaired vibratory and proprioceptive sense, hypotonia, seizures, ataxia, dementia, paralysis, abnormal movements, memory loss, personality changes, depression, irritability, weakness, and poor school performance.[21]

Symptoms in folate deficiency are restricted to those associated with anemia. Unlike vitamin B_{12} deficiency, neurologic complications are not seen. Patients may present with irritability, chronic diarrhea, and failure to thrive.[20]

Diagnosis

Complete blood cell count shows low hemoglobin, low hematocrit, elevated MCV, and low reticulocyte count. Peripheral blood smear contains oval macrocytic RBCs (macro-ovalocytes). White blood cell count is normal or low, but neutrophils show hypersegmentation with at least 5% of cells having 5 or more lobes. Platelet count may be normal or low.

Bone marrow aspiration, although not necessary to establish the diagnosis of megaloblastic anemia secondary to vitamin deficiency, shows hypercellularity with megaloblastic erythroid hyperplasia, contrasting with the reticulocytopenia, giant metamyelocytes, and many mitotic figures.

Diagnosis of folate deficiency is made by assessment of serum and RBC folate. Red blood cell folate concentration is theoretically a more reliable indicator of tissue folate adequacy because it reflects a time-averaged value of folate availability and is therefore not subject to short-term dietary fluctuations. Folate deficiency is also associated with increased serum concentration of homocysteine; however, serum and urine methylmalonic acid (MMA) levels remain normal—a feature that distinguishes it from vitamin B_{12} deficiency, in which homocysteine and MMA levels are elevated.

Diagnosis of cobalamin deficiency is made by determining the serum concentration of cobalamin. If serum concentrations are borderline low and the diagnosis of deficiency is uncertain, measuring plasma homocysteine as well as serum and MMA concentrations would be helpful. Cobalamin deficiency is confirmed if concentrations of both metabolites are increased. Presence of anti-IF antibodies highly confirms the diagnosis of pernicious anemia.

Differential Diagnosis of Megaloblastic Anemia

Fifty percent to 80% of megaloblastic anemia cases are associated with neutropenia or thrombocytopenia, thus mimicking aplastic anemia. Similarly, 30% to 40% of these cases are associated with hepatosplenomegaly and may be confused with leukemia.[18] Bone marrow aspiration is diagnostic in addition to the other laboratory tests mentioned previously.

Macrocytosis may also result from increased cell destruction (hemolytic anemia) or blood loss, with reticulocytes released into the peripheral circulation. Careful history and examination of a peripheral blood smear may help distinguish these cases from megaloblastic anemia. Treating HIV with reverse transcriptase inhibitors (eg, stavudine, lamivudine, zidovudine) may cause macrocytosis because they interfere with DNA production, which may lead to megaloblastic changes. Additionally, other medications, such as anticonvulsants (eg, phenytoin, valproic acid), chemotherapeutic drugs (methotrexate, mercaptopurine, and 5-fluorouracil), and antimicrobials (eg, trimethoprim, valacyclovir) may also cause macrocytosis; thus, a complete medication history should be obtained. In addition, hypothyroidism, Down syndrome, liver and renal disease, and chronic obstructive pulmonary disease are associated with less-dramatic elevations in MCV. Splenectomy may also cause macrocytosis because the cells are not processed as thoroughly when the spleen is absent.[22]

Treatment

Patients with documented folate deficiency should be treated with oral folic acid. Generally, 100 mcg/kg of folic acid is sufficient to correct folate deficiency whether dietary or secondary to malabsorption. Daily treatment with 1 mg is more than adequate; however, larger doses are usually given because folic acid is available in 5-mg tablets.[9] Treatment may continue for 1 to 4 months or until complete hematologic recovery occurs. Concomitant vitamin B_{12} deficiency must be ruled out and treated, if present, before giving folic acid to a patient with megaloblastic

anemia because administration of folic acid may worsen neurologic complications of untreated vitamin B_{12} deficiency.

Once confirmed, vitamin B_{12} deficiency is treated by administering large doses of cobalamin orally or parenterally. Conventional therapy consists of low-dose injections of cyanocobalamin 0.2 mcg/kg/day administered subcutaneously for 2 days because of the risk of hypokalemia with initial treatment, followed by 1,000 mcg/day on days 2 through 7, then 100 mcg weekly for 1 month, and then monthly thereafter. Alternatively, oral therapy with 1 to 2 mg of cobalamin daily has been found to yield comparable benefits, particularly with regard to correction of megaloblastic anemia; cobalamin is cheaper, better tolerated, and is now standard treatment in many countries.[9]

Reticulocyte count begins to increase on day 3 or 4, rise to a maximum on day 6 to 8, and gradually falls to normal in about 3 weeks. Bone marrow reversal from megaloblastic to normoblastic cells begins within 6 hours and is complete in 72 hours.

Patients with a permanently decreased ability to absorb dietary vitamin B_{12} (eg, pernicious anemia, total gastrectomy, surgical removal of the terminal ileum) require lifelong treatment. If the cause of cobalamin deficiency is temporary (eg, diet, drugs, reversible malabsorption syndrome), treatment may be discontinued when the deficiency is fully reversed and the underlying cause eliminated.

SICKLE CELL DISEASE

Sickle cell disease is a genetic blood disorder characterized by abnormal hemoglobin causing deformity and premature destruction of RBCs. Although primarily a blood disorder, SCD affects multiple organ systems in the body because of hemolysis and vasoocclusive phenomena.[23]

Epidemiology

With approximately 275,000 babies born with the condition globally every year, SCD is the most common hemoglobinopathy in the world. It is particularly common among people whose ancestors come from sub-Saharan Africa, South America, Cuba, Central America, Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy. It is estimated that 85% of births affected with SCD occur in Africa. Most children born with hemoglobinopathies in high-income countries survive to adulthood as a result of universal newborn screening, prophylactic penicillin, and better-quality medical care. In contrast, approximately 50% to 80% of the infants born with SCD in Africa die before 5 years of age.[24,25]

Pathophysiology

The hemoglobin molecule is a tetramer of 4 protein chains, 2 α-globins and 2 β-globins, each encoded by genes on different chromosomes. The HbS mutation (β^S) is a single nucleotide substitution in the sixth codon of the β-globin gene that results in hydrophobic valine residue replacing the normal hydrophilic glutamic acid at the sixth position. In a deoxygenated state, HbS is insoluble and undergoes polymerization within the RBCs, change their shape to a sickled form. This often damages the RBC membrane, causing decreased RBC life span and making the cells abnormally adhesive, which obstructs small blood vessels, causing ischemic injury of multiple organs and tissue.[23]

Table 34-3 summarizes different types of SCD depending on homozygous inheritance (HbSS) versus compound heterozygosity, with certain other mutations in β-globin gene including HbC and β-thalassemia. These compound heterozygous states produce SCD types called sickle hemoglobin C disease (HbSC), sickle-β^+-thalassemia ($HbS\beta^+$), and sickle-β^0-thalassemia ($HbS\beta^0$). In general, HbSS and $HbS\beta^0$ are the most severe forms of SCD and may be clinically indistinguishable. In comparison, HbSC and $HbS\beta^+$ are usually less severe.[23]

Sickle Cell Trait

Heterozygosity for β^S is called sickle cell trait. This is a benign carrier state, and the vast majority of individuals have no clinical symptoms. Sickle cell trait can cause hematuria and a loss of urine concentrating capacity. Symptoms from intravascular sickling have been reported with strenuous exercise at high altitudes and flying at high altitudes in unpressurized aircraft. Sickle cell trait provides some protection against severe malarial infection.[23,26]

Clinical Manifestations/Complications

Infants in their first 5 to 6 months of life are usually asymptomatic due to protection offered by a physiologically increased amount of fetal Hb (HbF), which inhibits polymerization of HbS.[23]

Hemolytic Anemia

The RBC life span in HbSS may be as short as 12 days compared with the normal 120 days, resulting in chronic hemolytic anemia. Anemia is usually seen by 6 months of age and becomes more severe as the child grows older. Degree of anemia varies by SCD genotype. Table 34-3 summarizes typical Hb concentrations at a steady state among various SCD genotypes. Because of its chronic nature, most children are reasonably well compensated physiologically for their anemia. However, it may get

Table 34-3. Common Hematologic Findings in Untreated Patients With Sickle Cell Disease

GENOTYPE	ABBREVIATION	NAME	MAIN Hb PRESENT	HB (g/dL)	MCV (fL)	RETICULOCYTES (%)	SEVERITY
β^S/β^S	HbSS	Sickle cell anemia	S	6–9	Normal	10–25	+++
β^S/β^o	HbSβ^o	Sickle-β^{o-} thalassemia	S	6–9	Decreased	10–25	+++
β^S/β^C	HbSC	Sickle-HbC disease	S, C	9–12	Normal–mildly decreased	5–10	++
β^S/β^+	HbSβ^+	Sickle-β^{+-} thalassemia	S, A	10–13	Decreased	2–10	+

Abbreviation: MCV, mean corpuscular volume.

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acutely exacerbated in conditions such as transient aplastic crisis, acute splenic sequestration, and concurrent illnesses.[23]

Hyposplenism, Fever, and Sepsis

Patients with SCD undergo functional asplenia or hyposplenism because of splenic infarcts, which puts them at increased risk (300–500 times higher than general populations) for potentially fatal invasive pneumococcal infections, including bacteremia, sepsis, meningitis, and pulmonary infection. Hyposplenism is detectable by 3 months of age in HbSS and HbSβ^0. Accordingly, high fever (eg, >101°F–101.5°F) is a medical emergency in patients with SCD because it can be the first sign of bacteremia. Patients and caregivers need to present promptly to medical attention. Febrile patients should be promptly evaluated, with careful attention to cardiopulmonary status and identification of possible infection sites. After obtaining a CBC and blood culture, a broad-spectrum parenteral antibiotic (eg, ceftriaxone) should be given without delay, as well as a close follow-up of the patient and blood cultures. Reserve inpatient management for septic or toxic-appearing children and strongly consider for those who have high-risk features, such as the very young (<6 months), those with concomitant pulmonary disease, blood counts that are significantly different from baseline, missed doses of prophylactic penicillin, or follow-up uncertainty. Prescribe prophylactic penicillin and additional vaccinations to children with SCD, especially those with HbSS and HbSβ^0, to prevent early fatal infections with encapsulated organisms (Box 34-1).[23]

Splenic Sequestration

Splenic sequestration refers to acute painful enlargement of the spleen secondary to trapping of RBCs within splenic sinusoids. It typically occurs between 1 and 4 years (highest prevalence is 5–24 months) of age. Acute splenic sequestration leads to potentially severe anemia, hypovolemia, and possibly shock. It is important for the family and caregivers to be able to detect splenomegaly and signs and symptoms of acute severe anemia to prevent death. Transfusion is usually reserved for symptomatic or severe anemia. Initial transfusion of packed RBCs may need to be given rapidly to correct hypovolemic shock. Subsequent transfusions, if needed, should be given cautiously and in smaller volumes because of the potential for autotransfusion of sequestered blood that could lead to hyperviscosity. Splenectomy should be considered for severe or recurrent acute splenic sequestration. Splenic involution is usually complete by 5 years of age in HbSS and HbSβ^0, so sequestration is uncommon

Box 34-1. Penicillin Prophylaxis and Immunizations for Patients With Sickle Cell Disease

Penicillin Prophylaxis
For children with HbSS and HbSβ⁰

Begin at 1–2 months of age

Age <3 years: penicillin V potassium 125 mg by mouth twice a day

Age 3–5 years: penicillin V potassium 250 mg by mouth twice a day

Continue until at least 5 years of age

May continue past 5 years for pneumococcal sepsis, surgical splenectomy, or parental preference

For children with HbSC and HbSβ⁺

Hyposplenism occurs years later than in HbSS

Practice varies by center

Consider starting at 4–5 years of age or for a history of pneumococcal sepsis or surgical splenectomy

Immunizations
For all forms of sickle cell disease

The 23-valent pneumococcal polysaccharide vaccine (PPV23): ages 2 and 5 years (consider re-immunization at 5-year intervals)

4-valent meningococcal conjugate vaccine (MCV4): age 2 years (consider re-immunization at 5-year intervals)

Influenza vaccine: yearly

The normal vaccine series of childhood that includes the 13-valent pneumococcal conjugate vaccine (PCV13), *Haemophilus influenzae* type b, and hepatitis B virus vaccines.

From Quinn CT. Sickle cell disease in childhood: from newborn screening through transition to adult medical care. *Pediatr Clin North Am.* 2013;60(6):1363–1381. Copyright 2013, with permission from Elsevier.

thereafter. Splenic involution is delayed in HbSC and HbSβ⁺; thus, sequestration may occur in older children and adults.[23]

Transient Aplastic Crisis

Human parvovirus B19 infects RBC precursors in the bone marrow and temporarily impairs the production of new RBCs in patients with hemolytic anemia, resulting in severe anemia. Similarly, in SCD patients who have a shortened RBC life span, this can lead to severe anemia and reticulocytopenia. Spontaneous recovery begins in about 1 week. The need for RBC transfusion depends on severity of anemia and clinical status of the patient. Parvovirus aplastic crisis does not recur due to long-lasting humoral immunity.[23]

Painful Events and Bony Complications

Vasoocclusive ischemia and infarction of the bones due to sickling produce painful episodes. Pain is typically multifocal and often regional or bilaterally symmetric. Dactylitis or hand-foot syndrome is one of the earliest physical manifestations of SCD, characterized by painful and often symmetric swelling of the hands, feet, or both. About 30% of children with HbSS have dactylitis in the first 3 years of life. Treatment of painful events is primarily supportive. Mild to moderate pain is often managed at home with prompt use of oral analgesics and hydration. Severe pain may require inpatient management. A combination of a nonsteroidal anti-inflammatory drug (NSAID) and opiate analgesics, titrated to effect, can usually provide adequate relief.[23]

Sickle cell disease predisposes to osteomyelitis, which is thought to result from secondary infection of ischemic or avascular bone. Differentiating osteomyelitis from painful events is sometimes challenging because both can cause bony tenderness and joint effusions. Imaging studies may not be discriminative because sterile bony infarction and osteomyelitis often produce similar findings on radiographs, radionuclide scans, and magnetic resonance imaging (MRI). Clinical features that increase the likelihood of osteomyelitis over an uncomplicated painful event are a single focus of pain, fever, and bacteremia. Special imaging and biopsy of bone are best reserved for patients for whom there is high clinical suspicion of osteomyelitis. Empiric therapy should be directed against *Salmonella* and *Staphylococcus*, which are the most common causes of osteomyelitis in SCD. Specific therapy is given once an organism is identified.[23]

Avascular necrosis (AVN) of bone can occur as early as 5 years of age. The most common site of AVN is the femoral heads, but it also occurs in the proximal humerus and other bones. Approximately 50% of patients are asymptomatic, so pain in the hips or knees should prompt consideration of AVN. Plain radiographs are often sufficient to make the diagnosis, but MRI may be needed to detect early disease or plan surgery. No therapy is needed for incidentally detected, asymptomatic AVN. Symptomatic AVN is managed with long-acting NSAIDs and physical therapy. Some patients may require surgery.[23]

Pulmonary Complications

Acute chest syndrome (ACS) refers to a spectrum of acute pulmonary illness in a patient with SCD. It is the second most common cause of hospitalization in patients with SCD and the most common cause of death due to SCD. Diagnosis usually requires a new radiographic pulmonary

infiltrate and one or more of the following symptoms: fever, chest pain, and signs or symptoms of pulmonary disease, such as tachypnea, increased work of breathing, cough, or hemoptysis. Acute chest syndrome has many triggers, including infection, pulmonary fat embolism or thromboembolism, hypoventilation or atelectasis, bronchospasm, and inflammation of any cause. Additionally, 50% of ACS episodes may be associated with infections (including viral causes); rates of ACS are high in patients with asthma. Asthma prevalence is higher in patients with SCD. Acute chest syndrome often develops in children hospitalized for treatment of other conditions, such as a painful event, or after surgery. Therefore, ACS should be an anticipated complication and prevented, when possible, with adequate pain control, hydration, ambulation, and incentive spirometry. Management of ACS is primarily supportive. Exchange transfusion should be performed for hypoxemia despite oxygen supplementation, widespread (bilateral, multilobar) pulmonary infiltrates, or rapid clinical deterioration.[23]

Cardiopulmonary Complications

Cardiomegaly is common in children with SCD and usually represents a hyperdynamic state due to chronic anemia. Several studies conducted in the past decade demonstrated that cardiopulmonary complications, including pulmonary hypertension, are primary risk factors for death in patients with SCD. Right heart catheterization studies indicate that the prevalence of pulmonary hypertension is 6% to 11%. Echocardiography may also be used as a screening test to estimate pulmonary artery pressure, and a tricuspid regurgitant jet velocity (TRJV) greater than 2.5 m/s is consistent with elevated pressure.[23] An elevated TRJV is seen in approximately 10% to 20% of pediatric patients with SCD, although effects on survival are unclear. Annual 2-dimensional echocardiograms can be performed as part of comprehensive SCD evaluations.

Neurologic Complications

Overt stroke occurs in up to 11% of children with HbSS by 18 years of age; the highest incidence is in the first decade of life. Stroke is much less common in HbSC and HbSβ^+. Transient ischemic attacks (TIAs) may precede overt stroke. Most strokes in children are ischemic and associated with occlusive cerebral arterial vasculopathy in large intracranial vessels. Hemorrhagic strokes occur with increasing frequency in young adulthood. Suspicion of a neurologic event (overt stroke or TIA) requires emergent neuroimaging. Initial computed tomography to assess for hemorrhage can be considered due to easy availability, especially for patients with severe headache, prior stroke, or known vasculopathy

(eg, moyamoya vessels), but MRI and magnetic resonance angiography are more sensitive to define the timing and location of any ischemia or infarction and assess cerebral arteries. Transfusion is a critical component for managing acute overt stroke. Initial exchange transfusion is associated with a lower risk of recurrent stroke than initial simple transfusion. Chronic transfusion therapy to maintain HbS lower than 30% decreases the chance of recurrent overt stroke from 60% to 90% to about 20%.[23]

Abnormally increased transcranial Doppler (TCD) blood flow velocities identify children with HbSS who are at highest risk of overt stroke. An abnormal TCD status confers about a 10% risk of stroke per year for 3 years after the test. The Stroke Prevention Trial in Sickle Cell Anemia showed that chronic transfusions decreased the rate of first stroke in children with abnormal TCD status by 92% compared with observation.[23]

Silent cerebral infarction (SCI) is more common than overt stroke, occurring in up to 37% of children with HbSS or HbSβ^0 by 18 years of age. By definition, SCI produces no motor or sensory deficits, so it must be identified by an MRI of the brain. Silent cerebral infarction is associated with neurocognitive impairment, poor school performance, and increased risk for subsequent overt stroke. Low Hb concentration and high systolic blood pressure are risk factors for SCI.[23]

Renal and Genitourinary Complications

Repeated vasoocclusion damages the vasa recta, leading to urinary concentrating defect and resulting in dilute urine, which predisposes to dehydration and enuresis. This is the first renal manifestation of SCD, often occurring before 1 year of age. Renal ischemia also causes papillary necrosis and microscopic or gross hematuria.[23]

Priapism is an unwanted, painful erection of the penis. It occurs in all SCD genotypes but is far more common in HbSS. It can occur as soon as 3 years of age (mean age, 12 years), and 90% of males with HbSS will have at least one episode by 20 years of age. At onset of priapism, patients should urinate, drink water, and take a warm shower to promote detumescence. Immediate-release oral pseudoephedrine can be given at home to terminate priapism along with oral analgesics for pain. Patients should seek urgent medical attention for prolonged priapism (>4 hours). Intravenous (IV) hydration and pseudoephedrine should be administered if not taken recently by the patient. Aspiration and irrigation of the corpora cavernosa, which can be performed at the bedside, produce rapid detumescence. Surgical shunts should be avoided, if possible, to preserve erectile function.[23] Prolonged recurrent priapism in childhood

may be associated with later sexual dysfunction of adults (10%–50%) with SCD.

Hepatobiliary Complications

Sickle cell disease predisposes to cholelithiasis with bilirubinate or pigment gallstones. Prevalence of gallstones is about 10% in children 2 to 4 years of age, increasing to more than 50% in adults. Cholelithiasis and cholecystitis should be considered in differential diagnosis of abdominal pain in patients with SCD. Symptomatic cholelithiasis and cholecystitis are managed the same way in SCD as in other patients.[23] Additionally, patients on chronic transfusion therapy may develop iron overload with resultant hepatic dysfunction.

Diagnosis

Sickle cell disease diagnosis is made during routine newborn screening in many developed countries, including the United States. However, systematic screening of neonates is not common practice in most developing countries where SCD is a public health concern; as a result, diagnosis is only made when the child develops a severe complication. In many cases, the child dies without ever being diagnosed.[24]

A patient's clinical history and physical findings, along with laboratory evidence of hemolytic anemia and presence of sickle RBCs on peripheral smear, suggest SCD. Definitive diagnosis of SCD is made with the help of Hb separation technique, such as high-pressure liquid chromatography, isoelectric focusing, or citrate agar electrophoresis. These techniques determine the presence and relative proportions of the different types of Hb present in RBC hemolysates. Sickle Hb solubility testing (eg, Sickledex) is an inexpensive and highly sensitive test to detect the presence of HbS; it cannot, however, distinguish sickle trait from SCD.[23,26]

Disease-Modifying Therapies

Hydroxyurea

Hydroxyurea has multiple beneficial effects for patients with SCD and is still the only approved medication for preventing SCD complications. It increases the production of HbF, which inhibits polymerization of HbS; this is believed to be the principal mechanism of action of the drug. Hydroxyurea also lowers leukocyte and platelet counts and improves blood rheology, thereby decreasing propensity for vasoocclusion. Hydroxyurea reduces frequency of painful events, ACS, and transfusions by about 50%. Side effects are mostly mild and include dose-related,

reversible leukopenia and thrombocytopenia. Hydroxyurea does not appear to increase the risk of malignancy or impair growth.[23]

Due to limited access to and safety of alternative therapies such as transfusions and hematopoietic stem cell transplantation in the developing world, hydroxyurea may prove to be the ideal disease-modifying treatment. Accessibility to the drug; acceptability among patients, families, and caregivers; and cost are some of the main barriers. Considerable progress is being made in some middle-income countries in improving access to hydroxyurea therapy. For example, in Brazil, where health care maintenance for SCD is a component of primary care, the government supplies hydroxyurea to patients free of charge.[24]

Chronic Transfusions

Chronic transfusions are a prophylactic, disease-modifying therapy that involve regular, usually monthly, transfusions of packed RBCs to substantially suppress the percentage of HbS in peripheral blood and minimize the degree of chronic anemia. The most common indications are primary and secondary prophylaxis of overt stroke, for which duration of chronic transfusion therapy is indefinite. The usual goal of chronic transfusions is to maintain pre-transfusion HbS to less than 30% with a nadir pre-transfusion Hb concentration of 9 to 10 g/dL. Complications of transfusions include iron overload requiring the need for chelation therapy, alloimmunization, autoantibody formation, and transfusion-transmitted infections. Up to 30% of patients with SCD who are repeatedly transfused will become alloimmunized to RBC antigens (especially C, E, and Kell). Extended antigen matching can decrease the frequency of alloimmunization.[23]

Hematopoietic Stem Cell Transplantation

Currently, hematopoietic stem cell transplantation is the only cure for SCD and is reserved for patients who have severe and significant complications of SCD; this includes stroke or cerebrovascular disease, intractable vasoocclusive crises, and frequent ACS. Outcomes in hematopoietic stem cell transplantation are best with a human leukocyte antigen–matched sibling donor (without SCD). More transplants are being done with alternative donor sources using matched unrelated donors and cord blood transplants. There is currently an ongoing clinical trial in North America (Evaluating the Safety and Effectiveness of Bone Marrow Transplants in Children With Sickle Cell Disease [The SCURT Study]) that is using bone marrow from unrelated donors in children with severe SCD; these children will receive a reduced-intensity conditioning regimen prior to transplant.[27] Widespread use of hematopoietic stem cell

transplantation is limited by the lack of suitable related donors and concerns about toxicities associated with the procedure.[23] Lack of adequate infrastructure and cost of the procedure are some of the additional barriers for hematopoietic stem cell transplantation in developing countries.

DISORDERS OF HEMOSTASIS

Acquired disorders of hemostasis are extremely common and may be seen in children due to vitamin K deficiency, liver disease, or disseminated intravascular coagulopathy secondary to infections. The reader is referred to the following chapters for further reading: Chapter 22, Malnutrition; Chapter 32, Nephrology; and Chapter 23, Common Infections.

Inherited Disorders

Hemophilia A and B

Congenital hemophilia is an X-linked bleeding disorder caused by a deficiency of coagulation FVIII (hemophilia A) or FIX (hemophilia B) due to mutations in the respective clotting factor genes. Hemophilia A is more common than hemophilia B, representing 80% to 85% of the total hemophilia population. A family history of hemophilia in other male members on the maternal side of the family can be found in approximately two-thirds of patients. However, *F8* and *F9* genes are prone to new mutations, and approximately one-third of all cases are the result of spontaneous mutation where there is no prior family history. As both factors play a critical role in hemostasis, the characteristic phenotype of hemophilia is the lifelong bleeding tendency. Severity of bleeding usually correlates with clotting factor levels, and the disease may be classified based on these factor levels: severe (<1%), moderate (1%–5%), and mild (5%–40%).[28] Patients with severe and moderate hemophilia may present with spontaneous bleeding, while patients with mild hemophilia may not bleed excessively until they experience trauma or surgery. The hallmark of bleeding in hemophilia is joint or muscle bleeding, but other sites may also be involved (Table 34-4).

Management

The primary aim of treatment is to prevent and treat acute bleeding episodes.

Acute Bleeding

Whenever possible, specific factor deficiency should be treated with specific factor concentrate. Several purified plasma and recombinant

Table 34-4. Sites of Bleeding in Hemophilia

TYPE OF BLEEDING	SITE	DESCRIPTION	FREQUENCY
Serious	Joints (hemarthrosis)	More common into hinged joints: ankles, knees, and elbows; less common into multiaxial joints: shoulders, wrists, hips	70%–80%
Serious	Muscle	Deep compartments (iliopsoas, calf, and forearm)	10%–20%
Life threatening	Intracranial	Central nervous system	<5%
Life threatening	Neck, throat, intra-abdominal	Sites where bleeding may impinge on major organs	5%–10%

In general, mucous membrane bleeding is less common in patients with hemophilia, but hematuria may be seen.

Adapted from Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1–e47, with permission. © 2012 Blackwell Publishing Ltd.

FVIII and FIX concentrates are known to be efficacious and safe; however, availability depends on national, local, and individual resources. In developed countries, there is a trend toward using recombinant factors, while in underdeveloped nations, fresh frozen plasma and cryoprecipitate are used.

Acute bleeds should be treated as quickly as possible, encouraging the concept of home treatment in developed countries. During an episode of acute bleeding, an assessment should be performed to identify the site of bleeding (if not clinically obvious) and an appropriate clotting factor should be administered. In severe bleeding episodes that are potentially life-threatening, especially of the head, neck, chest, and gastrointestinal tract, treatment with a clotting factor should be initiated immediately, even before diagnostic assessment is completed. The amount of clotting factor to be infused depends on the desired target FVIII and FIX levels (Table 34-5).[29] In mild hemophilia A, therapy with exogenously administered desmopressin acetate (DDAVP), a synthetic derivative of the antidiuretic hormone arginine vasopressin that raises plasma levels of FVIII and von Willebrand factor (VWF), may be an option. Intravenous DDAVP shows peak activity within 30 minutes of infusion, raising FVIII levels 2-fold to 4-fold. Desmopressin acetate is most effective in patients with mild hemophilia A (FVIII >5%) and patients with type 1 von Willebrand disease (functionally normal VWF). Although there is no standard criteria for defining a response, most investigators

Table 34-5. Desired Levels for Clotting Factors VIII[a] and IX[b]

TYPE OF HEMORRHAGE	DESIRED LEVEL (IU/dL)	DURATION
Joint	40–60	1–2 d depending on response
Superficial muscle	40–60	1–2 d, sometimes longer if response is inadequate
Deep muscle	80–100 initially; 30–60 maintenance	Initial 1–2 d higher target levels; may need therapy for 3–5 d, sometimes longer as secondary prophylaxis during physical therapy
CNS/head, other life threatening	80–100 initially; 30–60 maintenance	Initial 1–7 d higher target levels; may need therapy for 8–21 d; initiation on prophylactic regimen should be considered if adequate resources are available.

Abbreviation: CNS, central nervous system.

[a] For factor VIII: Intravenous administration of factor VIII at a dose of 0.5 IU/kg of body weight will increase circulating factor VIII levels by approximately 1 IU/dL (ie, 1%).

[b] For factor IX: Intravenous administration of 1–1.2 IU/kg of body weight of factor IX will increase circulating factor IX levels by 1%.

Derived from Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia.* 2013;19(1):e1–e47.

define a response as a rise in FVIII and VWF levels of at least 2-fold to 3-fold, with FVIII and VWF levels greater than or equal to 0.3 IU/dL 1 to 2 hours after DDAVP administration. Desmopressin acetate is not recommended for children younger than 2 years because of decreased responsiveness and increased toxicity; however, children typically become more responsive as they age. The standard IV or subcutaneous dose of DDAVP is 0.3 µg/kg.[30] A synthetic analogue of vasopressin is available as a nasal spray (Stimate) in a concentration of 1.5 mg/mL; it has approximately two-thirds of the effect of IV DDAVP and is easy to use. The recommended dose of Stimate if the patient weighs less than 50 kg is 150 mcg; if the patient weighs more than 50 kg, it is 300 mcg. Peak effect is observed in 60 to 90 minutes. Caution should be used to avoid inadvertently dispensing the dilute intranasal DDAVP commonly used for diabetes insipidus.

Adjunctive Treatment

In resource-limited countries, adjunctive therapies are important and may lessen the amount of treatment product required. First aid measures generally consist of protection (splint), rest, ice, compression, and

elevation and may be used as adjunctive management for bleeding in muscles and joints. When available, physiotherapy or rehabilitation is particularly important for functional improvement and recovery after musculoskeletal bleeds. Antifibrinolytic drugs (eg, tranexamic acid, epsilon aminocaproic acid) are effective as adjunctive treatment for mucosal bleeds and dental extractions. Certain cyclooxygenase 2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis.[29]

Inhibitors

The most challenging complication of therapy is the development of neutralizing isoantibodies against FVIII or FIX. These inhibitors develop in approximately 25% to 30% of patients with severe hemophilia A and in 3% to 5% of patients with hemophilia B. Previously untreated hemophilia A patients are at greatest risk of inhibitor development within the first 20 exposure days to FVIII. Severity of disease, specific gene mutations, and other factors, such as race, intensity, and age of treatment, may also play a role in the development of inhibitors in patients with hemophilia A. Two general treatment options are available once an inhibitor develops: treat acute bleeds through bypassing agents, and eradicate the inhibitor permanently through immune tolerance induction. Bypassing agents in the form of activated prothrombin complex concentrates or recombinant activated factor VII are available for treatment in developed countries. Immune tolerance induction entails administering high doses of FVIII at regularly scheduled intervals in an attempt to eradicate neutralizing antibodies.[31,32] An extremely high cost of factor concentrates and lack of secure IV access remain the major barriers to immune tolerance induction.

Long-term Care of Patients With Hemophilia

Currently, various hemophilia clinical trials have demonstrated the utility of prophylactic clotting factor therapy in reducing joint bleeds and improving joint outcomes in patients with hemophilia. Prophylactic therapy is the treatment by IV injection of factor concentrate administered with the intention to prevent anticipated bleeding. Prophylaxis was conceived from the observation that patients with moderate hemophilia with a clotting factor level above 1 IU/dL seldom experience spontaneous bleeding and have much better preservation of joint function. Various regimens exist, but the most common is the Malmö regimen in which 25 to 40 IU/kg per dose is administered 3 times a week for those with hemophilia A and 2 times a week for those with hemophilia B. However, the protocol should be individualized as much as possible

based on age, venous access, bleeding phenotype, activity, and availability of clotting factor concentrates. There is considerable variability in the age at which prophylaxis is initiated. One option for treating very young children is to start prophylaxis 1 time a week and escalate depending on breakthrough bleeding and venous access. Additionally, it is recognized that the wide-ranging needs of people with hemophilia and their families are best met through coordinated delivery of comprehensive care by a multidisciplinary team of health care professionals, in accordance with accepted protocols that are practical and national treatment guidelines, if available.[29]

Recent Advances in Treatment

Current replacement therapy in hemophilia is relatively inconvenient because the most widely used prophylaxis regimens involve repeated IV infusions, generally 2 to 3 times weekly or even daily in some instances, owing to the short 10- to 12-hour half-life of available FVIII products (slightly longer for FIX). For this reason, approaches to prolong factor half-life in circulation were developed to improve factor replacement therapy for patients with hemophilia. Potential benefits of longer-acting factors include extended protection from bleeding, reduced infusion frequency, and less need to apply a central catheter for venous access with its associated problems. The main approaches under current investigation involve hydrophilic polymer conjugation (eg, PEGylation) and variant protein generation (eg, fusion protein strategy). Additionally, clinical trials using gene therapy as a treatment option for hemophilia B are ongoing.[33–35]

ONCOLOGY

Epidemiology

Burkitt lymphoma is the most common malignancy affecting children in sub-Saharan Africa, with an incidence rate up to 50-fold higher compared with the United States, and is more likely to be associated with Epstein-Barr virus infection.[36] Similarly, incidence of Kaposi sarcoma and hepatocellular carcinoma are high in developing countries, which is related to high prevalence of HIV/AIDS and hepatitis B infection, respectively.[8]

There is a markedly increased incidence rate of acute lymphoblastic leukemia (ALL) in children between 2 and 5 years of age in affluent societies, which is not seen in low-income countries. This observation supports the infection-based theories of leukemogenesis, which attribute peak incidence of ALL in children 2 to 5 years of age in developed

countries to insulation from infections early in life that predisposes the immune system of susceptible individuals to aberrant or pathologic responses after delayed exposure to common infections.[37,38]

Differences in the incidence of embryonal tumors between countries and ethnic groups have been consistently reported over the last decades, particularly for neuroblastoma and retinoblastoma. Age-adjusted incidence rates of retinoblastoma for children 0 to 4 years of age were as high as 15 to 27 per year in Brazil verses 10 to 12 in the United States and Europe. Studies have documented an inverse correlation between incidence of retinoblastoma and socioeconomic index in developing countries; however, the opposite was true for neuroblastoma in the Brazilian population, with a higher incidence of neuroblastoma in high socioeconomic groups.[37] Incidence of central nervous system tumor appears to be lower in developing countries compared with developed countries.[8]

Childhood Cancer Mortality in Developing Countries

Only 25% of pediatric cancer patients in low- and middle-income countries manage to survive, while the survival rate of such patients in high-income countries is close to 80%. The high cure rates reached in industrialized countries are not obtainable for most cancers in developing countries. Poor outcome of children with cancer in low- and middle-income countries is dictated by rapid increase in population, poverty, late presentation and underdiagnosis, high abandonment rates, high prevalence of malnutrition and other comorbidities, suboptimal supportive and palliative care, and limited access to curative therapies.[8,37]

Barriers to Successful Pediatric Oncology Care

Poverty

Extreme poverty is a barrier to effective cancer intervention in low- and middle-income countries, as developing cancer services in these areas is not a priority in the context of ongoing morbidity and mortality associated with potentially easily preventable conditions such as malnutrition, hygiene or sanitation, and vaccine-preventable infectious diseases and accidental deaths.

Late Presentation

Lack of education, limited access to health care, and complex and deficient socioeconomic environments result in delayed diagnosis and underdiagnosis in low- and middle-income countries.[37] Reliance on traditional or local "healers" may delay diagnosis and result in more

patients from low-income countries presenting with advanced disease. Lack of understanding the need for treatment is one of the major barriers associated with poverty.[7]

Underdiagnosis

Lack of awareness and low index of suspicion of the first-contact health practitioner plays an important role in delayed or missed diagnosis of cancer patients.[37]

Abandonment of Therapy

Refusal and abandonment of therapy is a major cause of therapeutic failure in countries with limited resources that affects 50% to 60% of children. Most patients abandon therapy after induction remission in leukemia or at the time of radical surgeries in solid malignancies. Some of the factors that predispose to treatment abandonment include low socioeconomic status, lack of supportive care, attitude of health care practitioners, and communication with the family.[37]

Malnutrition

Fifty percent to 70% of children in low- and middle-income countries are malnourished, which increases the risk of chemotherapy-associated toxicity rates, including prolonged neutropenia and infectious complications. Mid-upper arm circumference, triceps skinfold thickness, and serum albumin values are the 3 categories of nutritional status that appear to correlate with the outcome and could be used in initial assessment of children with cancer to outline nutritional intervention and adjust cancer treatment.[37]

Supportive Care

The ability to provide state-of-the-art curative treatments for children with cancer in low- and middle-income countries is severely limited by a lack of supportive care, such as proper infection control programs, transfusion support, availability of hematopoietic growth factors, and parental nutrition.[8,37]

Nursing

Specialized education and training are generally unavailable for nurses in low- and middle-income countries, which contributes to the disparity in outcome and overall survival.[37]

Limited Access to Multidisciplinary Pediatric Oncology Centers

A lack of adequate infrastructure to develop multidisciplinary pediatric oncology centers and limited awareness of existing centers play an important role in access to appropriate curative therapies. Generally, these centers are located in big cities, and it is expensive to reach them.[7,8]

Palliative Care

Most low- and middle-income countries lack properly developed and implemented palliative care programs, such as a palliative care counseling team, pain management, and bereavement care. Lack of trained nurses, poor government support, and highly restricted access to high-potency opiates and adjuvant drugs are major barriers.[37]

Strategies and Initiatives to Improve Outcomes of Pediatric Cancer Patients in Resource-Limited Countries

Twinning Partnerships

This model encourages establishing a partnership between pediatric cancer centers in resource-rich countries with those in resource-limited countries to provide advice, expertise, support, and technology transfer to help overcome the challenges that resource-limited countries face.[7,37] The program has helped to significantly improve pediatric cancer survival rate by increasing access to treatment, providing training to health care professionals in resource-limited countries, helping to develop locally appropriate treatment protocols, and developing database and hospital-based cancer registries.[7]

Adapted Treatments

Developing a less-intense, resource-adopted treatment regimen according to local capacity is essential to decrease treatment-associated morbidity and mortality and the cost of care, as well as increase treatment compliance, in resource-limited countries. In Malawi, treatment for Burkitt lymphoma includes a simple protocol: IV cyclophosphamide 40 mg/kg on day 1, followed by oral cyclophosphamide 60 mg/kg on days 8, 18, and 28, including intrathecal hydrocortisone and methotrexate. It resulted in a 1-year survival rate of 48%, a 5% treatment-related mortality rate, at a cost of less than US $50 for a 28-day cycle.[37] Similarly, in a 1990 study in Russia, 713 patients with ALL were randomized between a standard ALL treatment protocol widely used in Western Europe (ALL-BFM 90m) and a more feasible and less-intensive regimen (ALL-MB91) that limited administration of high-dose therapies, anthracycline, and

cranial irradiation. The 7-year event-free survival estimates were 67% and 68% for patients treated with the ALL-MB91 and ALL-BFM 90m regimens, respectively; however, the adapted regimen resulted in lower bone marrow suppression and hospitalization rates and less resource utilization.[37] The International Society of Paediatric Oncology Committee on Developing Countries is developing similar graduated-intensity treatment guidelines for treating solid malignancies such as retinoblastoma, sarcoma, and brain tumors, which require a multidisciplinary approach.[37]

Web-Based Data Management Programs and Cancer Registries

Quality improvement activities rely on accurate data to assess the effect of interventions of treatment outcome and quality of care. Establishing a cancer registry is a key element to monitor survival, abandonment, and toxicity and also provide epidemiologic information. For countries with limited resources, Web-based technologies can assist in building solid databases by enhancing the quantity and quality of clinical data and support international clinical collaborations to facilitate protocol-based treatment for children with cancer. The Pediatric Oncology Networked Database (www.POND4kids.org) is available in multiple languages at no cost. This software permits the storage of patient information, facilitated analysis, and flexible reporting.[7]

Education of Health Care Professionals

The Web-based resource Cure4Kids (www.cure4kids.org) is a comprehensive interactive platform that provides real-time access to protocols, education, and professional development opportunities. Participants in low-income countries can interact with colleagues in other centers or countries in real time to discuss patients and protocols and access a library of prerecorded lectures and tutorials on a comprehensive range of medical, nursing, and supportive care topics.[7]

KEY POINTS

- Hematologic and oncologic diseases have a major effect on global health.
- Anemia is a significant worldwide problem.
- The outcomes of many hematologic and oncologic diseases are significantly different in resource-limited and resource-replete countries.

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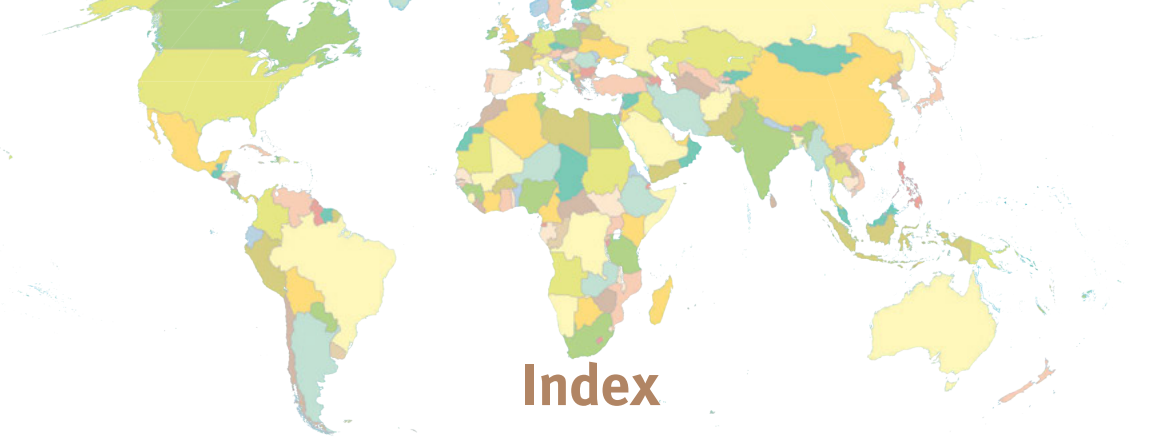

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Textbook of Global Child Health, 2nd Edition

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