

*Remington and Klein's*  
**INFECTIOUS DISEASES  
OF THE FETUS AND  
NEWBORN INFANT**

*Eighth Edition*

Wilson, Nizet, Maldonado, Remington, Klein

# Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant

EIGHTH EDITION

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*To those most dear to us  
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*And to the mentors, colleagues, fellows, and students  
who have enriched our academic and personal lives,  
and to the physicians and the women and infants with  
infectious diseases for whom they care*

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# Preface

Major advances in biology and medicine made during the past several decades have contributed greatly to our understanding of infections that affect the fetus and newborn. As the medical, social, and economic impact of these infections becomes more fully appreciated, the time is again appropriate for an intensive summation of existing information on this subject. Our goal for the eighth edition of this text is to provide a complete, critical, and contemporary review of this information. We have directed the book to all students of medicine interested in the care and well-being of infants, and hope to include among our readers medical students, residents and fellows, practicing physicians, microbiologists, and health care workers. We believe the text to be of particular importance for infectious disease specialists; obstetricians and physicians who are responsible for the pregnant woman and her developing fetus; pediatricians and family physicians who care for newborn infants; and primary care physicians, neurologists, audiologists, ophthalmologists, psychologists, and other specialists who are responsible for children who suffer the sequelae of infections acquired in utero or during the first month of life.

The scope of this book encompasses infections of the fetus and newborn, including infections acquired in utero, during the delivery process, and in early infancy. When appropriate, sequelae of these infections that affect older children and adults also are included. Infection in the adult is described when pertinent to recognition of infection in the pregnant woman and her developing fetus and newborn infant. The first chapter provides an introductory overview of the subsequent chapters, general information, and a report on new developments and new challenges in this area. Each subsequent chapter covers a distinct topic in depth and when appropriate touches on issues that overlap with the theme of other chapters or refers the reader to those chapters for relevant information. Chapters in Sections II, III, and IV cover specific types of infection, and each includes a review of the history, microbiology, epidemiology, pathogenesis and pathology, clinical signs and symptoms, diagnosis, prognosis, treatment, and prevention of the infection. Chapters in Sections I and V address issues of a more general nature.

For two of us (Jack S. Remington and Jerome O. Klein), it has been an extraordinary experience and privilege over the past 45 years to be participants in reporting the advances in understanding and management of the infectious diseases of the fetus and newborn infant. Consider the virtual elimination in the developed world of some infectious diseases (e.g., rubella, early-onset group B streptococcal diseases); the recognition of new diseases (e.g., *Borrelia*, HIV); the increased survival and vulnerability to infection of the very low-birth-weight infant; the introduction of new antimicrobial agents, in particular antiviral and antifungal drugs; and increased emphasis on immunization of women in the childbearing years to prevent transmission of disease to the

fetus and neonate. Of importance now and in the future is the recognition of the universality of infectious diseases. Of particular concern are the continued high mortality rates of infectious diseases for infants in the first weeks of life, particularly in low- and middle-income countries. Increased efforts are important to extrapolate advances in care of the pregnant woman and her newborn infant from developed countries to regions with limited resources.

The seventh edition of this text was published in 2011. In the ensuing 4 years, there have been several notable changes. The current edition includes a new chapter on pertussis, whose re-emergence warranted a more in-depth discussion than possible within another chapter. Conversely, the editors elected not to continue with a dedicated chapter on smallpox, incorporating relevant information into the chapter on less common viral infections. In many cases, authors have updated chapters they wrote for earlier editions, incorporating new knowledge, describing current practice, and bringing in new co-authors where appropriate. As has been our practice with each new edition, we have sought to completely refresh some chapters by collaborating with new authors, while thanking the previous authors for their important contributions to past editions. Major revisions of most chapters suggest the importance of new information about infections of the fetus and newborn infant.

Each author is a recognized authority in the field and has made significant contributions to our understanding of infections in the fetus and newborn infant. Almost all were supported, in part or totally, during their training period, and subsequently, by funds obtained from the National Institutes of Health, national health research funding agencies in other countries, or private agencies such as the March of Dimes and the Bill & Melinda Gates Foundation. The major advances in medicine during this period would not have been possible without these funding mechanisms and the freedom given to the investigators to pursue programs of their own choosing. The medical advances represented in this text are also a testimony to the trustees of agencies and the legislators and other federal officials who provided research funds from the 1960s to the present day.

Two of us (Remington and Klein) were fellows at the Thorndike Memorial Laboratory, Harvard Medical Unit, Boston City Hospital in the early 1960s under the supervision of Maxwell Finland. Although subsequently we worked in separate areas of investigation on the two coasts, one of us as an internist and the other as a pediatrician, we maintained close contact, and because of a mutual interest in infections of the fetus and newborn infant and their long-term effects, we joined forces to develop this text.

Christopher B. Wilson joined us in editing the sixth, seventh, and now eighth editions. Chris trained in immunology and infectious diseases in Palo Alto, then joined the University of Washington for 30 years before moving to the

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We are indebted to our teachers and associates, and especially to individuals such as Dr. Maxwell Finland, who guided our training and helped to promote our

development as physician-scientists through the early stages of our careers. We also wish to express our appreciation to Margaret Nelson, Stefanie Jewell-Thomas, Kate Dimock, and Louise King of Elsevier, for guiding this project to a successful conclusion, and to Ms. Valerie Berland for her editorial assistance.

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# 1

## Current Concepts of Infections of the Fetus and Newborn Infant

YVONNE A. MALDONADO, VICTOR NIZET, JEROME O. KLEIN, JACK S. REMINGTON, and CHRISTOPHER B. WILSON

### CHAPTER OUTLINE

#### Overview

##### Infections of the Fetus

##### Pathogenesis

##### Efficiency of Transmission of Microorganisms from Mother to Fetus

##### Diagnosis of Infection in the Pregnant Woman

##### Diagnosis of Infection in the Newborn Infant

##### Prevention and Management of Infection in the Pregnant Woman

##### Infections Acquired by the Newborn Infant During Birth

##### Pathogenesis

#### Microbiology

##### Diagnosis

##### Management

##### Prevention

##### Infections of the Newborn Infant in the First Month of Life

##### Pathogenesis and Microbiology

### Overview

Current concepts of pathogenesis, microbiology, diagnosis, and management of infections of the fetus and newborn are reviewed in this chapter with the goal of providing a brief synthesis and overview. Information within this chapter regarding specific infections or syndromes is illustrative only. Detailed discussions are provided in the subsequent sections, to which the reader should refer to gain the more comprehensive knowledge needed to properly evaluate and manage these conditions.

The first section of the book contains chapters providing the global perspective on fetal and neonatal infections as well as chapters addressing obstetric factors, immunity, host defenses, and the role of human breast milk in fetal and neonatal infections. Chapters containing detailed information about specific bacterial, viral, protozoan, helminthic, and fungal infections follow in subsequent sections. The final section contains chapters addressing nosocomial infections, the diagnosis and therapy of infections in the fetus and neonate, and prevention of fetal and neonatal infections through immunization of the mother or neonate.

Important changes continue to occur in the epidemiology, diagnosis, prevention, and management of infectious diseases of the fetus and newborn infant since publication of the last edition of this book. Some of these changes are noted in [Table 1-1](#) and are discussed in this and the relevant chapters.

To keep pace with these changes, with the eighth edition, the editors have sought to streamline the references while maintaining full citation formats both in the print and online editions. All chapters have been updated through extensive revisions, and in some cases, new chapters have been prepared by different authors to provide a fresh viewpoint on certain key topics. There is no longer a separate chapter devoted to smallpox, information about which is now incorporated into Chapter 30 (Less Common Viral Infections). Conversely, with the resurgence of pertussis cases in the United States and elsewhere, a new Chapter 21 on pertussis has been prepared by James Cherry.

Substantial progress has been made toward reducing the burden of infectious diseases in the fetus and newborn infant. The incidence of early-onset group B streptococcal (GBS) disease has been reduced by aggressive use of intrapartum chemoprophylaxis, in particular, as guided by the culture-based screening strategy now recommended for universal use in the United States and several other countries. Vertical transmission of human immunodeficiency virus (HIV) has been reduced by identification of the infected mother and subsequent treatment, including broader recommendations for the use of antiretroviral regimens among pregnant and postpartum women that are practical in countries with high prevalence but limited resources.

There has been a substantial commitment of resources by government agencies and philanthropies, such as the Bill and Melinda Gates Foundation, the Clinton Health Access

**Table 1-1** Changes in Epidemiology and Management of Infectious Diseases of the Fetus and Newborn Infant

Epidemiology	Increased viability of very-low-birth-weight infants at risk for invasive infectious diseases Increased number of multiple births (often of very low birth weight) because of successful techniques for management of infertility Global perspective of vertically transmitted infectious diseases Global decline in infant mortality but lesser decline of neonatal mortality
Diagnosis	Polymerase chain reaction assay for diagnosis of infection in mother, fetus, and neonate Relative decrease in use of fetal blood and chorionic villus sampling and increase in use of amniotic fluid sampling for diagnosis of fetal infectious diseases
Prevention	Intrapartum antibiotic prophylaxis widely implemented to prevent early-onset group B streptococcal infection Antiretroviral therapy in pregnancy and postpartum to prevent transmission of HIV to fetus
Treatment	Spread within nurseries of multiple antibiotic-resistant bacterial pathogens Increased use of vancomycin for $\beta$ -lactam-resistant gram-positive infections Increased use of acyclovir for infants with suspected herpes simplex infection Use of ganciclovir or valganciclovir for overtly symptomatic congenital CMV

CMV, Cytomegalovirus; HIV, human immunodeficiency virus.

Initiative, and Save the Children, among others, to combat global infectious diseases in mothers and children. Global mortality for children younger than 5 years fell by 41% between 1990 and 2011 from a rate of 87 to 51 deaths per 1000 live births, but still totals 6.9 million deaths per year globally. Neonatal mortality has not declined as quickly and now constitutes 40% of total under-5-years mortality, and great disparities remain; the global neonatal mortality rates in 2011 in the United States and European regions are 6.1 and 13 per 1000 live births, respectively, but in the African region the rate is 106 per 1000 live births<sup>1</sup> ([www.who.int/gho/child\\_health/mortality/mortality\\_under\\_five\\_text/en/index.html](http://www.who.int/gho/child_health/mortality/mortality_under_five_text/en/index.html)). Stillbirths, defined as late fetal deaths at greater than 1000 g or greater than 28 weeks of gestation, are estimated at 3 million cases annually, with 99% occurring in low- and middle-income countries.<sup>2</sup> Whereas infection accounts for approximately one third of neonatal deaths globally, it accounts for a considerably smaller fraction in the United States.

Setbacks facing initiatives to reduce the global burden of infectious disease in the fetus and newborn infant include the continuing epidemic of HIV infection in sub-Saharan Africa, particularly among women, and the lack of finances to provide effective treatment for these women and their newborn infants. In the United States, infectious disease challenges include the increase in antimicrobial resistance among nosocomial pathogens and in the incidence of invasive fungal infections among infants of extremely low birth weight. Moreover, the rate of pertussis is rising, notably so in older children and adolescents in the United States and other countries, with disproportional impact on morbidity and mortality of the newborn. This rising prevalence

**Table 1-2** Useful Internet Sites for Physicians Interested in Infectious Diseases of the Fetus and Newborn Infant

Agency for Healthcare Research and Quality	<a href="http://www.ahrq.gov">http://www.ahrq.gov</a>
American Academy of Pediatrics	<a href="http://www.aap.org">http://www.aap.org</a>
American College of Obstetricians and Gynecologists	<a href="http://www.acog.org">http://www.acog.org</a>
Centers for Disease Control and Prevention	<a href="http://www.cdc.gov">http://www.cdc.gov</a>
Food and Drug Administration	<a href="http://www.fda.gov">http://www.fda.gov</a>
Immunization Action Coalition	<a href="http://www.immunize.org">http://www.immunize.org</a>
Information on AIDS Trials	<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>
March of Dimes	<a href="http://www.marchofdimes.com">http://www.marchofdimes.com</a>
Morbidity and Mortality Weekly Report	<a href="http://www.cdc.gov/mmwr">http://www.cdc.gov/mmwr</a>
National Center for Health Statistics	<a href="http://www.cdc.gov/nchs">http://www.cdc.gov/nchs</a>
Pediatric Infectious Diseases Society	<a href="http://www.pids.org">http://www.pids.org</a>
General academic information	<a href="http://www.google.com">http://www.google.com</a> ; <a href="http://www.ncbi.nlm.nih.gov/pubmed">http://www.ncbi.nlm.nih.gov/pubmed</a>

is likely due, in part, to accelerated waning of immunity associated with the use of acellular vaccines, which have supplanted the killed whole-cell vaccine primarily in high-resource settings.<sup>3,4</sup>

Use of the Internet continues to expand rapidly, allowing access to information hitherto unavailable to physicians or parents. Physicians may obtain current information about diseases and management as well as various guidelines for diagnosis and treatment. Interested parents who have access to the Internet can explore various websites that present a vast array of information but, unfortunately, also misinformation. As an example of the latter, a case of neonatal tetanus was associated with the use of cosmetic facial clay (Indian Healing Clay) as a dressing on an umbilical cord stump. The product had been publicized as a healing salve by midwives on an Internet site dedicated to “cord-care.”<sup>5</sup> The antivaccination movement is active on the Internet, deploying a variety of tactics and rhetoric to effectively spread their messages.<sup>6</sup> Because much of the information on the Internet is from commercial sources and parties with varying interests and expertise, physicians should be prepared to assist interested parents and patients in finding Internet sites of genuine value. Several Internet sites pertinent to infectious diseases of the fetus and newborn infant are listed in Table 1-2.

Vital statistics relevant to infectious disease risk in neonates in the United States for 2010 to 2011 are listed in Table 1-3.<sup>1</sup> The disparities in birth weight, prenatal care, and neonatal mortality among different racial and ethnic groups in the United States are important to note and to consider in the context of the global disparities noted above.

The number of infectious diseases in fetuses and newborn infants must be extrapolated from selected studies (see chapters on specific diseases). Approximately 1% of newborn infants shed cytomegalovirus (CMV), greater than 4% of infants are born to mothers infected with *Chlamydia*

**Table 1-3** Percentage of Births with Selected Characteristics by Race and Hispanic Origin of Mother in the United States\*

	RACIAL/ETHNIC ORIGIN OF MOTHER							
	ALL RACES		NON-HISPANIC WHITE		NON-HISPANIC BLACK		HISPANIC	
	2010	1990	2010	1990	2010	1990	2010	1990
<b>MOTHER</b>								
<20 years old	9.3	12.8	6.7	9.6	15.2	23.2	13.1	16.8
≥40 years old	2.9	1.2	3.0	1.2	2.3	0.8	2.4	1.2
Diabetes during pregnancy	5.1	2.1	4.7	2.2	4.5	1.8	5.2	2.0
Cesarean delivery	32.8	22.7	32.6	23.4	35.5	22.1	31.8	21.2
<b>INFANT</b>								
<b>Birth weight<sup>†</sup></b>								
LBW	8.2	7.0	7.1	5.6	13.5	13.3	7.0	6.1
VLBW	1.5	1.3	1.2	0.9	3.0	2.9	1.2	1.0
<b>Gestational age<sup>‡</sup></b>								
Preterm	12.0	10.6	10.8	8.5	17.1	18.9	11.8	11.0
Preterm early	3.5	3.3	2.9	2.4	6.1	7.4	3.3	3.2
Preterm late	8.5	7.3	7.8	6.1	11.0	11.5	8.5	7.8

Modified from Hamilton BE, Hoyert DL, Martin JA, et al: Annual summary of vital statistics—2010-2011. *Pediatrics* 131:548-558, 2013.

\*All values are in percent births.

<sup>†</sup>LBW, low birth weight (<2500 g); VLBW, very low birth weight (<1500 g).

<sup>‡</sup>Preterm early: <34 weeks of gestation; late preterm: 34-36 weeks of gestation.

*trachomatis*, and bacterial sepsis develops in 1 to 4 infants per 1000 live births. Since the institution of intrapartum chemoprophylaxis in the United States, the number of infants with early-onset GBS disease has declined, with reduction in incidence from approximately 1.5 cases to 0.29 case per 1000 live births.<sup>7</sup> In the United States, the use of maternal highly active antiretroviral treatment and peripartum chemoprophylaxis reduced the rate of mother-to-child transmission of HIV from approximately 25% of infants born to mothers who received no treatment to less than 2%; less complex but practical regimens of intrapartum prophylaxis have helped to reduce the rate of perinatal HIV transmission in the developing world.<sup>8-10</sup> Recently revised World Health Organization (WHO) guidelines ([www.who.int/hiv/pub/guidelines/arv2013/intro/rag/en/index2.html](http://www.who.int/hiv/pub/guidelines/arv2013/intro/rag/en/index2.html)) now also recommend that all HIV-infected pregnant and breastfeeding women and HIV-infected partners of monogamous HIV-uninfected pregnant women receive highly active antiretroviral treatment regardless of their CD4 T-cell numbers, which should help to further lower the rates of HIV transmission in resource-limited settings. Among sexually transmitted diseases, the rate of congenital syphilis had declined substantially in the United States to 13.4 per 100,000 live births in 2000<sup>11</sup>; however, after 14 years of decline, the rate of congenital syphilis increased in 2006 and 2007 from 9.3 to 10.5 cases per 100,000 live births, in parallel with the increase in the syphilis rates among the general population.<sup>12</sup> Immunization has virtually eliminated congenital rubella syndrome in newborn infants of U.S.-born mothers, but cases continue to occur in infants of foreign-born mothers; the mothers of 24 of 26 infants with congenital rubella born between 1997 and 1999 were foreign born, 21 of them Hispanic.<sup>13</sup> Efforts led by the Pan American Health Organization to eliminate congenital rubella syndrome in the Americas by 2010 appears to have

been successful, with the last case reported in 2009, providing impetus for a global attack on the problem through universal immunization.<sup>7</sup>

Consequences of perinatal infections vary depending on whether the infection occurs in utero or during the intrapartum or postpartum periods. Infection acquired in utero can result in resorption of the embryo, abortion, stillbirth, malformation, intrauterine growth restriction, prematurity, or the untoward sequelae of chronic postnatal infection. Infection acquired during the intrapartum or early postpartum period may result in severe systemic disease that leads to death or the establishment of persistent postnatal infection. In utero infection and intrapartum infections may lead to late-onset disease. Such infections may not be apparent at birth but may manifest with signs or symptoms weeks, months, or years later, as exemplified by chorioretinitis of *Toxoplasma gondii* infection, hearing loss of rubella, and immunologic defects that result from HIV infection. The immediate and the long-term effects of these infections constitute a major problem throughout the world.

## Infections of the Fetus

### PATHOGENESIS

Pregnant women are not only exposed to infections prevalent in the community but are also likely to reside with young children or to associate with groups of young children, which represents a significant additional factor in exposure to infectious agents. Most infections in pregnant women affect the upper respiratory and gastrointestinal tracts, and either resolve spontaneously without therapy or are readily treated with antimicrobial agents. Such infections usually remain localized and have no effect on the

developing fetus. The infecting organism may invade the bloodstream, however, and subsequently infect the placenta and fetus.

Successful pregnancy is a unique example of immunologic tolerance—the mother must be tolerant of her allogeneic fetus (and vice versa). The basis for maternal-fetal tolerance is not completely understood but is known to reflect local modifications of host defenses at the maternal-fetal interface and more global changes in immunologic competence in the mother. Specific factors acting locally in the placenta include indoleamine 2,3-dioxygenase, which suppresses cell-mediated immunity by catabolizing the essential amino acid tryptophan, and regulatory proteins that prevent complement activation.<sup>14,15</sup> Based on data from murine models, there is an accumulating body of evidence that pregnancy is associated with maternal-fetal tolerance that depends in part on the development of maternal regulatory T-cell–mediated tolerance to fetal antigens inherited from the father.<sup>16</sup> Regulatory T cells are also relatively more abundant and active in the human fetus, whose T-cell populations are also otherwise naïve in phenotype and function (see Chapter 4). Further, as pregnancy progresses, a general shift from T-helper type 1 (Th1) cell-mediated immunity to T-helper type 2 (Th2) responses also occurs in the mother.<sup>17, 18</sup> Nonetheless, because Th1 cell-mediated immunity is important in host defense against intracellular pathogens, the reduced Th1 bias established during normal gestation may compromise successful immunity against organisms such as *T. gondii*. In addition, it has been proposed that a strong curative Th1 response against an organism may overcome protective T-regulatory and Th2 activity at the maternal-fetal interface, resulting in fetal loss.

Transplacental spread and invasion of the bloodstream after maternal infection is the usual route by which the fetus becomes infected. Uncommonly, the fetus may be infected by extension of infection in adjacent maternal tissues and organs, including the peritoneum and the genitalia, during parturition, or as a result of invasive methods for the diagnosis and therapy of fetal disorders, such as the use of monitors, chorionic villus biopsy, sampling of fetal blood, and intrauterine transfusion.

Microorganisms of concern are listed in Table 1-4 and include those identified in the acronym TORCH: *T. gondii*, rubella virus, CMV, and herpes simplex virus (HSV). As a point of historical interest, the O in TORCH originally

stood for “other infections/pathogens,” reflecting an early appreciation of this possibility. A new acronym is needed to include other, well-described causes of in utero infection: syphilis, enteroviruses, varicella-zoster virus (VZV), HIV, Lyme disease (*Borrelia burgdorferi*), and parvovirus. In certain geographic areas, *Plasmodium* and *Trypanosoma cruzi* are responsible for in utero infections. TORCHES CLAP (see Table 1-4) is an inclusive acronym. Case reports indicate other organisms that are unusual causes of infections transmitted by a pregnant woman to her fetus, including *Brucella melitensis*,<sup>19</sup> *Coxiella burnetii* (Q fever),<sup>20</sup> *Babesia microti* (babesiosis),<sup>21</sup> human T-cell lymphotropic virus (HTLV) types 1 and 2 (although the main route of transmission of these viruses is through breastfeeding),<sup>22,23</sup> hepatitis G and TT viruses,<sup>24,25</sup> human herpesvirus 6,<sup>26,27</sup> and dengue.<sup>28</sup>

Among these other organisms, investigators from France reported that *Coxiella burnetii* (the causative agent of the zoonotic disease Q fever) infection of the pregnant woman is associated with untoward pregnancy outcomes, including spontaneous abortion, intrauterine fetal demise, preterm delivery, and intrauterine growth retardation in a large majority (81%) of untreated women.<sup>20</sup> Restricting their analysis to women in whom such complications were not evident at presentation, complications were observed in 14 of 21 women who were not treated and 7 of 16 who received long-term (>5 weeks) daily cotrimoxazole therapy ( $P = .047$ ). They acknowledge the noncontrolled nature of their data and the possible selection bias but nonetheless propose that such therapy be given to all pregnant women with proven *Coxiella burnetii* infection. However, other, though smaller, reports have not observed a high rate of complications and would restrict such therapy to women with symptomatic acute infection or chronic Q fever.<sup>29</sup>

Before rupture of fetal membranes, organisms in the genital tract may invade the amniotic fluid and infect the fetus. These organisms can invade the placenta through microscopic defects in the membranes, particularly in devitalized areas overlying the cervical os. It also is possible that microorganisms gain access to the fetus from descending infection through the fallopian tubes in women with salpingitis or peritonitis, or from direct extension of an infection in the uterus, such as myometrial abscess or cellulitis. Available evidence does not suggest, however, that transtubal or transmyometrial passage of microbial agents is a significant route of fetal infection.

Invasive techniques developed for in utero diagnosis and therapy are potential sources of infection for the fetus. Abscesses have been observed in infants who had scalp punctures for fetal blood sampling or electrocardiographic electrodes attached to their scalps. Cases of osteomyelitis of the skull and streptococcal sepsis have followed local infection at the site of a fetal monitoring electrode<sup>30</sup>; HSV infections at the fetal scalp electrode site also have been reported. Intrauterine transfusion for severe erythroblastosis diagnosed in utero also has resulted in infection of the fetus. In one case, CMV infection reportedly resulted from intrauterine transfusion<sup>31</sup>; in another instance, contamination of donor blood with a gram-negative coccobacillus, *Acinetobacter calcoaceticus*, led to an acute placentitis and subsequent fetal bacteremia.<sup>32</sup>

**Table 1-4** Suggested Acronym for Microorganisms Responsible for Infection of the Fetus: TORCHES CLAP

TO	<i>Toxoplasma gondii</i>
R	Rubella virus
C	Cytomegalovirus
H	Herpes simplex virus
E	Enteroviruses
S	Syphilis ( <i>Treponema pallidum</i> )
C	Chickenpox (varicella-zoster virus)
L	Lyme disease ( <i>Borrelia burgdorferi</i> )
A	AIDS (HIV)
P	Parvovirus B19

AIDS, Acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Fetal infection in the absence of rupture of internal membranes usually occurs transplacentally after invasion of the maternal bloodstream. Microorganisms in the blood may be carried within white blood cells or attached to erythrocytes, or they may be present in serum independent of cellular elements.

### Microbial Invasion of the Maternal Bloodstream

The potential consequences of invasion of the mother's bloodstream by microorganisms or their products (Fig. 1-1) include placental infection without infection of the fetus, fetal infection without infection of the placenta, absence of fetal and placental infection, and infection of placenta and fetus (see Chapter 3 for additional discussion of this topic).

### Placental Infection Without Infection of the Fetus.

After reaching the intervillous spaces on the maternal side of the placenta, organisms can remain localized in the placenta without affecting the fetus. Evidence that placentitis can occur independently of fetal involvement has been shown for maternal tuberculosis, syphilis, malaria, coccidioidomycosis, CMV, rubella virus, and mumps vaccine virus infection. The reasons for the lack of spread to

the fetus after placental infection are unknown. Defenses of the fetus that may operate after placental infection include the villous trophoblast, placental macrophages, and locally produced immune factors, such as antibodies and cytokines.

### Fetal Infection Without Overt Infection of the Placenta.

Microorganisms may traverse the chorionic villi directly through pinocytosis, placental leaks, or diapedesis of infected maternal leukocytes and erythrocytes. Careful histologic studies usually reveal areas of placentitis sufficient to serve as a source of fetal infection, however.

### Absence of Fetal and Placental Infection.

Invasion of the bloodstream by microorganisms is common in pregnant women, yet in most cases, neither fetal nor placental infection results. Bacteremia may accompany abscesses, cellulitis, bacterial pneumonia, pyelonephritis, appendicitis, endocarditis, or other pyogenic infections; nevertheless, placental or fetal infection as a consequence is rare. In most cases, the fetus is likely protected through efficient clearance of microbes by maternal innate or preexisting adaptive immunity.

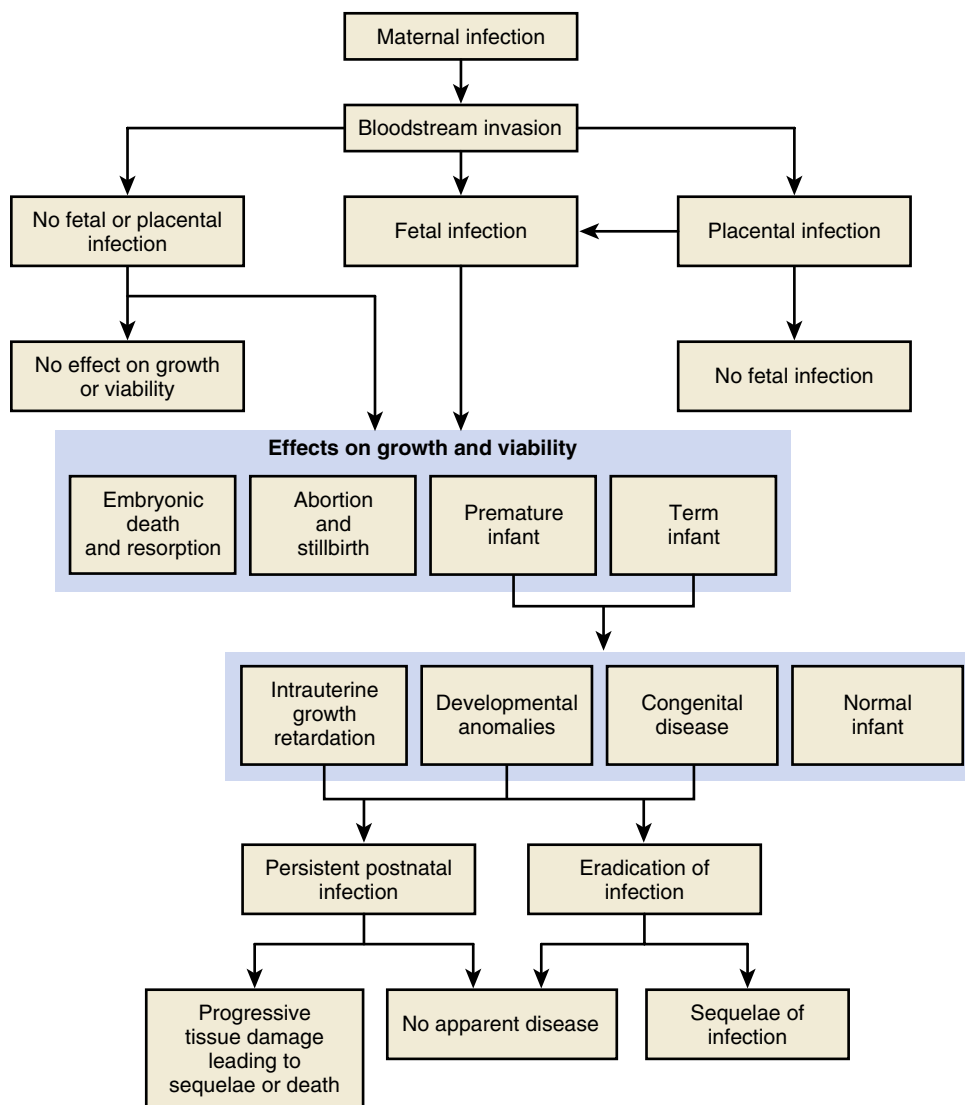


Figure 1-1 Pathogenesis of hematogenous transplacental infections.



Many bacterial diseases of the pregnant woman, including typhoid fever, pneumonia, gram-negative bacterial sepsis, and urinary tract infections, may affect the developing fetus without direct microbial invasion of the placenta or fetal tissues. Similarly, protozoan infection in the mother, such as malaria, and systemic viral infections, including varicella, variola, and measles, also may affect the fetus indirectly. Fever, anoxia, circulating toxins, or metabolic and hematologic derangements in the mother concomitant with these infections can affect the pregnancy, possibly resulting in abortion, stillbirth, or premature delivery.

The effects of microbial toxins on the developing fetus are uncertain. The fetus may be adversely affected by toxic shock in the mother secondary to *Staphylococcus aureus* or *Streptococcus pyogenes* infection.<sup>33</sup> Botulism in pregnant women has not been associated with disease in infants.<sup>34,35</sup> A unique case of Guillain-Barré syndrome in mother and child shows that infection-induced, antibody-mediated autoimmune disease in the mother may be transmitted to her infant. In this case, the disease was diagnosed in the mother during week 29 of pregnancy. A healthy infant was delivered vaginally at 38 weeks of gestation, while the mother was quadriplegic and on respiratory support. On day 12 of life, the infant developed flaccid paralysis of all limbs with absence of deep tendon reflexes, and cerebrospinal fluid (CSF) examination revealed increased protein concentration without white blood cells.<sup>36</sup> The delay in onset of paralysis in the infant seemed to reflect transplacentally transferred blocking antibodies specifically directed at epitopes of the mature, but not the fetal, neuromuscular junction. The infant improved after administration of intravenous immunoglobulin.<sup>37</sup>

The association of maternal urinary tract infection with premature delivery and low birth weight is a well-studied example of a maternal infection that adversely affects growth and development of the fetus, despite no evidence of fetal or placental infection. Asymptomatic bacteriuria in pregnancy has been linked to increased low-birth-weight deliveries.<sup>38,39</sup> A meta-analysis of interventional studies concluded that antibiotic treatment is effective in reducing the risk of pyelonephritis in pregnancy and the risk for preterm delivery, although the evidence supporting this latter conclusion is not as strong.<sup>40</sup> The basis for the premature delivery and low birth weight of infants of mothers with bacteriuria remains obscure<sup>41</sup> and may, in part, reflect an altered maternal genital tract microbiome and dysbiosis-associated preterm labor (see Chapter 3).

**Infection of Placenta and Fetus.** Microorganisms disseminate from the infected placenta to the fetal bloodstream through infected emboli of necrotic chorionic tissues or through direct extension of placental infection to the fetal membranes, with secondary amniotic fluid infection and aspiration by the fetus.

### Infection of the Embryo and Fetus

Hematogenous transplacental spread may result in death and resorption of the embryo, abortion and stillbirth of the fetus, and live birth of a premature or term infant who may or may not be healthy. The effects of fetal infection may appear in a live-born infant as low birth weight

(resulting from intrauterine growth restriction), developmental anomalies, congenital disease, or none of these. Infection acquired in utero may persist after birth and cause significant abnormalities in growth and development that may be apparent soon after birth or may not be recognized for months or years. The variability of the effects of fetal infection is emphasized by reports of biovular twin pregnancies that produced one severely damaged infant and one infant with minimal or no detectable abnormalities.<sup>42-47</sup>

**Embryonic Death and Resorption.** Various organisms may infect the pregnant woman in the first few weeks of gestation and cause death and resorption of the embryo. Because loss of the embryo usually occurs before the woman realizes she is pregnant or seeks medical attention, it is difficult to estimate the incidence of this outcome for any single infectious agent. The incidence of early pregnancy loss after implantation from all causes has been estimated to be 31%. The proportion of cases of loss because of infection is unknown.<sup>48</sup>

**Abortion and Stillbirth.** The earliest recognizable effects of fetal infection are seen after 6 to 8 weeks of pregnancy and include abortion and stillbirth. Intrauterine death may result from overwhelming fetal infection, or the microorganisms may interfere with organogenesis to such an extent that the development of functions necessary for continued viability is interrupted. The precise mechanisms responsible for early spontaneous termination of pregnancy are unknown; in many cases, it is difficult to ascertain whether fetal death caused or resulted from the expulsion of the fetus.

Numerous modifying factors probably determine the ultimate consequence of intrauterine infection, including virulence or tissue tropism of the microorganisms, stage of pregnancy, associated placental damage, and severity of the maternal illness. Primary infection is likely to have a more important effect on the fetus than recurrent infection.<sup>49</sup> Recurrent maternal CMV infection is less severe than primary infection and is significantly less likely to result in congenital CMV infection of the fetus. Available studies do not distinguish between the direct effect of the microorganisms on the developing fetus and the possibility of an indirect effect attributable to illness or poor health of the mother.

**Prematurity.** Prematurity is defined as the birth of a viable infant before week 37 of gestation. Premature birth may result from almost any agent capable of establishing fetal infection during the last trimester of pregnancy. Many microorganisms commonly responsible for prematurity are also implicated as significant causes of stillbirth and abortion (Table 1-5).

Previous studies have shown that women in premature labor with bacteria-positive amniotic fluid cultures have elevated amniotic fluid levels of multiple proinflammatory cytokines.<sup>50-55</sup> In many patients with elevated levels of interleukin-6 (IL-6), results of amniotic fluid culture were negative. Premature births are invariably observed, however, in women in premature labor having positive amniotic fluid culture and elevated amniotic fluid levels

**Table 1-5** Effects of Transplacental Fetal Infection on the Fetus and Newborn Infant

Organism	DISEASE				
	Prematurity	Intrauterine Growth Restriction/Low Birth Weight	Developmental Anomalies	Congenital Disease	Persistent Postnatal Infection
Viruses	CMV HSV Rubeola Smallpox HBV HIV*	CMV Rubella VZV* HIV*	CMV Rubella VZV Coxsackievirus B* HIV*	CMV Rubella VZV HSV Mumps* Rubeola Vaccinia Smallpox Coxsackievirus B Poliovirus HBV HIV LCV Parvovirus	CMV Rubella VZV HSV HBV HIV
Bacteria	<i>Treponema pallidum</i> <i>Mycobacterium tuberculosis</i> <i>Listeria monocytogenes</i> <i>Campylobacter fetus</i> <i>Salmonella typhi</i>			<i>T. pallidum</i> <i>M. tuberculosis</i> <i>L. monocytogenes</i> <i>C. fetus</i> <i>S. typhi</i> <i>Borrelia burgdorferi</i>	<i>T. pallidum</i> <i>M. tuberculosis</i>
Protozoa	<i>Toxoplasma gondii</i> <i>Plasmodium</i> * <i>Trypanosoma cruzi</i>	<i>T. gondii</i> <i>Plasmodium</i> <i>T. cruzi</i>		<i>T. gondii</i> <i>Plasmodium</i> <i>T. cruzi</i>	<i>T. gondii</i> <i>Plasmodium</i>

CMV, Cytomegalovirus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LCV, lymphocytic choriomeningitis virus; VZV, varicella-zoster virus.

\*Association of effect with infection has been suggested and is under consideration.

of IL-6. To clarify further the role of elevated levels of IL-6 in amniotic fluid, Hitti and colleagues<sup>51</sup> amplified bacterial DNA encoding 16S ribosomal RNA (rRNA) by using a polymerase chain reaction (PCR) assay to detect infection in amniotic fluid of women in premature labor whose membranes were intact. In patients who were culture-negative, PCR assay detected bacterial infection in a significant percentage of those with elevated IL-6 levels. These data suggest that 33% of women in premature labor with culture-negative amniotic fluid but with elevated IL-6 levels may have infected amniotic fluid. The investigators concluded that the association between infected amniotic fluid and premature labor may be underestimated on the basis of amniotic fluid cultures and that a broad-spectrum bacterial 16S rDNA PCR assay may be useful for detecting prenatal infection. The utility of amniotic fluid testing for IL-6 and other biomarkers in predicting risk for preterm birth is discussed further in Chapter 3.

In recent years, many studies have explored how abnormal composition of the vaginal flora, maternal vaginal colonization with *Ureaplasma* or *Mycoplasma* spp., or development of bacterial vaginosis (BV) during pregnancy can influence the risk of preterm birth.<sup>56,57</sup> Meta-analyses of recent interventional studies of antibiotic administration to correct such dysbiosis during the first trimester are, to date, inconclusive with respect to reducing preterm birth.<sup>58,59</sup> Further advances in the detection of microbes and the assessment of microbial diversity through high-throughput, next-generation sequencing-based assessment offer the promise to better understand the role of microbes in preterm labor and its untoward consequences (see Chapter 3).

**Intrauterine Growth Restriction and Low Birth Weight.** Infection of the fetus may result in birth of an infant who is small for gestational age. Although many maternal infections are associated with low-birth-weight infants and infants who are small for gestational age, causal evidence is sufficient only for congenital rubella, VZV infection, toxoplasmosis, and CMV infection, although it is likely that congenital syphilis can, in some cases, also result in intrauterine growth restriction (see Chapter 16).

The organs of infants dying with congenital rubella syndrome or congenital CMV infection contain reduced numbers of morphologically normal cells.<sup>60,61</sup> By contrast, in infants who are small for gestational age with growth deficit from noninfectious causes, such as maternal toxemia or placental abnormalities, the parenchymal cells are normal in number but have a reduced amount of cytoplasm, presumably because of fetal malnutrition.<sup>62,63</sup>

**Developmental Anomalies and Teratogenesis.** CMV, rubella virus, and VZV cause developmental anomalies in the human fetus. Coxsackieviruses B3 and B4 have been associated with congenital heart disease. Although the pathogenetic mechanisms responsible for fetal abnormalities produced by most infectious agents remain obscure, histologic studies of abortuses and congenitally infected infants have suggested that some viruses render these effects through mediating cell death, alterations in cell growth, or chromosomal damage. Inflammation and tissue destruction, rather than teratogenic activity, seem to be responsible for the widespread structural abnormalities characteristic of congenital syphilis, transplacental HSV and VZV infection, and toxoplasmosis. Infants with

**Table 1-6** Clinical Manifestations of Neonatal Infection Acquired In Utero or at Delivery

Rubella Virus	Cytomegalovirus	<i>Toxoplasma gondii</i>	Herpes Simplex Virus	<i>Treponema pallidum</i>	Enteroviruses
Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly
Jaundice	Jaundice	Jaundice	Jaundice	Jaundice	Jaundice
Pneumonitis	Pneumonitis	Pneumonitis	Pneumonitis	Pneumonitis	Pneumonitis
Petechiae or purpura	Petechiae or purpura	Petechiae or purpura	Petechiae or purpura	Petechiae or purpura	Petechiae or purpura
Meningoencephalitis	Meningoencephalitis	Meningoencephalitis	Meningoencephalitis	Meningoencephalitis	Meningoencephalitis
Hydrocephalus	Hydrocephalus	Hydrocephalus*	Hydrocephalus	Adenopathy	Adenopathy
Adenopathy	Microcephaly*	Microcephaly	Microcephaly	Maculopapular exanthems*	Maculopapular exanthems
Hearing deficits	Intracranial calcifications*	Maculopapular exanthems	Maculopapular exanthems	Bone lesions*	Paralysis*
Myocarditis	Hearing deficits	Intracranial calcifications*	Vesicles*	Glaucoma	Myocarditis*
Congenital defects*	Chorioretinitis or retinopathy	Myocarditis	Myocarditis	Chorioretinitis or retinopathy	Conjunctivitis or keratoconjunctivitis
Bone lesions*	Optic atrophy	Bone lesions	Chorioretinitis or retinopathy	Uveitis	
Glaucoma*		Chorioretinitis or retinopathy*	Cataracts		
Chorioretinitis or retinopathy*		Cataracts	Conjunctivitis or keratoconjunctivitis*		
Cataracts*		Optic atrophy			
Microphthalmia		Microphthalmia			
		Uveitis			

\*Has special diagnostic significance for this infection.

congenital toxoplasmosis may have microcephaly, hydrocephalus, or microphthalmia, but these manifestations usually result from an intense necrotizing process involving numerous organisms and are more appropriately defined as lesions of congenital infection, rather than as effects of teratogenic activity of the organism.

Some mycoplasmas<sup>64</sup> and viruses<sup>65,66</sup> produce chromosomal damage in circulating human lymphocytes or in human cells in tissue culture. The relationship of these genetic aberrations to the production of congenital abnormalities in the fetus is unknown.

**Congenital Disease.** Clinical evidence of intrauterine infections, resulting from tissue damage or secondary physiologic changes caused by the invading organisms, may be present at birth or may manifest soon thereafter or years later. The clinical manifestations of infection acquired in utero or at delivery in the newborn infant are summarized in Table 1-6. Signs of widely disseminated infection may be evident during the neonatal period in infants with congenital rubella; toxoplasmosis; syphilis; or congenital CMV, HSV, or enterovirus infection. These signs include jaundice, hepatosplenomegaly, and pneumonia, each of which reflects lesions caused by microbial invasion and proliferation, rather than by defects in organogenesis. Although these signs of congenital infection are not detected until the neonatal period, the pathologic processes responsible for their occurrence have been progressing for weeks or months before delivery. In some infants, the constellation of signs is sufficient to suggest the likely congenital infection (Table 1-7). In other infants, the signs are transient and self-limited and resolve as neonatal defense mechanisms control the spread of the microbial agent and tissue destruction. If damage is severe and widespread at the time of delivery, survival of the infant is unlikely.

It is frequently difficult to determine whether an infection in the newborn infant was acquired in utero, intrapartum, or postpartum. If the onset of clinical signs after birth occurs within the minimal incubation period for the

**Table 1-7** Syndromes in the Neonate Caused by Congenital Infections

Microorganism	Signs
<i>Toxoplasma gondii</i>	Hydrocephalus, diffuse intracranial calcification, chorioretinitis
Rubella virus	Cardiac defects, sensorineural hearing loss, cataracts, microcephaly, "blueberry muffin" skin lesions, hepatomegaly, interstitial pneumonitis, myocarditis, disturbances in bone growth, intrauterine growth restriction
CMV	Microcephaly, periventricular calcifications, jaundice, petechiae or purpura, hepatosplenomegaly, intrauterine growth restriction
HSV	Skin vesicles or scarring, eye scarring, microcephaly or hydranencephaly, vesicular skin rash, keratoconjunctivitis, meningoencephalitis, sepsis with hepatic failure
<i>Treponema pallidum</i>	Bullous, macular, or eczematous skin lesions involving palms and soles; rhinorrhea; dactylitis and other signs of osteochondritis and periostitis; hepatosplenomegaly; lymphadenopathy
VZV	Limb hypoplasia, cicatricial skin lesions, ocular abnormalities, cortical atrophy
Parvovirus B19	Nonimmune hydrops fetalis
HIV	Severe thrush, failure to thrive, recurrent bacterial infections, calcification of basal ganglia

CMV, Cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

disease (e.g., 3 days for enteroviruses, 10 days for VZV and rubella viruses), it is likely that the infection was acquired before delivery. The interval between malaria exposure in the mother and congenital malaria in the infant can be prolonged; one case of congenital malaria resulting from *Plasmodium malariae* occurred in an infant born in the United States 25 years after the mother had emigrated from China.<sup>67</sup> Children with perinatal HIV infection can be diagnosed by 6 months of age using a DNA (or RNA) PCR method, which has largely replaced other approaches for viral detection.<sup>68</sup> A variable fraction (less than half) of

children with perinatal HIV contract the infection in utero, depending on the setting and maternal treatment.<sup>69</sup> Virus-negative infants who later become virus-positive may have been infected in the intrapartum or early postpartum period, including via breastfeeding, especially when neither the infant nor the mother is receiving antiretroviral prophylaxis while breastfeeding. In this situation, up to a 54% increase in postpartum HIV transmission associated with breastfeeding has been documented.<sup>69,70</sup>

**Healthy Infants.** Most newborn infants infected in utero by rubella virus, *T. gondii*, CMV, HIV, or *Treponema pallidum* have no signs of congenital disease. Fetal infection by a limited inoculum of organisms or with a strain of low virulence or pathologic potential may underlie this low incidence of clinical disease in infected infants. Alternatively, gestational age may be the most important factor in determining the ultimate consequences of prenatal infection. When congenital rubella and toxoplasmosis are acquired during the last trimester of pregnancy, the incidence of clinical disease in the infected infants is lower than when microbial invasion occurs during the first or second trimester. Congenital syphilis most commonly results from exposure during the second or third trimesters but can be transmitted to the fetus in the first trimester.

Absence of clinically apparent disease in the newborn may be misleading. Careful observation of infected but healthy-appearing children over months or years often reveals defects that were not apparent at birth. The failure to recognize such defects early in life may be due to the inability to test young infants for the sensory and developmental functions involved. Hearing defects identified years after birth may be the only manifestation of congenital rubella. Significant sensorineural deafness and other central nervous system deficiencies have affected children with congenital CMV infection who were considered to be normal during the neonatal period. In utero infection with *Toxoplasma*, rubella, and CMV may have manifestations that are difficult to recognize, including failure to thrive, visual defects, and minimal-to-severe brain dysfunction, including motor, learning, language, and behavioral disorders. Infants infected with HIV are usually asymptomatic at birth and for the first few months of life. The median age of onset for signs of congenital HIV infection is approximately 3 years, but many children remain asymptomatic for more than 5 years. Signs of perinatal infection related to HIV include failure to thrive, persistent diarrhea, recurrent suppurative infections, and diseases associated with opportunistic infections that occur weeks to months or years after birth. Of particular concern is a report by Wilson and colleagues<sup>71</sup> showing stigmata of congenital *T. gondii* infection, including chorioretinitis and blindness, in almost all of 24 children at follow-up evaluations; the children had serologic evidence of infection but were without apparent signs of disease at birth and either did not receive treatment or received inadequate treatment.

Because abnormalities may become obvious only as the child develops and fails to reach appropriate physiologic or developmental milestones, it is crucial to perform careful and thorough follow-up examinations in infants born to women with known or suspected infections during pregnancy.

**Persistent Postnatal Infection.** Microbial agents may continue to survive and replicate in tissues for months or years after in utero infection. Rubella virus and CMV have been isolated from various body fluid and tissue compartments over long periods from healthy-appearing children and children with abnormalities at birth. Progressive tissue destruction has been shown in some congenital infections, including rubella; toxoplasmosis; syphilis; tuberculosis; malaria; and CMV, HSV, and HIV infection. Recurrent skin and eye infections can occur as a result of HSV infection acquired in utero or at the time of delivery. A progressive encephalitis occurred in children with congenital rubella infection; stable clinical manifestations of congenital infection over many years were followed by deterioration of motor and mental functions at ages 11 to 14 years.<sup>72,73</sup> Rubella virus was subsequently isolated from the brain biopsy specimen of a 12-year-old child. Finally, fetal parvovirus B19 infection can persist for months after birth with persistent anemia because of suppressed hematopoiesis.<sup>74</sup>

The mechanisms responsible for maintaining or terminating chronic fetal and postnatal infections are only partially understood. Humoral immune responses, as determined by measurement of either fetal immunoglobulin M (IgM) or IgA antibodies or specific IgG antibodies that develop in the neonatal period, seem to be intact in almost all infants (see Chapter 4). The importance of cell-mediated immunity, cytokines, complement, antimicrobial peptides, and other host defense mechanisms remains to be adequately defined; at present, there is insufficient evidence to support a causal relationship between deficiencies in any one of these factors and persistent postnatal infection. All of the diseases associated with persistent postnatal infection—with the exception of rubella, but including syphilis; tuberculosis; malaria; toxoplasmosis; hepatitis; and CMV, HSV, VZV, and HIV infections—can also produce prolonged and, in certain instances, lifelong infection when acquired later in life.

## EFFICIENCY OF TRANSMISSION OF MICROORGANISMS FROM MOTHER TO FETUS

The efficiency of transmission from the infected, immunocompetent mother to the fetus varies among microbial agents and can vary with the trimester of pregnancy. In utero transmission of rubella virus and *T. gondii* occurs mainly during primary infection, whereas in utero transmission of CMV, HIV, and *T. pallidum* can occur in consecutive pregnancies. The risk of congenital rubella infection in fetuses of mothers with symptomatic rubella was high in the first trimester (90% before 11 weeks of gestation), declined to a nadir of 25% at 23 to 26 weeks, and then increased to 67% after 31 weeks. Infection in the first 11 weeks of gestation was uniformly teratogenic, whereas no birth defects occurred in infants infected after 16 weeks of gestation.<sup>75</sup> By contrast, the frequency of stillbirth and clinical and subclinical congenital *T. gondii* infections among offspring of women who acquired the infection during pregnancy was lowest in the first trimester (14%), increased in the second trimester (29%), and was highest in the third trimester (59%).<sup>76</sup>

Congenital CMV infection can result both from primary and recurrent infections. On the basis of studies in Birmingham, Alabama, and other centers, Whitley and Stagno and their colleagues<sup>77,78</sup> estimate that 1% to 4% of women have

primary infection during pregnancy, 40% of these women transmit the infection to their fetuses, and 5% to 15% of the infants have signs of CMV disease. Congenital infection as a result of recurrent CMV infection occurs in 0.5% to 1% of live births, but less than 1% of the infected infants have clinically apparent disease.

The transmission rate of HIV infection from an untreated mother to the fetus is estimated to be about 25%, but the data are insufficient to identify efficiency of transmission in each trimester. Risk of transmission does not seem to be greater in mothers who acquire primary infection during pregnancy than in mothers who were infected before they became pregnant.<sup>79</sup>

## DIAGNOSIS OF INFECTION IN THE PREGNANT WOMAN

### Clinical Diagnosis

**Symptomatic or Clinical Infection.** In many instances, infection in the pregnant woman and congenital infection in the newborn infant can be suspected on the basis of clinical signs or symptoms. Careful examination can be sufficient to suggest a specific diagnosis, particularly when typical clinical findings are accompanied by a well-documented history of exposure (see [Tables 1-6 and 1-7](#)).

**Asymptomatic or Subclinical Infection.** Many infectious diseases with serious consequences for the fetus are difficult or impossible to diagnose in the mother solely on clinical grounds. Asymptomatic or subclinical infections may be caused by rubella virus, CMV, *T. gondii*, *T. pallidum*, HSV, and HIV. Most women infected with these organisms during pregnancy have no apparent signs of disease; only 50% of women infected with rubella virus have a rash, and although occasional cases of CMV mononucleosis are recognized, these constitute a very small proportion of women who acquire primary CMV infection during pregnancy. Similarly, the number of women with clinical manifestations of toxoplasmosis is less than 10%, and few women have systemic illness associated with primary HSV infection. The genital lesions associated with HSV infection and syphilis are often not recognized.

**Recurrent and Chronic Infection.** Some microorganisms can infect a susceptible person more than once, and when such reinfections occur in a pregnant woman, the organism can affect the fetus. These reinfections are generally associated with waning host immunity, but low levels of circulating antibodies may be detectable. Such specific antibodies would be expected to provide some protection against hematogenous spread and transplacental infection; however, fetal disease has followed reexposure of immune mothers to vaccinia,<sup>80</sup> variola,<sup>81</sup> and rubella<sup>82</sup> viruses.

In addition, an agent capable of persisting in the mother as a chronic asymptomatic infection could infect the fetus long after the initial infection. Such delayed infection is common for congenital CMV and HIV infections, which have been observed in infants from consecutive pregnancies in the same mother. Reports of infection of the fetus as a result of chronic maternal infection have been cited in cases of malaria,<sup>83</sup> syphilis,<sup>84</sup> hepatitis,<sup>85</sup> herpes zoster<sup>47</sup> and herpes simplex,<sup>86</sup> and *T. gondii* infection.<sup>87</sup> In the case of

*T. gondii*, congenital transmission from a chronically infected woman occurs almost solely when the woman is immunocompromised during pregnancy.

**Preconceptional Infection.** The occurrence of acute infection immediately before conception may result in infection of the fetus, and the association may go unrecognized. Congenital rubella has occurred in the fetus in cases in which the mother was infected 3 weeks to 3 months before conception. A prolonged viremia or persistence of virus in the maternal tissues may be responsible for infection of the embryo or fetus. The same phenomenon has occurred rarely in cases of maternal infection with *T. gondii*.<sup>88</sup>

### Isolation and Identification of Infectious Agents

**General Approach.** Diagnostic tests for microorganisms or infectious diseases are part of routine obstetric care; special care is warranted for selected patients with known or suspected exposure to the infectious agent or clinical signs of infection. [Table 1-8](#) lists general categories of diagnostic tests and interventions that may be required in the event of a diagnosis. The specific interventions for each disease are discussed in subsequent chapters.

The most direct mode of diagnosis is isolation of the microbial agent from tissues and body fluids such as blood, CSF, or urine. Isolation of the agent must be considered in context with its epidemiology and natural history in the host. Isolation of an enterovirus from stool during the summer months may represent colonization, rather than significant infection, with risk of hematogenous spread to the fetus. Isolation of an enterovirus from an atypical body fluid or identification of a significant increase in antibody titer would be necessary to define an acute infectious process.

Tests for the presence of hepatitis B virus (HBV) surface antigen (HBsAg) should be performed in all pregnant women. The Centers for Disease Control and Prevention (CDC) has estimated that 16,500 births occur each year in the United States to women who are positive for HBsAg. Infants born to HBsAg-positive mothers may have a 90% chance of acquiring perinatal HBV infection. If maternal infection is identified soon after birth, use of hepatitis B immunoglobulin combined with hepatitis B vaccine is an effective mode of prevention of infection. For these reasons, the Advisory Committee on Immunization Practices of the U.S. Public Health Service<sup>89</sup> and the American Academy of Pediatrics (AAP)<sup>7</sup> recommend universal screening of all pregnant women for HBsAg.

The seminal publication by Daffos and colleagues<sup>90</sup> in 1983, in which fetal blood sampling for prenatal diagnosis was first described, provided a method for diagnosing various infections in the fetus that previously could be diagnosed only after birth. Their methods were widely adopted and have contributed significantly to our understanding of the immune response of the fetus to various pathogens, including rubella virus, VZV, CMV, and *T. gondii*,<sup>91-94</sup> and to a more objective approach to treating infection in the fetus before birth.

Fetal blood sampling and amniocentesis are performed with ultrasound guidance. The method is not free of risk; amniocentesis alone carries a risk of fetal injury or death of 1%,<sup>54,95</sup> and fetal blood sampling carries a risk of approximately 1.4%.<sup>96</sup> Because the amniotic fluid contains viruses

**Table 1-8** Management of Infections in the Pregnant Woman

Microorganism	Diagnostic Test	First Visit	Third Trimester	At Delivery	Intervention*
<b>ROUTINE CARE</b>					
<i>Mycobacterium tuberculosis</i>	Tuberculin skin test	+			Chest radiograph, culture, antituberculous therapy
Gonorrhea	Culture	+	+		Antibiotic therapy
Hepatitis B	Serology	+			HBIG and hepatitis B vaccine to the infant within 12 hr of birth†
<i>Chlamydia</i>		+	+		Antibiotic therapy
Syphilis	Serology	+	+	+	Antibiotic therapy
Rubella	Serology	+			Postpartum vaccine
Group B <i>Streptococcus</i>	Culture		+		Intrapartum antibiotic prophylaxis
Herpes simplex virus	Examination, PCR, culture	+	+	+	Cesarean section‡ Antiviral therapy
Influenza	None needed				Vaccination
Neonatal pertussis	None needed				Vaccination for each pregnancy
<b>SPECIAL CARE IF EXPOSED OR WITH CLINICAL SIGNS</b>					
CMV	Serology	+			Education regarding hygiene to prevent infection
HIV	ELISA + Western blot, RNA testing	+			Antiretroviral therapy
Malaria	Rapid diagnostic testing, blood smear	+			IPTp and bed nets, anti-malarial treatment
Parvovirus	Ultrasonography, serology				Intrauterine transfusion
Toxoplasmosis	Serology, PCR assay (amniotic fluid)				Anti- <i>Toxoplasma</i> therapy
VZV	Examination, PCR, ultrasonography				Antiviral therapy

Modified from table prepared by Riley L, Fetter S, Geller D: Boston City Hospital and Boston University School of Medicine.

ELISA, Enzyme-linked immunosorbent assay; HBIG, hepatitis B immune globulin; HIV, human immunodeficiency virus; IPTp, intermittent preventive therapy in pregnancy; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

\*See appropriate chapters.

†Hepatitis B immunoglobulin only in neonates born to women with high-risk factors, and in addition, hepatitis B vaccine for neonate.

‡When signs or symptoms of active genital herpes simplex virus are present at the onset of labor.

or bacteria shed from the placenta, skin, urine, or tracheal fluid of the infected fetus, this fluid may also be used to detect the infecting organism by culture, antigen detection test, or the presence of its nucleic acids by PCR. Amniotic fluid analysis is generally preferred over fetal blood sampling for this purpose and because the procedure, in experienced hands, appears to have a lower risk of complications than fetal blood sampling. Fetal blood can be examined for the same factors and antibodies formed by the fetus against the pathogen (e.g., IgA or IgM antibodies). These procedures are usually performed during or after week 18 of gestation. In any case, the decision to perform either procedure should be predicated on expectation that the information obtained will affect management. A fetus at high risk for infection (e.g., the fetus of a nonimmune woman who acquired infection with *T. gondii*, cytomegalovirus, or rubella virus during pregnancy) may be evaluated and followed by ultrasound

examination to detect abnormalities such as dilation of the cerebral ventricles that suggest the presence of fetal infection.

#### **Isolation, Culture, and Polymerase Chain Reaction.**

Isolation of CMV and rubella virus<sup>97</sup> and demonstration of HBsAg<sup>98</sup> from amniotic fluid obtained by amniocentesis have been reported. As PCR techniques have proved to be sensitive and specific for diagnosing many infections in the pregnant woman, fetus, and newborn, in many instances, isolating the infectious agent to make a definitive diagnosis is no longer necessary if PCR techniques are used. PCR techniques decrease the time to diagnosis and increase the sensitivity for diagnosis of many infectious agents, as exemplified by the prenatal diagnosis of infections caused by parvovirus,<sup>99,100</sup> CMV,<sup>101-103</sup> *T. gondii*,<sup>104,105</sup> and rubella virus.<sup>106,107</sup>

As with all diagnostic testing, caution is required in interpreting the results of prenatal PCR testing, however, because the sensitivity of PCR results on amniotic fluid is uncertain. One third of cases of congenital toxoplasmosis yield a negative result on amniotic fluid PCR assay,<sup>105,107</sup> and infants with congenital rubella may have negative amniotic fluid PCR assay results but positive fetal blood tests. Also, false-positive rates of 5% for viral DNA detection in fluids obtained for genetic testing have been observed when congenital fetal infection was not suspected or documented. Combined diagnostic approaches in which PCR is used in concert with fetal serology and other diagnostic modalities (e.g., serial fetal ultrasonography) to test amniotic fluid and fetal blood may offer the greatest sensitivity and predictive power in cases in which congenital infection is suspected, and this information is important in management decisions.<sup>105,108</sup>

**Cytologic and Histologic Diagnosis.** Histologic review of cytologic preparations and tissue sections is no longer used as the primary method of diagnosing maternal infections; however, it may provide a preliminary diagnosis of certain infections. Cervicovaginal smears or cell scrapings from the base of vesicles are valuable in diagnosing VZV and HSV infections. Typical histologic changes include multinucleated giant cells and intranuclear inclusions. The diagnosis of acute toxoplasmosis can be made from characteristic histologic changes in lymph nodes or by demonstration of the tachyzoite in biopsy or autopsy specimens of infected tissues. These morphologic approaches have been replaced, however, by more specific methods, such as PCR and serologic testing, to detect VZV, HSV, CMV, and toxoplasmosis. Detailed descriptions of the changes associated with infections of the placenta are presented in a monograph by Fox.<sup>109</sup> Examination of the placental parenchyma, the membranes, and the cord may provide valuable information for diagnosis of the infection and identification of the mode of transmission to the fetus (in utero or ascending infection).

**Serologic Diagnosis.** The serologic diagnosis of infection in the pregnant woman most often requires demonstration of elevated antibody titer against the suspected agent. Ideally, the physician should have available information about the patient's serologic status at the onset of pregnancy to identify women who are unprotected against *T. pallidum*, *T. gondii*, and rubella virus or who are infected with HBV or HIV. Many obstetricians have adopted this valuable practice.

Difficulties in interpreting serologic test results seldom arise when patients are seen shortly after exposure or at the onset of symptoms. In certain infections, including rubella and toxoplasmosis, however, a relatively rapid increase in antibody levels may preclude demonstration of a significant titer increase, especially in patients who are tested more than 7 days after the onset of the suspected illness. In these circumstances, a diagnosis may be obtained through the measurement of antibodies that increase more slowly over several weeks. Demonstration of IgA and IgE antibodies (in addition to the more conventional use of tests for IgG and IgM antibodies) is useful in the early diagnosis of infection in the pregnant woman, fetus, and newborn, and this should serve as an impetus for commercial firms to make these methods more widely available for health care providers. The same pertains to IgG avidity tests, which have

proved accurate in ruling out recently acquired infection with *T. gondii*,<sup>110</sup> CMV,<sup>111,112</sup> and rubella virus.<sup>113,114</sup> At present, these tests require special techniques and are not performed routinely by most laboratories, so local or state health departments should be consulted for further information regarding their availability.

**Use of Skin Tests.** Routine skin tests for diagnosis of tuberculosis should be considered a part of prenatal care. Tuberculin skin tests can be administered to the mother without risk to the fetus.

### Universal Screening

Prenatal care in the United States includes routine screening for serologic evidence of syphilis and rubella infection; culture or antigen evidence of *Chlamydia trachomatis*, group B streptococcus, or HBV infection; screening for urinary tract infection; and skin testing for tuberculosis. Evidence that treatment of the HIV-infected mother significantly reduces virus transmission to the fetus has led to recommendations by the U.S. Public Health Service for universal HIV screening of all pregnant women in the United States. Current CDC guidelines support voluntary HIV testing under conditions that simplify consent procedures, while preserving a woman's right to refuse testing, that is, an opt-out approach.<sup>8,115,116</sup>

Pregnant women with known HIV infection should be monitored and given appropriate treatment to enhance maternal and fetal health and to prevent maternal-to-fetal transmission. Pregnant women should be examined carefully for the presence of HIV-related infections, including gonorrhea, syphilis, and *C. trachomatis*. Baseline antibody titers should be obtained for opportunistic infections, such as *T. gondii*, which are observed commonly in HIV-infected women and which may be transmitted to their fetuses. More detailed information on management of the HIV-infected pregnant woman and her infant is given in Chapter 22.

## DIAGNOSIS OF INFECTION IN THE NEWBORN INFANT

Infants with congenital infection as a result of rubella virus, CMV, HSV, *T. gondii*, or *T. pallidum* may present similarly with one or more of the following abnormalities: purpura, jaundice, hepatosplenomegaly, pneumonitis, and meningoencephalitis. Some findings have specific diagnostic significance (see Tables 1-5 and 1-6). Diagnostic tests for specific agents are described in detail in the relevant chapters, and general features are briefly reviewed here; a discussion of laboratory tests that may aid in the diagnosis of neonatal sepsis is given in Chapter 36.

In certain congenital infections, the organism may be isolated or its nucleic acids detected from tissues and body fluids. Infants may excrete CMV and rubella virus in the urine for weeks to months after birth. *T. pallidum* may be found in the CSF, in nasal secretions, and in syphilitic skin lesions. In infants with congenital HIV infection, approximately 30% are PCR positive at birth, but nearly 100% are positive by 4 to 6 months of life.

Serologic tests are available through state or commercial laboratories for the TORCH group of microorganisms

(*T. gondii*, rubella virus, CMV, and HSV) and for certain other congenitally acquired infections. To distinguish passively transferred maternal IgG antibody from antibody produced by the neonate in response to infection in utero, it is necessary to obtain two blood specimens from the infant. Because the half-life of IgG is approximately 3 weeks, the first sample is obtained soon after birth, and the second sample should be obtained at least two half-lives, or approximately 6 weeks, after the first specimen.

IgA, IgE, and IgM antibodies do not cross the placenta. Antigen-specific IgA, IgE, and IgM antibodies in the infant's blood provide evidence of current infection, but few commercial laboratories use reliable assays for these antibodies for the purpose of identifying congenital infections (as described in a Public Health Advisory from the U.S. Food and Drug Administration outlining the limitations of *Toxoplasma* IgM commercial test kits).

Although most congenital infections occur as a single entity, many HIV-infected mothers are coinfecting with other infectious agents that may be transmitted to the newborn. A neonate born to a mother with HIV infection should be considered at risk for other sexually transmitted diseases, such as syphilis, gonorrhea, and *C. trachomatis* infection. Coinfection also has been documented for CMV.<sup>117,118</sup>

## PREVENTION AND MANAGEMENT OF INFECTION IN THE PREGNANT WOMAN

### Prevention of Infection

The pregnant woman should avoid contact with individuals with communicable diseases, particularly if she is known to be naïve to those infections. In some cases, specific measures can be taken. The pregnant woman should use barrier methods during intercourse with her sexual partner if he has a vesicular lesion on the penis that may be associated with HSV or if he is known or suspected to be infected with HIV. The WHO also recommends that HIV-infected partners of HIV-uninfected women in monogamous long-term relationships should be treated with highly active antiretroviral therapy regardless of their CD4 T-cell count, to prevent transmission to the uninfected partner.

Pregnant women should avoid eating raw or undercooked lamb, pork, and beef because of risk of *T. gondii* contamination. They also should avoid contact with cat feces or objects or materials contaminated with cat feces because these are highly infectious if they harbor oocysts of *T. gondii* (see Chapter 31). Pregnant women should not eat unpasteurized dairy products (including all soft cheeses), prepared meats (hot dogs, deli meat, and pâté), and undercooked poultry because these foods often contain *Listeria monocytogenes*, which is associated with maternal infection, miscarriage, fetal infection, and stillbirth (see Chapter 13), as well as other pathogens such as enterohemorrhagic *E. coli* O157 and *Staphylococcus aureus*.

Prevention of infection in the mother and of transmission of maternal infection to the fetus and neonate through antimicrobial therapy is discussed in Chapter 3 and in chapters on the relevant infections. Prevention through active or passive immunization of the mother or neonate is discussed in Chapter 38.

## Infections Acquired by the Newborn Infant During Birth

### PATHOGENESIS

The developing fetus is protected from the microbial flora (microbiota) of the maternal genital tract. Initial colonization of the newborn and of the placenta usually occurs after rupture of maternal membranes. If delivery is delayed after membranes rupture, components of the vaginal microbiota can ascend and, in some cases, produce inflammation of fetal membranes, umbilical cord, and placenta (see Chapter 3). Fetal infection also can result from aspiration of infected amniotic fluid. Some viruses are present in the genital secretions (HSV, CMV, HBV, or HIV) or blood (HBV, hepatitis C virus, or HIV). If delivery occurs shortly after rupture of the membranes, the infant can be colonized during passage through the birth canal, where various, potentially pathogenic microorganisms may be present. These include gram-positive cocci (staphylococci and streptococci); gram-negative cocci and coccobacilli (*Neisseria gonorrhoeae* and *Haemophilus influenzae*); gram-negative enteric bacilli (*Escherichia coli*, *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Salmonella*, and *Shigella*); anaerobic bacteria; viruses (CMV, HSV, rubella virus, and HIV); fungi (predominantly *Candida albicans*); *C. trachomatis*; mycoplasmas and ureaplasmas; and protozoa (*Trichomonas vaginalis* and *T. gondii*). The newborn is initially colonized on the skin; mucosal surfaces, including the nasopharynx, oropharynx, conjunctivae, umbilical cord, and external genitalia; and the gastrointestinal tract (from swallowing infected amniotic fluid or vaginal secretions). In most infants, the organisms proliferate at these sites without causing illness. A few infants become infected by direct extension from the sites of colonization (e.g., otitis media from nasopharyngeal colonization). Alternatively, invasion of the bloodstream can ensue, with subsequent dissemination of infection. The umbilical cord was a particularly common portal of entry for systemic infection before local disinfection methods became routine because the devitalized tissues are an excellent medium for bacterial growth and because thrombosed umbilical vessels provide direct access to the bloodstream. Microorganisms also can infect abrasions or skin wounds. At present, the most frequent routes for bloodstream invasion are the lung from aspirated infected amniotic fluid or vaginal contents and the gastrointestinal tract from transmigration of microbial flora across the gut wall.

Infants who develop bacterial sepsis often have specific risk factors absent in infants who do not develop significant infections. Among these factors are preterm delivery at gestational age less than 37 weeks, low birth weight, prolonged rupture of maternal membranes, maternal intra-amniotic infection, traumatic delivery, and fetal anoxia. Relative immaturity of the immune system is considered to be one factor increasing risk of infection during the neonatal period. The role of host defenses in neonatal infection is discussed in detail in Chapter 4.

Preterm birth is the most significant risk factor for acquisition of infections in infants immediately before or during delivery or in the nursery. Because of the increasing number of infants with extremely or very low birth weight, infection remains an important cause of morbidity and



mortality. Expansion of treatments for infertility has continued to increase the number of pregnancies with multiple births (see [Table 1-3](#)), and a gestational age of less than 28 weeks is common in multiparity. A summary of 6215 very-low-birth-weight neonates (birth weight, 401 to 1500 g) from the National Institute of Child Health and Human Development Neonatal Research Network reported a 2% incidence of early-onset sepsis, 3% incidence of meningitis, and remarkable 36% incidence of blood culture–positive late-onset sepsis.<sup>119</sup> Infection rate was inversely correlated with birth weight and gestational age; rates of early-onset sepsis were 6% at 22 weeks and 1% at 28 weeks, and rates of late-onset sepsis were 58% at 22 weeks and 20% at 28 weeks. Mortality and morbidity were inversely related to gestational age regardless of whether the infant also experienced late-onset sepsis.

The effectiveness of certain innate host defense mechanisms of the neonate remains controversial. Vernix caseosa contains antimicrobial proteins (see [Chapter 4](#)), and retention of vernix probably provides a protective barrier to the skin. Breast milk influences the composition of the fecal flora by suppression of *E. coli* and other gram-negative enteric bacilli and encouragement of *Lactobacillus* growth. In addition, breast milk contains secretory IgA, lysozymes, white blood cells, and lactoferrin (an iron-binding protein that significantly inhibits the growth of *E. coli* and other microorganisms); however, the role of these constituents in mitigating colonization and systemic infection in the neonate acquired at or shortly after birth is uncertain (see [Chapter 5](#)).

The virulence of the invading microorganism is also a factor in the pathogenesis of neonatal sepsis. Certain phage types of *S. aureus* (types 80 and 81) were responsible for most cases of disease in the staphylococcal pandemic of the 1950s. Phage group 2 *S. aureus* strains have been responsible for staphylococcal scalded skin syndrome sometimes seen in neonates (toxic epidermal necrolysis). Other evidence suggests that the K1 capsular antigens of *E. coli* and type III strains of group B streptococcus possess virulence properties that enhance their propensity for invasion of the blood-brain barrier during bacteremia, compared with non-K1 and non-type III strains of the same species, respectively.

## MICROBIOLOGY

The agents responsible for early-onset (before 7 days) neonatal sepsis are found in the maternal birth canal.<sup>120,121</sup> Most of these organisms are considered to be saprophytic but occasionally can be responsible for maternal infection and its sequelae, including endometritis and puerperal fever. Before the introduction of the sulfonamides and penicillin in the 1940s, gram-positive cocci, particularly group A streptococci, were responsible for most cases of neonatal sepsis. After the introduction of antimicrobial agents, gram-negative enterics, in particular *E. coli*, were the predominant causes of serious bacterial infections of the newborn. An increase in serious neonatal infection caused by group B streptococci was noted in the early 1970s, and group B streptococci and *E. coli* continue to be the most frequent causative agents for early-onset neonatal sepsis and late-onset sepsis in term infants. By contrast,

late-onset (after 7 days) sepsis in preterm neonates, remaining in the neonatal intensive care unit for weeks or months, is typically caused by commensal organisms (e.g., coagulase-negative staphylococci and *Candida* spp.) and organisms acquired from the mother and from the nursery environment.

The bacteria responsible for neonatal sepsis are discussed in [Chapter 6](#). Mycoplasmas, anaerobic bacteria, and viruses (including HSV, HBV, CMV, and HIV) that colonize the maternal genital tract are also acquired during birth.

## DIAGNOSIS

Review of the maternal record provides important clues for diagnosis of infection in the neonate. Signs of illness during pregnancy; exposure to sexual partners with transmissible infections; and results of cultures (e.g., for *C. trachomatis*, *N. gonorrhoeae*, or group B streptococci), serologic tests (e.g., for HIV infection, rubella, HBV, hepatitis C virus, or syphilis), and tuberculin skin tests or chest radiographs should be identified in the pregnancy record. The delivery chart should be checked for peripartum events that indicate risk of sepsis in the neonate, including premature rupture of membranes; prolonged duration (>18 hours) of rupture of membranes; evidence of fetal distress and fever; or other signs of maternal infection, such as bloody diarrhea, respiratory or gastrointestinal signs (i.e., enterovirus), indications of large concentrations of pathogens in the genitourinary tract (as reflected in bacteriuria caused by group B streptococci), and evidence of invasive bacterial infections in prior pregnancies.

The clinical diagnosis of systemic infection in the newborn can be difficult because the initial signs of infection may be subtle and nonspecific. Not only are the signs of infectious and noninfectious processes similar, but also the signs of in utero infection are indistinguishable from signs of infections acquired during the birth process or during the first few days of life. Respiratory distress, lethargy, irritability, poor feeding, jaundice, emesis, and diarrhea are associated with various infectious and noninfectious causes.

Some clinical manifestations of neonatal sepsis, such as hepatomegaly, jaundice, pneumonitis, purpura, and meningitis, are common to many infections acquired in utero or during delivery. Certain signs are related to specific infections (see [Tables 1-6 and 1-7](#)). Many signs of congenital infection are not evident at birth. HBV infection should be considered in an infant with onset of jaundice and hepatosplenomegaly between 1 and 6 months of age; CMV infection acquired at or soon after delivery may be associated with an afebrile protracted pneumonitis; enterovirus infection should be considered in an infant with CSF pleocytosis in the first months of life. Most infants with congenital HIV infection do not have signs of disease during the first months of life. Uncommonly, signs may be present at birth. Srugo and colleagues<sup>122</sup> described an infant with signs of meningoencephalitis at 6 hours of life; HIV was subsequently isolated from CSF. Clinical manifestations associated with infection by specific agents are discussed in greater detail in the relevant chapters.

Most early-onset bacterial infections are nonfocal except in the circumstance of respiratory distress at or shortly after birth, in which the chest radiograph reveals pneumonia.

Focal infections are frequent with late-onset neonatal sepsis and include otitis media, pneumonia, soft tissue infections, urinary tract infections, septic arthritis, osteomyelitis, and peritonitis. Bacterial meningitis is of particular concern because of the substantial mortality rate and the significant morbidity in survivors. Few infants have overt meningeal signs, and a high index of suspicion and examination of the CSF are required for early diagnosis.

Available routine laboratory methods can provide limited assistance in the diagnosis of systemic infections in the newborn infant, as described in Chapter 36. Immunoglobulin is produced by the fetus and newborn infant in response to infection, and increased levels of IgM have been measured in the serum of newborns with infections acquired transplacentally (i.e., syphilis, rubella, cytomegalic inclusion disease, toxoplasmosis, and malaria). Increased levels of IgM may also result from postnatally acquired bacterial infections. Not all infected infants have increased levels of serum IgM, however, and some infants who do have elevated concentrations of total IgM are apparently uninfected; thus increased levels of total IgM are neither sufficiently specific nor sensitive for clinical decision making.

Because inflammation of the placenta and umbilical cord may accompany peripartum sepsis, pathologic examination of sections of these tissues may assist in the diagnosis of infection in the newborn. Histologic evidence of inflammation may also be noted in the absence of evidence of neonatal sepsis, however. In the immediate postnatal period, gastric aspirate, pharyngeal mucus, or fluid from the external ear canal has been used to delineate exposure to potential pathogens, but are not useful in the diagnosis of neonatal sepsis.

Isolation of microorganisms from a usually sterile site, such as blood, CSF, or skin vesicle fluid, or from a suppurative lesion or a sterilely obtained sample of urine remains the only valid method of diagnosing systemic infection. Aspiration of any focus of infection in a critically ill infant (e.g., needle aspiration of middle ear fluid in an infant with otitis media or from the joint or metaphysis of an infant with osteoarthritis) should be performed to determine the etiologic agent. In infants with very low birth weight, commensal microorganisms, such as coagulase-negative staphylococci, *Enterococcus*, or *Candida*, isolated from a usually sterile body site should be considered pathogens until proven otherwise. Culture of infectious agents from the nose, throat, skin, umbilicus, or stool indicates colonization; these agents may include the pathogens that are responsible for the disease but, in themselves, do not establish the presence of active systemic infection.

PCR assays are useful to detect the nucleic acid of various important pathogens, including viruses and *Pneumocystis jirovecii*. When appropriate, serologic studies should be performed to ascertain the presence of in utero or postnatal infection for pathogens, such as HIV, rubella, parvovirus B19, *T. gondii*, and *T. pallidum*. For some of these infections (e.g., rubella), the diagnostic serologic assay measures IgG. To distinguish passively transferred maternal antibody from antibody derived from infection in the neonate, it is necessary to obtain two blood specimens from the infant. Because the half-life of IgG is estimated to be 23 days, the first sample is obtained soon after birth, and the second sample should be obtained at least two half-lives, or approximately 6 weeks, after the first specimen. Measurement of

IgM antibody provides evidence of current infection in the neonate, but none of these assays has proven reliability at present.

## MANAGEMENT

Successful management of neonatal bacterial sepsis depends on a high index of suspicion based on maternal history and infant signs, prompt initiation of appropriate antimicrobial therapy while diagnostic tests are performed, and meticulous supportive measures. If the physician suspects bacterial infection in a newborn, culture specimens should be obtained, and treatment with appropriate antimicrobial agents should be initiated immediately. In general, initial therapy must provide coverage against gram-positive cocci, particularly group B and other streptococci, *Listeria monocytogenes*, and gram-negative enteric bacilli. Ampicillin is the preferred agent with effectiveness against gram-positive cocci and *L. monocytogenes*. Most experts prefer ampicillin and gentamicin therapy for early-onset presumptive sepsis and for initial therapy for *E. coli*, GBS, and *L. monocytogenes* infections, with the addition of cefotaxime for presumptive bacterial meningitis.<sup>7</sup> The choice of therapy for gram-negative infections depends on the current pattern of antimicrobial susceptibility in the local community. Intrapartum antimicrobial therapy can yield drug concentrations in the blood of the newborn infant sufficient to suppress growth of group B streptococci and possibly other susceptible organisms in blood obtained for culture. An algorithm has been devised to guide empirical management of neonates born to mothers who received intrapartum antimicrobial prophylaxis for prevention of early-onset GBS infection or in whom prophylaxis was indicated but not given at least 4 hours before delivery,<sup>7</sup> and the algorithm is discussed in Chapter 12.

The choice of antibacterial drugs should be reviewed when results of cultures and susceptibility tests become available. The clinician should take care to select drugs that have been studied for appropriate dose, interval of dosing, and safety in neonates, especially for very-low-birth-weight infants, and that have the narrowest antimicrobial spectrum that would be effective (see Chapter 37). The duration of therapy depends on the initial response to the appropriate antibiotics—typically 10 days in most infants with sepsis, pneumonia, or minimal or absent focal infection; a minimum of 14 days for uncomplicated meningitis caused by group B streptococci or *L. monocytogenes*; and 21 days for gram-negative enteric bacilli.<sup>123</sup> The clinical pharmacology of antibiotics administered to the newborn infant is unique and cannot be extrapolated from adult data on absorption, excretion, and toxicity. The safety of new antimicrobial agents is a particular concern because toxic effects may not be detected until several years later (see Chapter 37).

Development of antimicrobial drug resistance in microbial pathogens is a constant concern. Group B streptococci remain uniformly susceptible to penicillins and cephalosporins, but many isolates now are resistant to erythromycin and clindamycin.<sup>124</sup> Administration of one or two doses of a penicillin or cephalosporin as part of a peripartum prophylactic regimen for prevention of GBS infection in the neonate should not significantly affect the genital flora, but monitoring should be continued to detect alterations

in flora and antibiotic susceptibility. Because the nursery is a small, closed community, development of resistance is a greater concern with nosocomial infections than with infections acquired in utero or at delivery.

Antiviral therapies are available for newborns infected with HSV (acyclovir), VZV (acyclovir), HIV (combination antiretroviral therapy), and overtly symptomatic CMV (ganciclovir or valganciclovir). Because early use of acyclovir for herpes simplex infections in neonates has been associated with improved outcome, physicians may choose to begin therapy for presumptive HSV disease and reevaluate when information on clinical course and results of cultures and PCR assay become available. A phase II trial examining safety, pharmacodynamics, and efficacy of ganciclovir treatment for symptomatic congenital CMV infection established the safe dose in infants and showed an antiviral effect with suppression of viremia.<sup>125, 126</sup> Neutropenia (63%), thrombocytopenia, and altered hepatic enzymes were noted in most of the infants, with nearly half of the infants requiring dosage adjustments because of severe neutropenia. A phase III randomized, controlled trial of intravenous ganciclovir for 6 weeks in 100 CMV-infected infants with central nervous system involvement at birth showed that ganciclovir treatment maintained hearing or allowed hearing improvement in 84% of infants, compared with 41% of control infants<sup>126</sup>; neurodevelopmental delays were also significantly reduced at 6 and 12 months of age in the treated compared to the control infants.<sup>127</sup> Twice daily oral valganciclovir administered for 6 weeks or 6 months twice daily in amounts expected to achieve blood concentrations of valganciclovir (VGCV) comparable to those achieved with intravenous ganciclovir in the phase III trial is currently being evaluated by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Preliminary results suggest that 6 months of oral VGCV with symptomatic congenital CMV improves audiologic and neurodevelopmental outcomes through at least 2 years of age.<sup>128</sup> The use of hyperimmune gamma globulin preparations to prevent or modify perinatal infections have been used with some success after newborn exposure to some pathogens, such as varicella, but with equivocal results for others, such as cytomegalovirus.<sup>129-131</sup> Further information regarding treatment of these infections is provided in the relevant chapters.

## PREVENTION

### Immunoprophylaxis

Passive immunoprophylaxis with specific hyperimmune immunoglobulin or monoclonal antibody preparations is indicated for the prevention of hepatitis B, varicella, and respiratory syncytial virus infection in infants at risk for these infections. Details are provided in Chapter 38.

Universal immunization of infants with hepatitis B vaccine has been recommended by the AAP since 1992.<sup>132</sup> Prior strategies of selective vaccination in high-risk populations and serologic screening of all pregnant women for HBsAg had little impact on control of HBV infections or their sequelae, and public health authorities believe that

infant immunization offers the most feasible approach to universal protection and eventual eradication of the disease. Infants born to HBsAg-positive women should be immunized at birth and receive hepatitis B immunoglobulin at or shortly after birth. This prevention strategy may be improved if a birth dose of hepatitis B vaccine is universally recommended, providing additional coverage for infants whose maternal records are incorrect or unavailable before hospital discharge.

### Chemoprophylaxis

After administration to the mother, antimicrobial agents capable of crossing biologic membranes can achieve pharmacologic concentrations in the fetus comparable with concentrations in well-vascularized maternal tissues. Prevention of newborn GBS infection by administration of ampicillin to the mother was first shown by Boyer and colleagues<sup>133</sup> and other investigators in 1983 (see Chapter 12). A prevention strategy initially recommended by the AAP in 1992<sup>134</sup> was revised in 1997, and current recommendations from the CDC are endorsed by the AAP, the American College of Obstetricians and Gynecologists, and the American Academy of Family Physicians. These organizations recommend universal culture screening of all pregnant women at 35 to 37 weeks of gestation and administration of intravenous penicillin during labor to those who are culture positive, the only exception being women with GBS bacteriuria during pregnancy or women who have had a previous neonate with invasive GBS infection; these groups should always receive intravenous penicillin during labor.<sup>7</sup>

Fetal drug concentrations can exceed 30% of the maternal blood concentrations,<sup>135</sup> and concentrations bactericidal against group B streptococci can be achieved in amniotic fluid 3 hours after a maternal dose (see Chapters 12 and 37). Parenteral antimicrobial therapy administered to the mother in labor essentially treats the fetus earlier in the course of the intrapartum infection. If the fetus has been infected, the regimen is treatment, not prophylaxis, and for some infected fetuses, the treatment administered in utero is insufficient to prevent early-onset GBS disease.<sup>136</sup>

Other modes of chemoprophylaxis administered to the neonate include ophthalmic drops or ointments for prevention of gonococcal ophthalmia and antiretroviral therapy for infants born to HIV-infected mothers. Empirical administration of antibacterial agents to infants with minimal or ambiguous clinical signs is considered therapy for presumed sepsis and should not be considered prophylaxis.

## Infections of the Newborn Infant in the First Month of Life

When fever or other signs of systemic infection occur in the first weeks or months of life, various sources of infection should be considered: (1) congenital infections with onset in utero; (2) infections acquired during the birth process from the maternal genital tract; (3) infections acquired in the nursery; (4) infections acquired in the household after discharge from the nursery; and (5) infection that suggests an anatomic defect, underlying immunologic disease, or metabolic abnormality.

## PATHOGENESIS AND MICROBIOLOGY

### Congenital Infections

Signs of congenital infection may not appear for weeks, months, or years after birth. Diagnosis and management are discussed in the disease chapters.

### Infections Acquired During Delivery

Although maternal intrapartum prophylaxis has reduced the incidence of early-onset GBS disease (by >80% in a Pittsburgh survey),<sup>137</sup> the regimen has had no impact on the incidence of late-onset disease,<sup>138</sup> with signs occurring from 6 to 89 days of life and up to 6 months of age in infants with very low birth weight. The pathogenesis of late-onset GBS disease remains obscure, but it is likely that even when vertical transmission from the mother at birth is prevented, exposure to either the mother (in whom colonization resumes after delivery) or other colonized family members and caregivers can serve as a source for colonization through direct contact. It is unknown why sepsis develops without warning in an infant who has no risk factors for sepsis and was well for days to weeks; this concern also is relevant in infants who acquire late-onset disease as a result of *E. coli* and *L. monocytogenes*.

### Nursery-Acquired Infections

After arrival in the nursery, the newborn may become infected by various mechanisms involving either human carriers or contaminated materials and equipment. Human sources in the hospital include personnel, mothers, and other infants. The methods of transmission may include the following:

- Respiratory droplet spread from adults or other newborn infants. Outbreaks of respiratory virus infections, including influenza, respiratory syncytial, and parainfluenza viruses, in prolonged-stay nurseries are frequent.<sup>136</sup> Methods for identification and control are provided in Chapter 35.
- Carriage of the microorganism on the hands of hospital personnel. A study has suggested that the hands may be not only a means of transmission, but also a significant reservoir of bacteria.<sup>139</sup>
- Suppurative lesions. Although spread of staphylococcal and streptococcal infections to infants or mothers may be associated with asymptomatic carriers, the most serious outbreaks have been caused by a member of the medical or nursing staff with a significant lesion.
- Human milk. CMV, HIV, HSV, hepatitis C virus, HTLV-1,<sup>140</sup> HTLV-2,<sup>141</sup> and HBsAg have been identified in mother's milk and may be transmitted to the neonate by this route. CMV-infected milk from banks can be dangerous for infants lacking passively transferred maternal antibody, especially among premature infants. The risk of breast-milk transmission of hepatitis C appears to be low and avoidance of breastfeeding by a hepatitis C infected mother is not recommended.

Breast-milk transmission of HIV is of concern because of the importance of breastfeeding in providing nutrition and immunologic protection in the first year of life. Breast milk has been documented as the likely source of HIV infection in

neonates whose mothers were transfused with HIV-infected blood after delivery or in whom disease developed postpartum through sexual contact.<sup>142</sup> Because of the importance of breastfeeding for infant nutrition and survival, WHO guidelines for infant feeding of HIV-exposed infants living in resource-poor settings recommend exclusive breastfeeding through 6 months, with extended breastfeeding through 12 months, and several antiretroviral options for prevention of mother to child transmission.<sup>143-145</sup> By contrast, in the United States and Western Europe, HIV-infected mothers are discouraged from breastfeeding because other forms of nutrition are available.<sup>146</sup> The recommendation also notes that in some regions and cultures, women are stigmatized for not breastfeeding, and alternatives such as formula are unaffordable or unsafe. The number of antenatal women in developing countries that lack resources for prevention in pregnancy has reached alarming proportions: 70% of women at a prenatal clinic in Zimbabwe and 30% of women in urban areas in six African countries were infected. The United Nations survey indicated that by 2000, breastfeeding would be responsible for more than one third (>200,000) of children newly infected with HIV, unless some attempts were made to limit this route of transmission.<sup>147</sup> Current efforts to prevent breastfeeding transmission include improved universal testing of pregnant women for HIV infection as well as dissemination of prophylactic regimens for pregnant women and their newborns.<sup>148</sup> However, availability of such regimens appears to be limited to approximately 45% of HIV-infected pregnant women in low- and middle-income countries.<sup>149</sup>

Infection of breast milk by bacterial pathogens, such as *S. aureus*, group B streptococci, *L. monocytogenes*,<sup>150</sup> and *Salmonella* spp., can result in neonatal disease. Bacteria that are components of skin flora, including *Staphylococcus epidermidis* and  $\alpha$ -hemolytic streptococci, are frequently cultured from freshly expressed human milk and are unlikely to be associated with disease in the breastfed infant. Other possible sources of infection in the nursery include the following:

- Blood used for replacement or exchange transfusion in neonates should be screened for safety using validated, efficacious methods, including tests for hepatitis B antigen and anti-hepatitis B core antibody, hepatitis C antibody and nucleic acids, HIV antibody and nucleic acids, West Nile Virus nucleic acids, HTLV-1 and HTLV-2 antibodies, CMV antibody, *Trypanosoma cruzi*, and *Plasmodium* spp. in malaria-endemic areas.
- Equipment has been implicated in common-source nursery outbreaks, usually including contaminated solutions used in nebulization equipment, room humidifiers, and bathing solutions. Several gram-negative bacteria, including *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Flavobacterium*, are able to multiply in aqueous environments at room temperature. In recent years, few solution-related or equipment-related outbreaks caused by these organisms have been reported because of the scrupulous infection control practices enforced in most intensive care nurseries.
- Catheterization of the umbilical vein and artery has been associated with sepsis, umbilical cellulitis, and abscess formation, but careful hygienic practices with insertion

of these devices make these complications rare. Intravenous alimentation using central venous catheters has been lifesaving for some infants, but also is associated with increased risk for catheter-related bacteremia or fungemia.

- Parenteral feeding with lipid emulsions has been associated with neonatal sepsis caused by coagulase-negative staphylococci and *Candida* and *Malassezia* spp. Strains of staphylococci isolated from infected ventricular shunts or intravascular catheters produce a biofilm that promotes adherence and growth of colonies on the surfaces and in the walls of catheters manufactured with synthetic polymers. The biofilm also protects the bacteria against antibiotics and phagocytosis. The introduction of lipid emulsion through the venous catheter provides nutrients for growth of the bacteria and fungi.<sup>151</sup>

Hand hygiene remains the most important element in controlling the spread of infectious diseases in the nursery (see Chapter 35). Hand hygiene measures should be implemented before and after every patient contact. Surveys of hospital employees indicate that rigorous adherence to hand hygiene, although the most simple of infection control techniques, is still lacking in most institutions. A study by Brown and colleagues<sup>152</sup> in a Denver neonatal intensive care unit indicated that compliance with appropriate hand-washing techniques was low for medical and nursing personnel. Compliance was monitored using a direct observation technique; of 252 observed encounters of nurses, physicians, and respiratory therapists with infants, 25% of the personnel broke contact with the infant by touching self (69%) or touching another infant (4%), and 25% did not wash before patient contact.

Waterless, alcohol-based hand hygiene products are routinely used in nurseries, with surveys indicating their rapid acceptance by nursery personnel, including physicians. Their ease of application and time saved through reduction in the need for hand washing should increase adherence with hand hygiene recommendations.

### Community-Acquired Infections

The newborn infant is susceptible to many of the infectious agents that colonize other members of the household and caregivers. The physician should consider illnesses in these contacts before discharging an infant from the hospital. If signs of an infectious disease develop after 15 to 30 days of life in an infant who was healthy at discharge and had no significant risk factors during gestation or delivery, the infection was probably acquired from a household or community contact. Suppurative lesions related to *S. aureus* in a household member can expose an infant to a virulent strain capable of disseminated infection. A careful history of illness in family members can suggest the source of the infant's disease (e.g., respiratory viruses, skin infections, prolonged illness with coughing).

Conversely, an infant can be a source of infection for household contacts. An infant with congenital rubella syndrome can shed virus for many months and is a significant source of infection for susceptible close contacts. The same is true for an infant with vesicular lesions of herpes simplex or a syphilitic infant with rhinitis or skin rash.

### Infections That Indicate Underlying Abnormalities

Infection may serve as a first clue indicating an underlying anatomic, metabolic, or immune system abnormality. Infants with galactosemia, iron overload, chronic granulomatous disease, and leukocyte adhesion defects are susceptible to certain invasive bacterial infections. Genitourinary infection in the first months of life can suggest an anatomic or a physiologic defect of the urinary tract. Similarly, otitis media in the first month of life may be an indication of a midline defect of the palate or a eustachian tube dysfunction. Meningitis caused by agents that are less invasive (e.g., coagulase-negative staphylococci) can be a clue to the presence of a dermoid sinus tract to the intradural space. In infants with underlying humoral immune defects, systemic infections may not develop until passively acquired maternal antibody has dissipated. Because the half-life of IgG is about 3 weeks, such infections are likely to occur after 3 months of age.

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