Neonatal Infections

Pathophysiology, Diagnosis, and Management

Joseph B. Cantey
Editor

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Preface

If pressed, those of us in the medical profession who are fortunate enough to care for children can produce a variety of reasons why we picked this particular field. If you ask enough people—or read enough personal statements—a few themes recur. Children are rarely to blame for their condition, the odd swallowed quarter aside. Children, by and large, get better over time. And the chance to have an early impact on a long, meaningful, productive life is immeasurably valuable. Neonates are the quintessential pediatric patients—they literally have their entire lives in front of them. All they did to acquire their disease was be born. Too often, though, these infants are born with or soon acquire infection—unwanted stowaway pathogens that these infants neither invited nor deserve. Timely recognition and treatment of these infections can have a major impact on infant survival and quality of life.

Neonatal Infections: Pathophysiology, Diagnosis, and Management is intended as a quick reference guide for the busy clinician caring for newborns and young infants, whether in the nursery, the neonatal intensive care unit, the ward, or the clinic. It covers infections acquired during birth or while in the hospital (Part I) as well as congenital infections (Part II). Summary chapters regarding prevention strategies, including infection control, outbreak management, antibiotic stewardship, and immunizations, are also included (Part III). *Neonatal Infections* is intended to be concise yet thorough and as visual as possible. I am extremely thankful to all of the authors who contributed their time and expertise to this effort. If you find this text useful, as I hope you will, it is because of them.

I am indebted to so many teachers, mentors, and friends who helped me through my training. To Julia McMillan, my residency director at Johns Hopkins—thank you for convincing me to pursue pediatric infectious diseases. To George McCracken, thank you for offering me a fellowship spot in the parking lot of Love Field in Dallas all those years ago. To Pablo J. Sánchez, thank you for being a patient, considerate, wonderful mentor and for convincing me to add a neonatology fellowship—it was just crazy enough to work! Most importantly, thank you to my wife, Leticia Shanley. You are the best pediatrician I know, and without your unwavering support I would be personally and professionally adrift.

And to you, reader—thank you for taking care of newborns. This book is for you… and them.

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J. B. Cantey

Contents

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Part I

Perinatal Infections

Early-Onset Sepsis

Susan A. Lee

Epidemiology

Sepsis is a systemic condition that includes infection of a sterile site with concomitant signs of illness [1]. Blood, urine, and cerebrospinal fluid (CSF) are most commonly evaluated, but other normally sterile sites (e.g., peritoneal, pleural, pericardial, synovial, bone) can also be infected. Neonatal sepsis can be classified by age of onset and timing of the sepsis episode (Table 1). The etiology and management of EOS are distinct from that of late-onset sepsis, which is discussed in detail in chapter "Late-Onset Sepsis."

In the United States, the overall rate of early-onset sepsis is approximately 0.8–1 per 1000 live births [2, 3]. GBS accounts for the greatest proportion of EOS cases (35–40%), followed by *E. coli*. GBS is more common among term infants; *E. coli* accounts for a greater proportion of EOS among preterm infants. However, a wide variety of organisms are capable of causing EOS. *Listeria monocytogenes* has become less common, accounting for <1% of EOS cases.

Risks for EOS include both maternal and neonatal factors (Box 1):

Maternal risk factors. The leading risk factor for EOS is chorioamnionitis. Chorioamnionitis is defined as an intra-amniotic infection that typically results from ruptured membranes allowing for microbial invasion [4]. Approximately 40% of infants with EOS are born to mothers with chorioamnionitis [2, 3]. Chorioamnionitis can be diagnosed clinically or with histopathology, although histopathology is generally not available in time to inform clinical decisions [5]. The duration of rupture

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Table 1 Definitions of early-onset and late-onset sepsis in neonates

	Early-onset sepsis	Late-onset sepsis
Etiology	~40% GBS ~30% *E. coli* ~30% other	1. Coagulase-negative *Staphylococcus* 2. *Staphylococcus aureus* 3. *E. coli* and other gram-negatives 4. GBS and other gram-positives 5. *Candida*
Age of onset	Age ≤ 72 h	Age > 72 h
Time of acquisition	Before or during delivery	After delivery
Mode of acquisition	Perinatal (mother-to-infant transmission)	Postnatal (acquired from hospital environment and community)
Clinical findings	Rapid onset Systemic disease more common than focal infection Bacteremia/pneumonia common	Onset may be slower or fulminant Focal infection (e.g., meningitis, osteomyelitis, urinary tract infection) more likely

Box 1 Risk Factors for Early-Onset Sepsis

Maternal

- Chorioamnionitis
- Intrapartum fever (without chorioamnionitis diagnosis)
- Prolonged rupture of membranes
- Colonization with GBS
- Inadequate intrapartum antibiotic prophylaxis

Infant

- Prematurity
- Low birth weight
- Low Apgar scores
- Need for endotracheal intubation

of membranes is also associated with increased risk for sepsis, largely due to the development of chorioamnionitis. However, prolonged rupture—defined as ≥18 h—is independently associated with increased risk even in the absence of chorioamnionitis.

Infant risk factors. The most important infant characteristic is the degree of prematurity. EOS rates are inversely proportional to gestational age and birth weight, with the highest incidence occurring in the smallest infants.

As discussed below, risk calculators use the presence or absence of these risk factors along with the infant's clinical status to determine the need for evaluation and treatment for EOS [6].

Pathogenesis

Early-onset sepsis can occur one of two ways:

1. In utero infection usually results from ascending bacteria reaching the amniotic fluid and subsequently being aspirated or swallowed by the fetus. Many bacteria, including GBS and *E. coli*, have attachment proteins that allow them to ascend from the birth canal to the amnion. Rupture of membranes facilitates this process by removing a major physical barrier between the fetus and the organisms, but bacteria can invade even with intact membranes. Organisms aspirated in utero cause pneumonia or systemic infection at or shortly after birth. Of note, transplacental transmission of GBS and *E. coli* are rare, but this is the primary route for *Listeria*.
2. Perinatal infection is acquired during the delivery process, either during descent or expulsion of the infant. The risk for perinatal disease is reduced—but not eliminated—by cesarean delivery. Organisms that attach to and colonize the infant during delivery can subsequently invade, with onset of symptoms usually within 24–36 h of delivery.

Clinical Findings

Clinical signs of EOS are very nonspecific (Table 2). Temperature instability (either fever or hypothermia) is the most common finding but is present in less than half of cases. In addition, many noninfectious conditions can mimic the clinical presentation of neonatal sepsis. Noninfectious respiratory conditions such as transient tachypnea of the newborn or respiratory distress syndrome and hypotension secondary to prematurity routinely lead to sepsis evaluations and empiric antibiotic therapy [7–9]. Given the nonspecific presentation and the adverse outcomes associated with delayed therapy, nursery providers should have a relatively low threshold for consideration of sepsis in an ill-appearing infant.

Early-onset sepsis is virtually always rapid in onset, with the vast majority of infants presenting either at delivery or within 24 h. EOS is generally a systemic illness; focal findings are most often limited to pulmonary involvement. Meningitis or other focal compartmental infections are possible but less common than with late-onset sepsis (see chapter “Late-Onset Sepsis”).

The mortality of EOS is approximately 15%; the majority of deaths occur by age 3 days [2, 3]. The case fatality rate of EOS is inversely related to the gestational age. Among survivors of EOS, morbidity is usually limited to those with early-onset meningitis or those who require prolonged mechanical ventilation due to sepsis with a concomitant increased risk for bronchopulmonary dysplasia.

Table 2 Clinical findings of neonatal sepsis

System	Sign
Systemic	• Hyperthermia • Hypothermia • Temperature instability
Pulmonary	• Tachypnea • Grunting • Retractions or nasal flaring
Neurologic	• Apnea • Irritability • Lethargy • Seizures • Hypotonia • Full or bulging fontanelle
Cardiovascular	• Tachycardia • Bradycardia • Hypotension • Poor perfusion • Cyanosis • Pallor
Gastrointestinal	• Poor feeding • Jaundice • Abdominal distention or ileus • Vomiting • Hepatomegaly • Diarrhea
Other	• Petechiae • Purpura • Coagulopathy

Diagnosis

The gold standard to diagnose sepsis is blood culture. A minimum of 1 mL of blood should be obtained [10]. Since EOS is a systemic illness that presents with bacteremia, typically only blood cultures are required when EOS is suspected. This is in contrast to late-onset sepsis, in which sampling of other sites (urine, CSF) is routinely indicated. However, CSF should be obtained for culture and cytology if signs of central nervous system involvement are present (e.g., apnea, seizures) or when blood cultures turn positive. Urine cultures are not indicated.

Non-culture-based ancillary testing, such as complete blood counts with differential, C-reactive protein, procalcitonin, and others, has good negative predictive value but limited positive predictive value. If used, ancillary testing should be used to reassure providers when the infant appears ill, but cultures are sterile. However, abnormal values in an otherwise well-appearing neonate should not prompt initiation or continuation of empiric antibiotic therapy [11].

There are several guidelines to help guide decisions regarding which infants to test and empirically treat for early-onset sepsis. Unquestionably, ill-appearing

Table 3 American Academy of Pediatrics 2012 recommendations for management of infants with suspected early-onset sepsis

Sepsis evaluation	All ill-appearing infants Well-appearing infants IF • Chorioamnionitis-exposed • <37 weeks and either prolonged rupture of membranes or inadequate intrapartum antibiotic prophylaxis
Diagnosis	Blood: Culture of ≥1 mL CSF: Not routinely indicated[a] Urine: Not indicated Ancillary tests[b]: Not routinely indicated but may provide additional negative predictive value
Treatment	Ampicillin and gentamicin Cefotaxime should be restricted to infants with suspected or proven meningitis with gram-negative organism

Adapted from reference 10. *CSF* cerebrospinal fluid
[a]CSF should be obtained if infant has overt signs of central nervous system involvement, if blood cultures identify a pathogen, or those who are critically ill or strongly suspected of having sepsis
[b]White blood cell counts with differential, c-reactive protein, procalcitonin, etc.

infants should be evaluated. For well-appearing infants, the current American Academy of Pediatrics recommendations use maternal and infant-risk factors to determine need for cultures and treatment (Table 3) [10].

Sepsis calculators are multivariable prediction models that estimate the risk of EOS among late preterm and term neonates based on objective data and the neonate's clinical status. This method has been prospectively validated and significantly reduces the number of neonates who require sepsis evaluations and empirical antibiotic therapy relative to existing guidelines without adversely affecting outcomes [6]. However, sepsis calculators have not yet been widely adopted or applied to more preterm infants.

Treatment

Empiric therapy. Ampicillin and gentamicin remain the primary empiric therapy for early-onset sepsis. GBS remains universally susceptible to penicillin, and gentamicin provides good coverage for *E. coli* and other gram-negative causes of EOS. The proportion of ampicillin-resistant *E. coli* has increased markedly over the past several decades, but aminoglycoside resistance has not [12–14]. In addition, the rise in cephalosporin resistance and extended-spectrum-beta-lactamase-producing gram-negative organisms has outpaced aminoglycoside resistance [15, 16]. Therefore, third- and fourth-generation cephalosporins should be reserved for suspected or proven gram-negative meningitis, as gentamicin does not achieve sufficient concentrations in the CSF. Empiric therapy can be discontinued as early as 24–36 h if blood cultures remain sterile.

Definitive therapy. When a pathogen is recovered, treatment should be altered to provide effective coverage with the narrowest possible agent or agents. The use of

two active agents to treat a given organism has not been shown to be beneficial in neonates and is not recommended under usual circumstances [17]. However, when gram-negative rods are identified from the blood of a critically ill infant (e.g., shock, acute respiratory failure), the use of a second agent from a different antibiotic class (e.g., piperacillin/tazobactam and gentamicin) will increase the likelihood that at least one of the agents has activity against the organism and should be considered. Once the speciation and susceptibility of the pathogen is known, therapy should be narrowed to a single agent. The optimal duration of therapy for early-onset sepsis has not been well studied. Treatment recommendations vary by organism and by compartment; gram-negatives are generally treated with longer durations than gram-positive organisms; meningitis is treated for longer than bacteremia alone. At minimum, antibiotics should be continued until cultures are sterile, and the neonate shows clinical recovery [18].

Adjunctive therapy. Currently, adjunctive therapies are not recommended in the treatment of early-onset sepsis. Neutropenia is associated with poor prognosis and mortality in neonatal sepsis. However, studies of therapies aimed at increasing neutrophil concentration—including granulocyte transfusions, granulocyte/macrophage colony-stimulating factor, pentoxifylline, and intravenous immune globulin—have had mixed results [19–22]. Currently, adjunctive therapies are not recommended in the treatment of early-onset sepsis; additional research is required to determine the potential benefit of these strategies.

Prevention

Prevention of EOS requires multiple strategies. Since GBS accounts for the greatest share of cases, prevention of GBS is a priority. Universal screening of pregnant women for GBS colonization and intrapartum antibiotic prophylaxis for colonized women has dramatically reduced the incidence of GBS EOS to the point where late-onset infection (see chapter "Late-Onset Sepsis") is more common [23]. The majority of EOS cases occur when screening is missed or intrapartum antibiotic therapy is not given in time [24]. Optimizing systems will prevent some, but not all, EOS due to GBS [25]. Ultimately, a GBS vaccine might have the most impact on neonatal sepsis rates worldwide [26]. In 2018, the World Health Organization in 2018 issued a statement with research priorities and technical requirements in order to facilitate creation and implementation of an effective GBS vaccine [27].

Another major aspect of prevention of EOS is reduction in preterm deliveries. Prematurity is a major risk factor for EOS, second only to chorioamnionitis. Strategies that reduce preterm delivery, such as prevention of teen pregnancy, comprehensive prenatal care, smoking and drug cessation, 17-hydroxyprogesterone prophylaxis for women with a history of a preterm delivery, and others, would also be expected to reduce early-onset sepsis rates, particularly cases due to *E. coli* and the gram-negatives that are more common among preterm infants [3, 28].

References

1. Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770–80.
2. Schrag SJ, Farley MM, Petit S, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. Pediatrics. 2016;138:e20162013.
3. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B streptococcal and *E coli* disease continues. Pediatrics. 2011;127:817–26.
4. Higgins RD, Saade G, Polin RA, et al. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. Obstet Gynecol. 2016;127:426–36.
5. Wortham JM, Hansen NI, Schrag SJ, et al. Chorioamnionitis and culture-confirmed, early-onset neonatal infections. Pediatrics. 2016;137:e20152323.
6. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr. 2017;171:365–71.
7. Weintraub AS, Cadet CT, Perez R, et al. Antibiotic use in newborns with transient tachypnea of the newborn. Neonatology. 2013;103:235–40.
8. Shani L, Weitzman D, Melamed R, et al. Risk factors for early sepsis in very low birth weight neonates with respiratory distress syndrome. Acta Paediatr. 2008;97:12–5.
9. Dempsey EM, Barrington KJ. Diagnostic criteria and therapeutic interventions for the hypotensive very low birth weight infant. J Perinatol. 2006;26:677–81.
10. Polin RA. Committee on fetus and newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129:1006–15.
11. Cantey JB, Baird SD. Ending the culture of culture-negative sepsis in the neonatal ICU. Pediatrics. 2017;140:e2017044.
12. Lu Q, Zhou M, Tu Y, Yao Y, Yu J, Cheng S. Pathogen and antimicrobial resistance profiles of culture-proven neonatal sepsis in Southwest China, 1990-2014. J Paediatr Child Health. 2016;52:939–43.
13. Bizzaro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. Pediatrics. 2008;121:689–96.
14. Heideking M, Lander F, Hufnagel M, et al. Antibiotic susceptibility profiles of neonatal invasive isolates of *Escherichia coli* from a 2-year nationwide surveillance study in Germany, 2009-10. Eur J Clin Microbiol Infect Dis. 2013;32:1221–3.
15. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics – systematic review and meta-analysis. Arch Dis Child. 2013;98:146–54.
16. Greenhow TL, Cantey JB. The disputed champion: ampicillin and gentamicin for febrile young infants. Hosp Pediatr. 2017; Available online Jul 20 2017.
17. Johnson SJ, Ernst EJ, Moores KG. Is double coverage of gram-negative organisms necessary? Am J Heatlh Syst Pharm. 2011;68:119–24.
18. Stockmann C, Spigarelli MG, Campbell SC, et al. Considerations in the pharmacologic treatment and prevention of neonatal sepsis. Pediatr Drugs. 2014;16:67–81.
19. Mohan P, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropaenia. Cochrane Database Syst Rev. 2003;4:CD003956.
20. INIS Collaborative Group, Brocklehurst P, Farrell B, et al. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med. 2011;265:1201–11.
21. Pammi M, Haque KN. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Database Syst Rev. 2015;3:CD004205.
22. Carr R, Brocklehurst P, Dore CJ, Modi N. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicenter, randomised controlled trial. Lancet. 2009;373:226–33.

23. Clifford V, Garland SM, Grimwood K. Prevention of neonatal group B streptococcus disease in the 21st century. J Paediatr Child Health. 2012;48:808–15.
24. Vergnano S, Embleton N, Collinson A, Menson E, Russell AB, Heath P. Missed opportunities for preventing group B streptococcus infection. Arch Dis Child Fetal Neonatal Ed. 2010;95:F72–3.
25. Van Dyke MK, Phares CR, Lynfield R, et al. Evaluation of universal antenatal screening for group B streptococcus. N Engl J Med. 2009;360:2626–36.
26. Baker CJ. Vaccine prevention of group B streptococcal disease. Pediatr Ann. 1993;22:711–4.
27. Vekemans J, Moorthy V, Friede M, et al. Maternal immunization against Group B streptococcus: World Health Organization research and development technological roadmap and preferred product characteristics. Vaccine. 2018; Available online Feb 2 2018.
28. Shapiro-Mendoza CK, Barfield WD, Henderson Z, et al. CDC grand rounds: public health strategies to prevent preterm birth. MMWR Morb Mortal Wkly Rep. 2016;65:826–30.

Late-Onset Sepsis

Niraj Vora

Epidemiology

Late-onset sepsis (LOS) is defined as infection of a sterile site (e.g., blood, urine, cerebrospinal fluid [CSF]) after age 72 h [1, 2]. The only exception is that the current definition of late-onset group B *Streptococcus* (GBS) infection begins after age 7 days, with the first week of life being considered early-onset sepsis [3]. The primary risk factor for LOS is prematurity; the most preterm infants are at highest risk for LOS. Approximately 25–30% of extremely low birth weight (ELBW, <1000 g) infants will have LOS during their NICU stay [1, 4]. This number decreases to about 10–15% for infants 1001–1500 g birth weight and to <2% for infants >1500 g birth weight [2, 5, 6].

The organisms responsible for LOS vary over time and between locations. Yale New Haven Hospital has produced a series of reports describing the changing patterns of organisms responsible for LOS from 1928 to 2003 showing the evolution of LOS over almost a century [7–12]. Prior to introduction of antibiotics in the 1930s and 1940s, gram-positive cocci, including *Staphylococcus aureus* and *Streptococcus pyogenes* (group A strep), were responsible for the majority of neonatal sepsis. Once antibiotics were introduced, gram-negative enteric bacilli such as *Escherichia coli* became the leading cause of serious infections in newborn.

However, over the last several decades, coagulase-negative *Staphylococcus* (CoNS) species have emerged as the most commonly identified organism in LOS (Table 1). This may be due to increased survival of the most preterm infants and a concomitant increase in reliance on indwelling catheters and other medical devices. Other gram-positives such as *S. aureus*, GBS, *Enterococcus*, and others; gram-negatives including *E. coli* and other coliforms; *Pseudomonas*, *Serratia*, and others;

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Table 1 Organisms associated with late-onset sepsis and their approximate prevalence

Organism	Frequency
Gram-positives	75%
Coagulase-negative staphylococci	60–70%
Staphylococcus aureus[a]	10%
Group B streptococci	3–5%
Enterococcus sp.	3–5%
Group A streptococci	1–2%
Gram-negatives	20%
Escherichia coli	5–7% each
Klebsiella	
Enterobacter	
Citrobacter	1–2% each
Pseudomonas	
Serratia	
Others	
Candida sp.	5%

[a]In the United States, approximately 75% of isolates are methicillin-susceptible and 25% are methicillin-resistant, but proportion varies between neonatal intensive care units

and fungal species (primarily *Candida*; see chapter "*Candida*") are frequently encountered causes of LOS [1–6].

Pathogenesis

LOS has a distinct pathogenesis compared with early-onset sepsis (Table 2). In contrast to early-onset sepsis, which is acquired during the perinatal period (see chapter "Early-Onset Sepsis") and is caused by organisms common to the delivery tract such as GBS or *E. coli*, LOS is caused by acquisition of pathogenic organisms during the postnatal period, colonization, and subsequent invasion [13]. These differences manifest as later presentation (hence the 72 h cutoff between early-onset and late-onset sepsis) and a broader range of causative organisms. Horizontal transfer of pathogenic bacteria on contaminated hands or medical equipment leads to either immediate invasion (e.g., if bacteria are infused in a contaminated infusion or procedure) or colonization of the skin, mucous membranes, or gastrointestinal tract. Colonized infants can then develop subsequent invasion either by autoinoculation (e.g., if their stool comes in contact with a central catheter hub) or translocation directly into the bloodstream [14]. Unsurprisingly, therefore, the causative organism of LOS is often one that the infant is already colonized with [15].

Once an organism reaches the bloodstream, it can cause a nonspecific sepsis syndrome or it can localize to one or more body sites and cause focal infection. In addition, some cases of LOS are caused by direct infection of a body site without preceding bacteremia; examples include ascending urinary tract infection, direct

Table 2 Early-onset versus late-onset sepsis in neonates and young infants

	Early-onset sepsis	Late-onset sepsis
Etiology	~40% GBS ~30% *E. coli* ~30% other	1. Coagulase-negative *Staphylococcus* 2. *Staphylococcus aureus* 3. *E. coli* and other gram-negatives 4. GBS and other gram-positives 5. *Candida*
Age of onset	Age ≤ 72 h	Age > 72 h
Time of acquisition	Before or during delivery	After delivery
Mode of acquisition	Perinatal (mother-to-infant transmission)	Postnatal (acquired from hospital environment and community)
Clinical findings	Rapid onset Systemic disease more common than focal infection Bacteremia/pneumonia common	Onset may be slower or fulminant Focal infection (e.g., meningitis, osteomyelitis, urinary tract infection) more likely

inoculation of skin or soft tissue during phlebotomy, or ventilator-associated pneumonia.

Clinical Findings

The initial signs of LOS are often subtle and nonspecific such as decreased activity, poor feeding, lethargy, apnea, fever or hypothermia, respiratory distress, and jaundice [16, 17]. As a result, sepsis evaluations are often performed when clinical changes are detected, since virtually every finding has been associated with sepsis. In an effort to improve specificity, clinical prediction models that use trends in vital signs, propensity scores, or laboratory values have been used with varying degrees of success [18–20]. In some cases, more specific localizing findings may be present (Table 3). For example, osteomyelitis may present with pseudoparalysis or irritability with movement of the affected limb. Skin and soft tissue infections can present with skin changes or swelling. Meningitis may present with seizures. However, focal infection is possible even when localizing signs are absent [21].

Diagnosis

The diagnosis of LOS based solely on clinical signs is not possible due to the nonspecific nature of the presentation [22]. The gold standard for diagnosis is isolation of a pathogen from a normally sterile site (blood, CSF, urine, pleural or peritoneal fluid, bone or joint aspirate) [23]. For non-sterile sites such as the upper respiratory tract or the skin, culture remains critical but should be used in conjunction with clinical findings and pretest probability of sepsis.

Table 3 Clinical findings, approach to diagnosis, and treatment of common systemic and focal manifestations of late-onset sepsis

Condition	Clinical findings	Diagnosis	Antibiotic treatment[a]
Bacteremia	• Decreased activity • Poor feeding • Lethargy • Hypotension • Apnea, bradycardia, or desaturations • Temperature instability • Respiratory distress or failure • Jaundice • Leukopenia or leukocytosis • Thrombocytopenia • Anemia	• Blood culture	7–10 days
Meningitis	• Similar to bacteremia AND: • Seizures • Lethargy/unresponsiveness • Bulging fontanelle • Nuchal rigidity	• Cerebrospinal fluid culture	14–21 days
Urinary tract infection	• Similar to bacteremia	• Urine culture	7–10 days
Osteomyelitis or septic arthritis	• Decreased movement • Pseudoparalysis • Irritability with passive movement • Swelling or redness	• Blood culture • Bone or joint fluid culture • Radiographic changes	21–42 days
Pneumonia	• Respiratory deterioration or failure • New findings on chest radiographs • Changes in sputum	• Endotracheal tube culture[b] • Radiographic changes	5–7 days
Skin and soft tissue	• Redness • Swelling • Drainage • Induration or fluctuance	• Wound culture[b]	Drainage procedure and antibiotics until clinical findings resolve (5–7 days)

[a]Treatment durations are guides only; duration of therapy should take into consideration infant's clinical status, response to therapy, persistence of any infected material, etc.
[b]Culture of non-sterile sites such as upper airway and skin should be interpreted with caution

Cultures

Blood culture. A blood sample of at least 1 mL ensures excellent sensitivity [24]. Sending two cultures from two different sites will help to differentiate contaminants (e.g., if CoNS grows in one culture but not the other) but requires a second blood draw and does not improve sensitivity compared to an equal volume of blood obtained from a single site. Of note, *Candida* will grow in regular blood culture media; specific fungal cultures are not required.

Urine culture. Urine culture should be obtained in all cases of suspected LOS; 5–10% of LOS cases are due to isolated urinary tract infection [25, 26]. Urine should be obtained by catheterization or suprapubic aspiration; bag specimens are frequently contaminated. The value of urinalysis in preterm infants has not been well studied, but the absence of leukocyte esterase, nitrites, or pyuria does not preclude the possibility of UTI in preterm infants [27].

Cerebrospinal fluid culture. Lumbar puncture for CSF analysis and culture is critical for infants with suspected LOS. Approximately 5% of infants with LOS have associated meningitis, and one-third of infants with meningitis have sterile blood cultures [21, 28]. Therefore, if blood cultures alone are utilized, cases of meningitis will inevitably be missed [29, 30]. Meningitis requires different antimicrobial therapy and a longer duration of treatment than other LOS, and therefore determining the presence or absence of meningitis is a critical step in the evaluation of LOS.

Endotracheal tube cultures. Endotracheal tubes are rapidly colonized by normal upper airway flora shortly after placement [31]. Therefore, detection of bacteria from endotracheal tube culture may represent either colonization or infection. When the pretest probability of lower respiratory tract disease is low (e.g., when another source of infection is likely or in the absence of radiographic or clinical changes), positive tracheal cultures are virtually worthless. Therefore, endotracheal tube cultures should only be considered when both clinical and radiographic findings are suggestive of pneumonia. In contrast, bronchoalveolar lavage specimens from the lower respiratory tract would be expected to be sterile and therefore are more helpful. However, bronchoalveolar lavage is not routinely available for preterm infants in most centers.

Skin cultures. As with the upper airway, the skin is not sterile. Normal cutaneous flora includes CoNS, *Corynebacterium* and other diphtheroids, and other gram-positives. Colonization with potential pathogens including group A streptococci, *S. aureus*, and *Candida* can also be identified and must be differentiated from active infection [32]. Interpretation of culture results should be done in consideration of the infant's clinical status.

Other cultures. Other sterile sites can be sampled for culture under specific situations. Infants with suspected bone or joint infections can undergo percutaneous aspiration of bone or synovial fluid [33]. Peritoneal fluid can be obtained during drain placement or laparotomy. Pericardial or pleural fluid may be obtained during drainage procedures. In general, fluid should be sent for cytology, gram stain, and culture whenever infection is suspected; providing as much detail as possible to the microbiology lab regarding patient history and sample source will ensure that the cultures are processed appropriately.

Non-culture-Based Microbiologic Tests

PCR and nucleic acid-based testing, rapid antigen detection, direct fluorescent antibody testing, and other similar tests may be available. These tests vary in terms of

sensitivity and specificity and at present do not preclude the need for bacterial cultures. PCR in particular is becoming increasingly prevalent. Benefits to PCR include its impressive sensitivity and rapid turnaround time. However, PCR testing of blood or spinal fluid has been associated with false-positive results. PCR will also detect dead bacteria that has been previously treated or resolved, which may prompt additional, unnecessary antibiotic therapy [34]. As PCR is increasingly used and studied, our understanding of how it fits into the clinical management of these infants will grow.

Ancillary Laboratory Testing

Ancillary lab tests such as white blood cell counts and differentials, C-reactive protein, procalcitonin, and others are often used to determine an infant's risk for infection. Although these tests have been relatively well-studied for suspected early-onset sepsis, validation for late-onset sepsis has not been as robust. In most cases, the normative values for age <72 h have been extrapolated out to older ages. The evidence suggests that these ancillary tests have reasonably good negative predictive value but poor positive predictive value [35, 36]. This means that normal ancillary testing will support discontinuation of antibiotic therapy in an infant with sterile culture results. However, abnormal laboratory tests should not be used as a reason to extend therapy for children with sterile culture results, particularly if their clinical findings are resolved or improving.

Treatment

Empiric Therapy

Since sepsis has significant clinical implications and can progress rapidly, empiric antimicrobial therapy should be initiated promptly when LOS is suspected. An understanding of local epidemiology (for the patient in question, within the nursery, and within the hospital or community) is essential in order to choose appropriate empiric therapy. In general, empiric therapy for LOS should include coverage against common hospital-acquired organisms such as *S. aureus* and gram-negative enteric bacilli (Fig. 1). The use of empiric antifungal therapy depends on the incidence of *Candida* in the nursery, the gestational age of the infant, and severity of presentation (see chapter "*Candida*").

Default empiric therapy with a semisynthetic penicillin (e.g., oxacillin, nafcillin) will provide coverage against methicillin-susceptible *S. aureus*, GBS, and group A *Streptococcus*. An aminoglycoside (e.g., gentamicin, tobramycin) should be used in combination to provide coverage against most gram-negative organisms. Other antibiotics should be used in certain situations:

Vancomycin. Although CoNS is the most common cause of LOS, it is not associated with mortality or significant morbidity, and therefore empiric vancomycin can

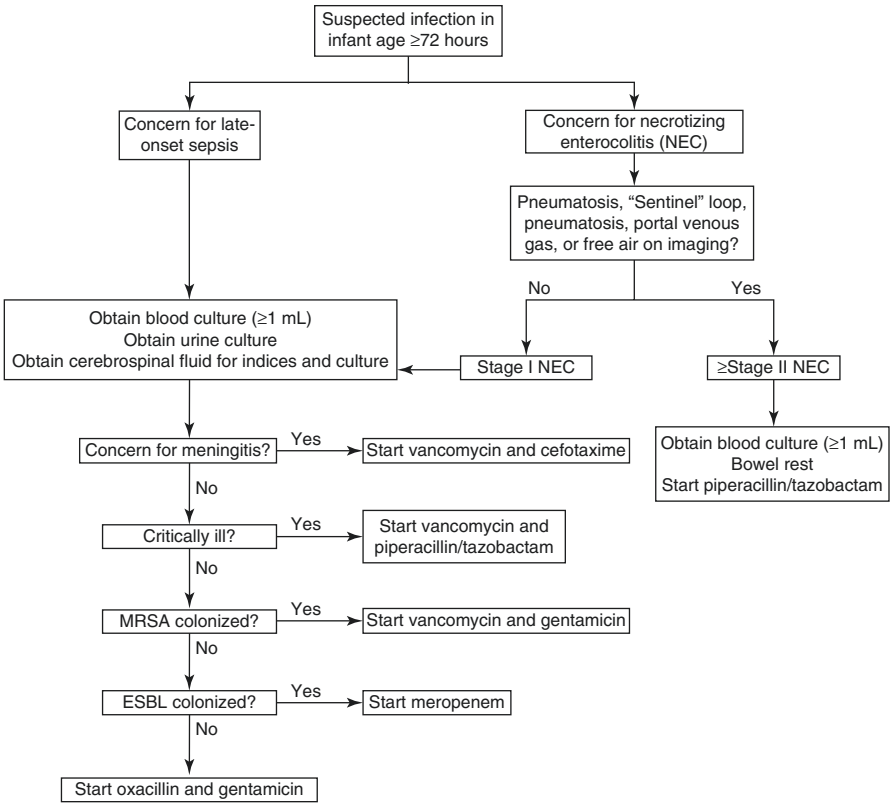

Fig. 1 Approach to suspected late-onset sepsis in the neonatal intensive care unit. For infants with suspected late-onset sepsis or stage I necrotizing enterocolitis (NEC), which has significant overlap with late-onset sepsis, cultures of blood, urine, and cerebrospinal fluid should be obtained. *Oxacillin* (or a similar semisynthetic penicillin) and *gentamicin* (or another aminoglycoside) should then be started promptly in most cases. Exceptions include (1) when meningitis is suspected based on clinical findings or cerebrospinal fluid indices (vancomycin and cefotaxime), (2) if the infant is critically ill (generally defined as new requirement for pressors, disseminated intravascular coagulation, or acute and severe respiratory failure; vancomycin and piperacillin/tazobactam), and (3) if the infant is known to be colonized with methicillin-resistant *Staphylococcus aureus* (vancomycin in lieu of oxacillin) or an extended-spectrum beta-lactamase- (ESBL) producing gram-negative organism (meropenem in lieu of oxacillin and gentamicin). Note that if NEC is confirmed (stage II or higher), then cerebrospinal fluid and urine cultures are not required and piperacillin/tazobactam should be started once blood culture is obtained

be withheld until CoNS infection is confirmed [37]. However, vancomycin should be used empirically when an infant who is known to be colonized with methicillin-resistant *S. aureus* has suspected LOS or when an infant with suspected LOS is critically ill (e.g., hypotensive, acute respiratory failure, DIC). Vancomycin should be used for definitive treatment when required, usually for CoNS (which is usually resistant to oxacillin) and methicillin-resistant *S. aureus* [38].

Cephalosporins. Third- and fourth-generation cephalosporins (e.g., cefotaxime, ceftriaxone, cefepime) are associated with increased antibiotic resistance and increased risk for *Candida* in the neonatal intensive care unit [39, 40]. Therefore, their use should be restricted to three clinical situations:

1. Treatment of suspected or proven gonococcal disease (see chapter "Neonatal Conjunctivitis")
2. Treatment of suspected or proven gram-negative meningitis
3. Treatment of early- or late-onset sepsis among infants with significant renal dysfunction for whom aminoglycosides are contraindicated

Piperacillin/tazobactam. In addition to gram-negative coverage, piperacillin/tazobactam also provides good activity against *Pseudomonas* and anaerobes. It can be used for the treatment of proven or suspected necrotizing enterocolitis (see chapter "Necrotizing Enterocolitis") or as a first- or second-line agent for critically ill infants with suspected LOS. However, it is unnecessarily broad for routine empiric use compared with aminoglycosides.

Meropenem. Carbapenems such as meropenem should be reserved for infections with extended-spectrum beta-lactamase-producing gram-negative organisms.

Definitive Therapy

If a pathogen is identified in culture, empiric therapy should be converted to definitive therapy by choosing the narrowest effective agent that will reach the infected compartment(s). Since the optimal duration of therapy has not been well established for LOS, treatment durations vary widely (Table 3). Source control is critically important in treating LOS; infected catheters or tubes should be removed whenever possible, and purulent collections should be drained.

Prevention

Since the majority of LOS episodes are associated with nosocomial transmission of and infection with pathogenic bacteria, prevention is largely centered around appropriate infection control practices. Consistent hand hygiene practices are the single most important aspect of prevention in the NICU setting [41]. Meticulous care practices during insertion and maintenance of indwelling hardware, particularly central venous catheters, can markedly reduce the risk for late-onset bacteremia (see chapter "Principles of Infection Prevention in the Nursery") [42]. Avoiding placement of catheters and removing them as soon as they are no longer needed is critical.

Other well-studied strategies include the increased use of human milk and antibiotic stewardship programs (see chapter "Antibiotic Stewardship"). There has been increasing attention paid to the use of probiotic agents for the prevention of sepsis or necrotizing enterocolitis; early studies appear promising [43].

References

1. Greenberg RG, Kandefer S, Do BT, et al. Late-onset sepsis in extremely premature infants: 2000-2011. Pediatr Infect Dis J. 2017;36:774–9.
2. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110:285–91.
3. Verani JR, McGee L, Schrag SJ, et al. Prevention of perinatal group B streptococcal disease – revised guidelines from the CDC, 2010. MMWR Recomm Rep. 2010;59:1–36.
4. Gowda H, Norton R, White A, Kandasamy Y. Late-onset neonatal sepsis – a 10-year review from North Queensland, Australia. Pediatr Infect Dis J. 2017;36:883–8.
5. Cailes B, Kortsalioudaki C, Buttery J, et al. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Arch Dis Child Fetal Neonatal Ed. 2017; Available online Dec 5 2017.
6. Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011;96:F9–14.
7. Dunham EC. Septicemia in the newborn. Am J Dis Child. 1933;45:229.
8. Nyhan WL, Fousek MD. Septicemia of the newborn. Pediatrics. 1958;22:268–78.
9. Gluck L, Wood HF, Fousek MD. Septicemia of the newborn. Pediatr Clin N Am. 1966;13:1131–48.
10. Freedman RM, Ingram DL, Cross I, et al. A half century of neonatal sepsis at Yale: 1928 to 1978. Am J Dis Child. 1981;35:140–4.
11. Gladstone IM, Ehrenkranz RA, Edberg SC, et al. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. Pediatr Infect Dis J. 1990;9:819–25.
12. Bizzarro MJ, Raskind C, Baltimore RS, et al. Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics. 2005;116:595–602.
13. Pammi M, Weisman LE. Late-onset sepsis in preterm infants: update on strategies for therapy and prevention. Expert Rev Anti-Infect Ther. 2015;13:487–504.
14. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed. 2015;100:F257–63.
15. Tarr PI, Warner BB. Gut bacteria and late-onset neonatal bloodstream infections in preterm infants. Semin Fetal Neonatal Med. 2016;21:388–93.
16. Das A, Shukla S, Rahman N, Gunzler D, Abughali N. Clinical indicators of late-onset sepsis workup in very low-birth-weight infants in the neonatal intensive care unit. Am J Perinatol. 2016;33:856–60.
17. Bekhof J, Reitsma JB, Kok JH, Van Straaten IH. Clinical signs to identify late-onset sepsis in preterm infants. Eur J Pediatr. 2013;172:501–8.
18. Okascharoen C, Hui C, Cairnie J, Morris AM, Kirpalani H. External validation of bedside prediction score for diagnosis of late-onset neonatal sepsis. J Perinatol. 2007;27:496–501.
19. Coggins SA, Weitkamp JH, Grunwald L, et al. Heart rate characteristic index monitoring for bloodstream infection in an NICU: a 3-year experience. Arch Dis Child Fetal Neonatal Ed. 2016;101:F329–32.
20. Chauhan N, Tiwari S, Jain U. Potential biomarkers for effective screening of neonatal sepsis infections: an overview. Microb Pathog. 2017;107:234–42.
21. Wu IH, Tsai MH, Lai MY, et al. Incidence, clinical features, and implications on outcomes of neonatal late-onset sepsis with concurrent infectious focus. BMC Infect Dis. 2017;17:465.
22. Fischer JE. Physicians' ability to diagnose sepsis in newborns and critically ill children. Pediatr Crit Care Med. 2005;6:S120–5.
23. Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770–80.
24. Schelonka RL, Chai MK, Yoder BA, et al. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996;129:275–8.
25. Mohseny AB, van Velze V, Steggerda SJ, et al. Late-onset sepsis due to urinary tract infection in very preterm neonates is not uncommon. Eur J Pediatr. 2018;177:33–8.

26. Visser VE, Hall RT. Urine culture in the evaluation of suspected neonatal sepsis. J Pediatr. 1979;94:635–8.
27. Utsch B, Klaus G. Urinalysis in children and adolescents. Dtsch Arztebl Int. 2014;111:617–26.
28. Isaacs D, Barfield C, Clothier T, et al. Late-onset infections of infants in neonatal units. J Paediatr Child Health. 1996;32:158–61.
29. Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. Pediatrics. 2004;113:1181–6.
30. Flidel-Rimon O, Leibovitz E, Eventov Friedman S, Juster-Reicher A, Shinwell ES. Is lumbar puncture required in every workup for suspected late-onset sepsis in neonates? Acta Paediatr. 2011;100:303–4.
31. Gibbs K, Holzman IR. Endotracheal tube: friend or foe? Bacteria, the endotracheal tube, and the impact of colonization and infection. Semin Perinatol. 2012;36:454–61.
32. Bertone SA, Fisher MC, Mortensen JE. Quantitative skin cultures at potential catheter sites in neonates. Infect Control Hosp Epidemiol. 1994;15:315–8.
33. Frederiksen B, Christiansen P, Knudsen FU. Acute osteomyelitis and septic arthritis in the neonate, risk factors and outcome. Eur J Pediatr. 1993;152:577–80.
34. Pammi M, Flores A, Leeflang M, Versalovic J. Molecular assays in the diagnosis of neonatal sepsis: a systematic review and meta-analysis. Pediatrics. 2011;128:e973–85.
35. Hedegaard SS, Wisborg K, Hvas AM. Diagnostic utility of biomarkers for neonatal sepsis – a systematic review. Infect Dis. 2015;47:117–24.
36. Bhandari V. Effective biomarkers for diagnosis of neonatal sepsis. J Pediatric Infect Dis Soc. 2014;3:234–45.
37. Cantey JB, Anderson KR, Kalagiri RR, Mallett LH. Morbidity and mortality of coagulase-negative staphylococcal sepsis in very-low-birth-weight infants. World J Pediatr. 2018; Available online Feb 25, 2018.
38. Chiu CH, Michelow IC, Cronin J, et al. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J. 2011;30:273–8.
39. de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. Lancet. 2000;355:973–8.
40. Cotten CM, McDonald S, Stoll B. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006;118:717–22.
41. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. J Hosp Infect. 2008;68:293–300.
42. Sinha AK, Murhy V, Nath P, Morris JK, Millar M. Prevention of late onset sepsis and central-line associated blood stream infection in preterm infants. Pediatr Infect Dis J. 2016;35:401–6.
43. Dermyshi E, Wang Y, Yan C, et al. The “golden age” of probiotics: a systematic review and meta-analysis of randomized and observational studies in preterm infants. Neonatology. 2017;112:9–23.

Necrotizing Enterocolitis

Sarah Henen and Jennifer Duchon

Epidemiology

The incidence of NEC varies greatly between NICUs, with an overall incidence of approximately 5% for all infants <32 weeks gestation [1]. The incidence increases as gestational age and birth weight decrease, with an incidence of approximately 12% in infants born between 501 and 750 g, and approximately 9% in infants with a birth weight of less than 1500 g [2]. However, full-term infants comprise 10% of NEC cases [3]. There does not appear to be a differential incidence by sex, and the role of race in NEC is unclear. Outbreaks of NEC have been described, lending support to bacterial or viral agents contributing to disease.

Pathogenesis

NEC is typically described as a multifactorial disease with many predisposing elements interacting with each other in a complex manner, making the contribution of individual risk factors difficult to assess. As well, most studies evaluating risk factors are retrospective, showing associations but not causation. Most unifying theories about the etiology of NEC involve a combination of abnormal inflammatory response (both systemically and in the gut environment), colonization of intestinal mucosa by pathogenic bacteria (dysbiosis), and abnormal vascular regulation in a vulnerable host with intestinal immaturity [3].

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Prematurity is the single most consistent risk factor for NEC, with the incidence of the disease inversely proportional to gestational age [2, 4, 5]. Low birth weight, independent of gestational age, has been cited as a risk factor, implying that prenatal factors that cause growth restriction can predispose the developing gut to be vulnerable to NEC [6, 7]. Other risk factors include infants born to mothers with chorioamnionitis, preterm premature rupture of membranes, and neonatal sepsis, all of which presumably increase risk by increasing inflammation [8]. Infants who have experienced hypotension have been shown to be at higher risk of NEC, and the association between NEC and a hemodynamically significant patent ductus arteriosus has been described, with the "steal" of blood flow from the ductus implicated in vascular compromise of the preterm intestine [9, 10].

Enteral feeding practices and use of medications, specifically antibiotics and histamine-2 (H2) antagonists, are well-established targets for interventions to prevent NEC.

Enteral feeding. Most infants who get NEC have been fed; however, most infants who are fed do not develop NEC. The optimal feeding strategy for preterm infants is unknown; the optimal rate of advancement, target volume, and composition of enteral feeds in infants at risk for NEC are unclear. Many studies clearly show the protective effect of human milk**,** and this has led to the extrapolation of formula use as a risk factor for NEC [11, 12]. Most authors would cite prolonged delay in initiation of feeds and exclusive use of formula in place of breast milk as risk factors for NEC. High osmolarity of feeds via the use of bovine fortification products and rapid advancement of feeds (>30 cc/kg/day) are felt to be associated with NEC; however, the optimal osmolar threshold and timing of feeding fortification and advancement to promote growth but mitigate NEC risk are unclear.

Antibiotic use. Several observational studies have shown and increased risk of NEC or death with prolonged (typically ≥5 days) duration of antibiotics in the early neonatal period. This association is now felt to be mediated by changes in the intestinal microbiome [13, 14]. These epidemiologic studies are being confirmed with the advent of techniques that allow rapid and detailed identification of the intestinal microbial community. Through amplification and sequencing of the 16S ribosomal RNA subunit DNA or whole-genome sequencing, the contribution of the neonatal microbiome to the development of NEC has become clear. Infants with NEC have been shown to have a higher predominance of gram-negative organisms and a decreased diversity of bacteria prior to disease onset [15].

H2 Antagonists. Infants receiving H2 blockers (e.g., ranitidine, cimetidine, famotidine) have shown an increased risk of NEC. The mechanism of this association is also likely mediated in part by the alterations in the gut microbiome as well through loss of the protective effect of lowered gastric pH [16, 17].

Packed Red Blood Cell (PRBC) Transfusion. NEC temporally related to PRBC transfusion is well described and often termed transfusion-associated acute gut injury. Although the mechanism of this association is not clear, both age of blood, changes in mesenteric vascular regulation during transfusion, and degree of anemia at transfusion have been implicated [18, 19].

Full-term infants who develop NEC have a unique risk factor profile, likely because NEC in these infants is due to different underlying processes. Intestinal anomalies such as gastroschisis or Hirschsprung's disease, cyanotic congenital heart disease, maternal cocaine use, perinatal asphyxia, and growth restriction have been linked to NEC in term and near-term infants. This risk factor profile suggests perinatal or congenital conditions which result in reduced blood flow to the neonatal intestine as an important consideration in older infants who develop NEC [20, 21].

Clinical Findings

The age at presentation of NEC is inversely proportional to gestational age. In the smallest infants, the median time to onset is approximately 20 days of life, corresponding to a post-menstrual age of 28–32 weeks, when patients are typically beginning the convalescent phase of extreme prematurity [22]. Full-term or late preterm infants typically present within the first week of life, again indicating the strong contribution of perinatal insults or congenital conditions.

Clinical signs. The initial stages of NEC are comprised of non-specific signs and symptoms which overlap with other conditions such as sepsis, apnea, or feeding intolerance. Increased episodes of apnea, temperature instability, decreased activity level, oliguria, as well as intestinal signs such as feeding intolerance and abdominal distention may be present. More specific local signs include abdominal tenderness and bloody stool; abdominal wall erythema and abdominal mass are specific signs of NEC but often difficult to discern [23, 24]. Infants may rapidly progress to severe systemic signs, such as hypotension, circulatory arrest, renal failure, or respiratory failure.

Laboratory signs. Abnormal lab indices include abnormal serum glucose, hyponatremia, leukopenia, neutropenia, thrombocytopenia, and accompanying anemia. Elevated inflammatory makers are typically present. Severely affected patients will show metabolic acidosis and associated hyperkalemia as well as disseminated intravascular coagulopathy (DIC) [25]. Elevated eosinophil count, when present, may be specific for NEC.

Radiographic signs. Pneumatosis intestinalis, or the projection of gas in the bowel wall as seen on X-ray, is the pathognomonic finding of NEC. Portal venous gas, which is an extension of this intraluminal air into the portal venous system, is also classic radiographic criterion of NEC. Infants who progress to intestinal perforation may display free intraperitoneal air on radiographs; this can be illustrated by the "football sign," an illumination of the falciform ligament by free intra-abdominal air. Other, less specific findings of NEC that may overlap with other conditions are fixed and/or dilated intestinal loops of bowel, bowel wall edema, and/or stacked loops of bowel with or without air fluid levels [23, 26]. Figure 1 shows radiographic examples of pneumatosis, portal venous gas, and perforation.

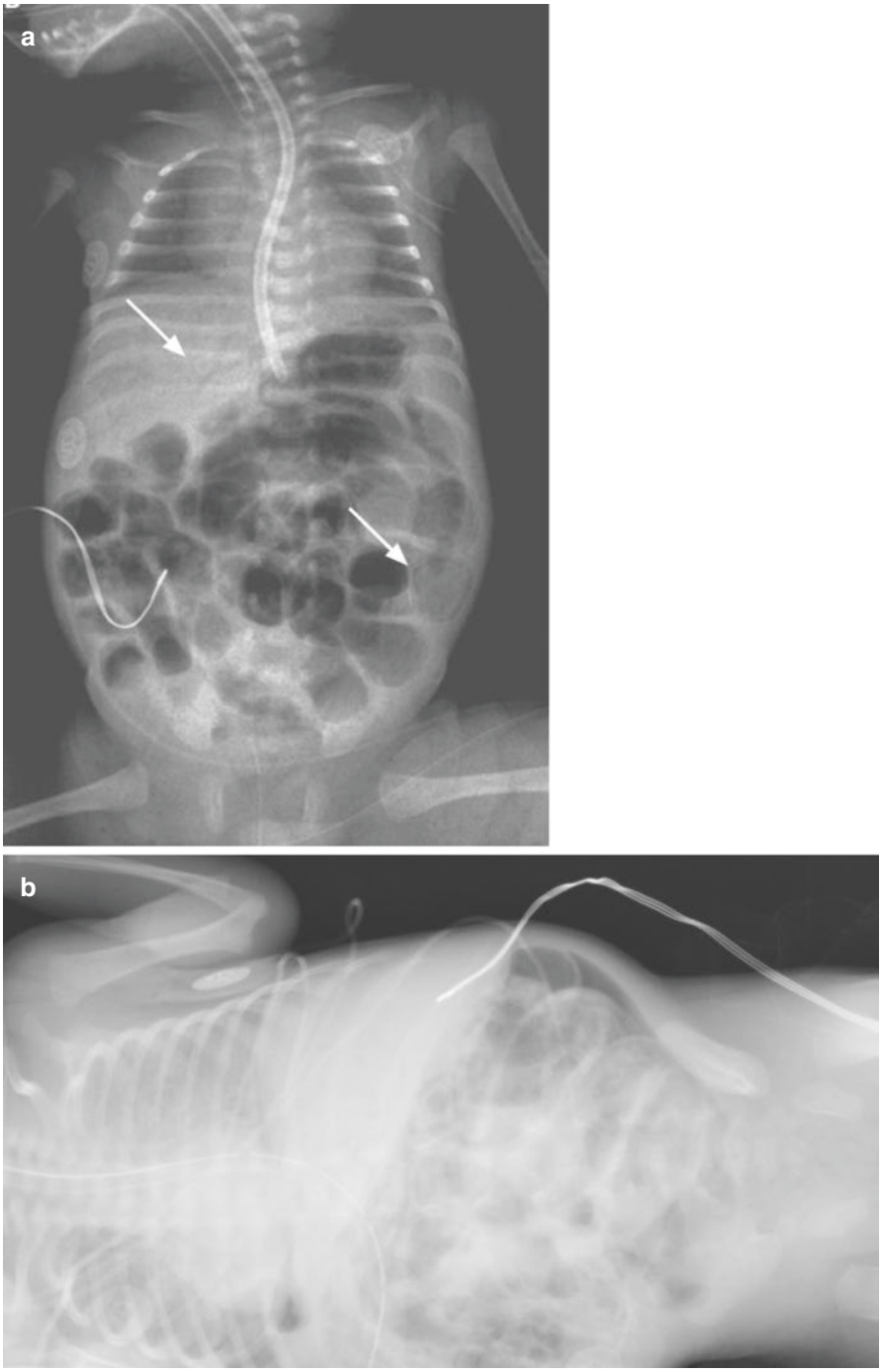

Fig. 1 Radiographic findings of necrotizing enterocolitis. (**a**) Pneumatosis intestinalis (lower arrow) and portal venous gas (upper arrow); (**b**) free intraperitoneal air as seen on a decubitus radiograph. Used with permission from [23]

Diagnosis

The diagnosis of NEC is based on a combination of clinical, radiological, and lab findings as mentioned above. Historically, the most common clinical staging system is the modified Bell's staging (Table 1), which categorizes NEC into Stages I, II, and III (i.e., suspected, definite, and advanced/surgical) [27–29]. The Centers for Disease Control and Prevention National Healthcare Safety Network (NHSN) has also developed diagnostic criteria for NEC, which is categorized as a healthcare-acquired infection [30]. These overlap with the Vermont Oxford Network definition of NEC, which is widely used for quality assurance and research purposes among nurseries [31].

Table 1 Modified Bell's staging for necrotizing enterocolitis (NEC)

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric residuals, abdominal distention, emesis, occult blood in stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics for 3 days, pending cultures and stomach decompression
IB	Suspected	Same as IA	Grossly bloody stool	Same as above	Same as IA
IIA	Definite, mildly ill	Same as IA	Same as above; plus absent bowel sounds, +/− abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	Same as IA; NPO and antibiotics for 7–10 days
IIB	Definite, moderately ill	Same as IA, plus mild metabolic acidosis and thrombocytopenia	Same as above; absent bowel sounds, definite tenderness, +/− abdominal cellulitis or mass	Same as IIA, +/− ascites, +/− portal venous gas	Same as IIA, NPO and antibiotics for 14 days
IIIA	Advanced, severely ill, intact bowel	Same as above, plus hypotension, bradycardia, apnea, severe acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus definite ascites	Same as IIB plus volume replacement, inotropic and ventilator support. If no improvement, consider surgical intervention
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as IIIA, plus pneumoperitoneum	Same as IIIA plus surgical intervention

DIC disseminated intravascular coagulation. Adapted from 26–28

These classification systems are often used as a diagnostic tool, although Bell criteria are meant to be applied to infants already diagnosed with NEC. Abdominal radiographs in preterm neonates may be difficult to evaluate, and diagnosis of radiographic findings such as pneumatosis intestinalis may vary from reader to reader [26, 32, 33]. Some infants with severe disease requiring surgical management never develop pneumatosis or portal venous gas. Additionally, NEC in very preterm infants may not present with bloody stools. In this population, intestinal necrosis develops proximal to the ileocecal valve; when ileus is present, blood will fail to pass into the distal part of the colon. Pneumoperitoneum on radiographs may or may not be associated with intestinal necrosis; spontaneous intestinal perforation – an entity which is clinically and pathologically distinct from NEC – often presents as free air in the abdominal cavity. Table 2 highlights the differences between SIP and NEC. Rarely, dissected air from the pleural cavity in infants with severe lung disease or pneumothorax may present with pneumoperitoneum [34, 35]. Ultrasonography may detect bowel wall edema, pneumatosis, alterations in the intestinal vascular state, ascites, or intra-abdominal collections in infants with NEC. This technique provides specificity of diagnosis but requires both operator skill and an experience in interpretation [36, 37].

As discussed, many laboratory abnormalities occur with NEC, and inflammatory markers are usually quite elevated. However, specific serum, urine, or stool biomarkers have not yet been validated. Intestinal fatty acid-binding protein, a protein present in enterocytes and released with cell injury; fecal calprotectin, released from neutrophils during an inflammatory response; and serum amyloid A and IL-8,

Table 2 Clinical features of spontaneous intestinal perforation versus necrotizing enterocolitis

	Spontaneous intestinal perforation	Necrotizing enterocolitis
Onset	Age < 10 days	Age > 14 days
Abdominal signs		
Distention	+++	+++
Erythema	–	+
Tenderness	+/–	+++
Bilious aspirates	++/–	++
Laboratory markers		
Leukopenia/neutropenia	–	+++
Thrombocytopenia	–	+++
DIC	–	++
Physiologic signs		
Apnea	+/–	++
Temperature Instability	–	++
Hypoperfusion/shock	–	+++
Radiographic signs		
Pneumatosis intestinalis	–	+++/–
Hepatobiliary gas	–	++/–
Pneumoperitoneum	+++	++/–

DIC disseminated intravascular coagulation

general markers of inflammation, have been studied alone or in combination. However, none are in widespread use, and normal values in infants have not been established [38, 39].

Treatment

Treatment for NEC includes bowel decompression and rest, fluid resuscitation, antibiotic therapy, and supportive care.

Medical Therapy. Antibiotic treatment is indicated as bacteremia occurs in 20–30% in infants with NEC primarily from translocation of organisms through a compromised intestinal barrier [40]. The superiority of one regimen over another has not been well established by clinical trials. Most regimens consist of broad gram-negative and anaerobic coverage (e.g., ampicillin *AND* an aminoglycoside ± clindamycin or metronidazole, or piperacillin/tazobactam ± an aminoglycoside). Use of vancomycin is not routinely indicated but could be considered if the infant is colonized with methicillin-resistant *Staphylococcus aureus.* Although studies exist linking the addition of anaerobic therapy with later stricture formation, authors of a large multicenter cohort study note that this association is most likely caused by a "survival bias" in infants treated with these agents who then live to develop strictures [41, 42]. Duration of therapy is generally 10–14 days for medical NEC and may be longer for disease requiring surgical intervention. Most providers also continue bowel rest for this duration. However, as with antibiotic choice, no evidenced-based recommendations for resumption of feeding or cessation of antibiotics exist, and shorter courses of both may be indicated when evidence of intestinal inflammation has remitted.

Surgical Therapy. Pneumoperitoneum is an indication for urgent surgical intervention in infants with NEC. Treatment options include either primary peritoneal drain and/or exploratory laparotomy. Studies have failed to show consistent benefits of one approach [43, 44]. Relative indications for surgical exploration include refractory thrombocytopenia, acidosis, or shock, all of which may be indicative of necrotic bowel. The decision to operate and the specific intervention should be determined in collaboration with the pediatric surgeon. Weighing the risks and benefits of performing an operation on a severely ill neonate is always challenging; additionally, demarcating unsalvageable bowel from that which could potentially recover is not always a clear-cut surgical decision.

Prevention

Prevention of NEC is based on targeting modifiable risk factors.

Feeding Strategies

1. Swabbing of the mouth with colostrum may be protective against NEC by stimulating the production of secretory IgA and lactoferrin, substances known to have

a protective effect on the intestinal mucosa, and specifically targeting gram-negative bacteria [45].
2. As previously stated, feeding with mother's own milk has been shown to be protective against NEC, and maternal support and resources for breastfeeding and providing fresh expressed milk should be provided from birth. The amount and duration of milk provided needed to provide optimal protection is unclear, but exclusive use of breast milk should be a goal for as long as feasible for mother and infant [11, 12, 46–48]. The benefits of pasteurized donor or processed human milk products over formula are still unclear [49, 50].
3. The decision of when to initiate feeds, especially in in the smallest infants, is much debated and displays both inter- and intra-institution variability. A period of trophic feeding (approximately 10–20 cc/kg/day) initiated within 24–72 h of birth, followed by advancement of 20–30 cc/kg/day of milk, is generally considered as acceptable method of feeding very-low-birth-weight (<1500 g) infants. More aggressive pathways may be safe and preferable in larger infants to reduce central line and parenteral nutrition [51].
4. Despite a lack of precise evidence on the "correct" feeding strategy, there is clear evidence that the mere presence of a unit-wide standardized feeding protocol is preventative for NEC [52–54].

Medication Stewardship. Several studies have linked the prolonged use of antibiotics in the early neonatal period with an increase in NEC through the manipulation of the microbiome with a shift toward aberrant colonization, or dysbiosis. H2 antagonists (i.e., ranitidine, famotidine, cimetidine) are also associated with increased odds of NEC (and *Candida*—see chapter "*Candida*") [13, 14, 16, 17]. Recognition of this association has led to successful reduction in utilization of both medications, as well as development of antimicrobial stewardship programs targeted to the NICU population [55, 56]. Antimicrobial stewardship strategies are further discussed in chapter "Antibiotic Stewardship."

Probiotics. Probiotics have been shown in randomized trials and subsequent meta-analyses to be protective against NEC, primarily through the establishment of favorable intestinal microbiota in preterm infants. The most common strains used in the United States are *Lactobacillus acidophilus*, *Bifidobacterium infantis*, and *Lactobacillus rhamnosus*. Though the trials are compelling, there is a great deal of heterogeneity in the exposure [57–60]. As such, administration of probiotics for the prevention of NEC is not recommended by the American Academy of Pediatrics due to the lack of a commercial formulation that has been studied for dose, consistency, and safety. Case reports of bacteremia with study products, as well as infection from impure products, have been reported [61, 62].

Other Biologic Agents. The role of epidermal growth factors, prebiotics, glutamine, and oral lactoferrin on mitigating the risk of NEC has not yet been confirmed, with investigations into these products, particularly prebiotics, presently underway [63–66].

Quality Improvement Initiatives. Implementing the above preventative measures as bundled strategies rather than individual interventions alone is the most effective

approach to reducing NEC [67, 68]. Clinical risk assessment tools such as GutCheck [69], developed and validated by a large national dataset, highlight the need for timely provider awareness with a focus on multifactorial nature of risk factor profiles in preterm infants. Predictive models for NEC integrating real-time patient data and machine learning to predict impending disease are exciting uses of technology [70, 71].

References

1. Battersby C, Santhalingam T, Costeloe K, Modi N. Incidence of neonatal necrotising enterocolitis in high-income countries: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2018;103: F182–9
2. Stoll B, Hansen N, Bell E, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA. 2015;314:1039–51.
3. Lambert D, Christensen R, Henry E, et al. Necrotizing enterocolitis in term neonates: data from a multihospital health-care system. J Perinatol. 2007;27:437–43.
4. Patel R, Kandefer S, Walsh M, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med. 2015;372:331–40.
5. Yee W, Soraisham A, Shah V, Aziz K, Yoon W, Lee S. Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. Pediatrics. 2012;129:e298–304.
6. Temming L, Dicke J, Stout M, et al. Early second-trimester fetal growth restriction and adverse perinatal outcomes. Obstet Gynecol. 2017;130:865–9.
7. Boghossian N, Geraci M, Edwards E, Horbar J. Morbidity and mortality in small for gestational age infants at 22 to 29 weeks' gestation. Pediatrics. 2018;141: e20172533
8. Been J, Lievense S, Zimmermann L, Kramer B, Wolfs T. Chorioamnionitis as a risk factor for necrotizing enterocolitis: a systematic review and meta-analysis. J Pediatr. 2013;162:236–42.
9. Samuels N, van de Graaf R, de Jonge R, IKM R, Vermeulen M. Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies. BMC Pediatr. 2017;17:105.
10. Havranek T, Rahimi M, Hall H, Armbrecht E. Feeding preterm neonates with patent ductus arteriosus (PDA): intestinal blood flow characteristics and clinical outcomes. J Matern Fetal Neonatal Med. 2015;28:526–30.
11. Sullivan S, Schanler R, Kim J, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr. 2010;156:562–7.
12. Cacho N, Parker L, Neu J. Necrotizing enterocolitis and human milk feeding: a systematic review. Clin Perinatol. 2017;44:49–67.
13. Cotten C, Taylor S, Stoll B, et al. NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics. 2009;123:58–66.
14. Alexander V, Northrup V, Bizzarro M. Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. J Pediatr. 2011;159:392–7.
15. Pammi M, Cope J, Tarr P, et al. Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis. Microbiome. 2017;5:31.
16. Romaine A, Ye D, Ao Z, et al. Best pharmaceuticals for Children Act – Pediatric Trials Network. Safety of histamine-2 receptor blockers in hospitalized VLBW infants. Early Hum Dev. 2016;99:27–30.
17. More K, Athalye-Jape G, Rao S, Patole S. Association of inhibitors of gastric acid secretion and higher incidence of necrotizing enterocolitis in preterm very low-birth-weight infants. Am J Perinatol. 2013;30:849–56.

18. Wan-Huen P, Bateman D, Shapiro D, Parravicini E. Packed red blood cell transfusion is an independent risk factor for necrotizing enterocolitis in premature infants. J Perinatol. 2013;33:786–90.
19. Patel R, Knezevic A, Shenvi N, et al. Association of red blood cell transfusion, anemia, and necrotizing enterocolitis in very low-birth-weight infants. JAMA. 2016;315:889–97.
20. Christensen R, Lambert D, Baer V, Gordon P. Necrotizing enterocolitis in term infants. Clin Perinatol. 2013;40:69–78.
21. Becker KC, Hornik CP, Cotten CM, et al. Necrotizing enterocolitis in infants with ductal-dependent congenital heart disease. Am J Perinatol. 2015;32:633–8.
22. Gordon P, Clark R, Swanson J, Spitzer A. Can a national dataset generate a nomogram for necrotizing enterocolitis onset? J Perinatol. 2014;34:732–5.
23. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. 2011;364:255–64.
24. Valpacos M, Arni D, Keir A, et al. Diagnosis and management of necrotizing enterocolitis: an international survey of neonatologists and pediatric surgeons. Neonatology. 2017;113:170–6.
25. Maheshwari A. Immunologic and hematological abnormalities in necrotizing enterocolitis. Clin Perinatol. 2015;42:567–85.
26. Coursey C, Hollingsworth C, Gaca A, Maxfield C, Delong D, Bisset G. Radiologists' agreement when using a 10-point scale to report abdominal radiographic findings of necrotizing enterocolitis in neonates and infants. Am J Roentgenol. 2008;191:190–7.
27. Bell M, Ternberg J, Feigin R, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187:1–7.
28. Walsh M, Kliegman R. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin N Am. 1986;33(1):179–201.
29. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. Curr Probl Pediatr. 1987;17:213–88.
30. Centers for Disease Control and Prevention. CDC/NHSN Surveillance Definitions for Specific Types of Infections. Available at http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf. Accessed 31 Jan 2018.
31. Vermont Oxford Network. Manual of Operations Part 2: Data definitions and infant data forms. Available at https://public.vtoxford.org/wp-content/uploads/2013/08/Manual-of-Operations-Part-2_v18.0.pdf. Accessed 31 Jan 2018.
32. Di Napoli A, Di Lallo D, Perucci C, et al. Inter-observer reliability of radiological signs of necrotising enterocolitis in a population of high-risk newborns. Paediatr Perinat Epidemiol. 2004;18:80–7.
33. Markiet K, Szymanska-Dubowik A, Janczewska I, et al. Agreement and reproducibility of radiological signs in NEC using the Duke Abdominal Assessment Scale (DAAS). Pediatr Surg Int. 2017;33:335–40.
34. Gordon P, Swanson J, Attridge J, Clark R. Emerging trends in acquired neonatal intestinal disease: is it time to abandon Bell's criteria? J Perinatol. 2007;(11):661–71.
35. Epelman M, Daneman A, Navarro OM, et al. Necrotizing enterocolitis: review of state-of-the-art imaging findings with pathologic correlation. Radiographics. 2007;27:285–305.
36. Yikilmaz A, Hall N, Daneman A, et al. Prospective evaluation of the impact of sonography on the management and surgical intervention of neonates with necrotizing enterocolitis. Pediatr Surg Int. 2014;30:1231–40.
37. Cuna A, Reddy N, Robinson A, Chan S. Bowel ultrasound for predicting surgical management of necrotizing enterocolitis: a systematic review and meta-analysis. Pediatr Radiol. 2017. [Epub ahead of print]
38. Benkoe T, Mechtler T, Weninger M, Pones M, Rebhandl W, Kasper D. Serum levels of interleukin-8 and gut-associated biomarkers in diagnosing necrotizing enterocolitis in preterm infants. J Pediatr Surg. 2014;49:1446–51.
39. Ng E, Poon T, Lam HS, et al. Gut-associated biomarkers L-FABP, I-FABP, and TFF3 and LIT score for diagnosis of surgical necrotizing enterocolitis in preterm infants. Ann Surg. 2013;258:1111–8.

40. Heida FH, Hulscher JB, Schurink M, et al. Bloodstream infections during the onset of necrotizing enterocolitis and their relation with the pro-inflammatory response, gut wall integrity and severity of disease in NEC. J Pediatr Surg. 2015;50:1837–41.
41. Faix R, Polley T, Grasela T. A randomized, controlled trial of parenteral clindamycin in neonatal necrotizing enterocolitis. J Pediatr. 1988;112:271–7.
42. Autmizguine J, Hornik C, Benjamin D, et al. Anaerobic antimicrobial therapy after necrotizing enterocolitis in VLBW infants. Pediatrics. 2015;135:e117–25.
43. Rao S, Basani L, Simmer K, Samnakay N, Deshpande G. Peritoneal drainage versus laparotomy as initial surgical treatment for perforated necrotizing enterocolitis or spontaneous intestinal perforation in preterm low birth weight infants. Cochrane Database Syst Rev. 2011;6:CD006182.
44. Rees C, Pierro A, Eaton S. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2007;92:F193–8.
45. Lee J, Kim H, Jung Y, et al. Oropharyngeal colostrum administration in extremely premature infants: an RCT. Pediatrics. 2015;135:e357–66.
46. Cristofalo E, Schanler R, Blanco C, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. J Pediatr. 2013;163:1592–5.
47. Assad M, Elliott M, Abraham J. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. J Perinatol. 2016;36:216–20.
48. Abrams S, Schanler R, Lee M, Rechtman D. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. Breastfeed Med. 2014;9:281–5.
49. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev. 2014; CD002971.
50. Kantorowska A, Wei J, Cohen R, Lawrence R, Gould J, Lee H. Impact of donor milk availability on breast milk use and necrotizing enterocolitis rates. Pediatrics. 2016;137:e20153123.
51. Oddie S, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2017;8:CD001241.
52. Patole S, de Klerk N. Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies. Arch Dis Child Fetal Neonatal Ed. 2005;90:F147–51.
53. McCallie K, Lee H, Mayer O, Cohen R, Hintz SR, Rhine W. Improved outcomes with a standardized feeding protocol for very low birth weight infants. J Perinatol. 2011;31(S1):S61–7.
54. Gephart S, Hanson C. Preventing necrotizing enterocolitis with standardized feeding protocols: not only possible, but imperative. Adv Neonatal Care. 2013;13:48–54.
55. Cantey J, Patel S. Antimicrobial stewardship in the NICU. Infect Dis Clin N Am. 2014;28:247–61.
56. Cantey J, Wozniak P, Pruszynski J, Sánchez P. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. Lancet Infect Dis. 2016;16:1178–84.
57. Al Faleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2014;4:CD005496.
58. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics. 2010;125:921–30.
59. Lau C, Chamberlain R. Probiotic administration can prevent necrotizing enterocolitis in preterm infants: a meta-analysis. J Pediatr Surg. 2015;50:1405–12.
60. Patel R, Underwood M. Probiotics and necrotizing enterocolitis. Semin Pediatr Surg. 2018;27:39–46.
61. Bertelli C, Pillonel T, Torregrossa A, et al. Bifidobacterium longum bacteremia in preterm infants receiving probiotics. Clin Infect Dis. 2015;60:924–7.
62. Jenke A, Ruf E, Hoppe T, Heldmann M, Wirth S. Bifidobacterium septicaemia in an extremely low-birthweight infant under probiotic therapy. Arch Dis Child Fetal Neonatal Ed. 2012;97:F217–8.

63. Pammi M, Suresh G. Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2017;6:CD007137.
64. Srinivasjois R, Rao S, Patole S. Prebiotic supplementation in preterm neonates: updated systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2013;32:958–65.
65. Moe-Byrne T, Brown JV, McGuire W. Glutamine supplementation to prevent morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2016;4:CD001457.
66. Coursodon C, Dvorak B. Epidermal growth factor and necrotizing enterocolitis. Curr Opin Pediatr. 2012;24:160–4.
67. Talavera M, Bixler G, Cozzi C, et al. Quality improvement initiative to reduce the necrotizing enterocolitis rate in premature infants. Pediatrics. 2016;137:e20151119.
68. Patel A, Trivedi S, Bhandari N, et al. Reducing necrotizing enterocolitis in very low birth weight infants using quality-improvement methods. J Perinatol. 2014;34:850–7.
69. Gephart S, Spitzer A, Effken J, Dodd E, Halpern M, McGrath J. Discrimination of GutCheck (NEC): a clinical risk index for necrotizing enterocolitis. J Perinatol. 2014;34:468–75.
70. Fairchild K, Lake D, Kattwinkel J, et al. Vital signs and their cross-correlation in sepsis and NEC: a study of 1,065 very-low-birth-weight infants in two NICUs. Pediatr Res. 2017;81:315–21.
71. Ji J, Ling X, Zhao Y, et al. A data-driven algorithm integrating clinical and laboratory features for the diagnosis and prognosis of necrotizing enterocolitis. PLoS One. 2014;9:e89860.

Candida

Hillary B. Liken and David A. Kaufman

Epidemiology

Epidemiology and Case Definition

Invasive *Candida* infections (ICI) are defined as the presence of *Candida* species in a body fluid or tissue sample and include bloodstream infections (BSI), urinary tract infections (UTI), peritonitis, meningitis, cutaneous candidiasis, and any infection of otherwise sterile tissue, such as bones and joints [1]. These invasive infections are diagnosed based on a positive culture of blood, urine, cerebrospinal fluid (CSF), peritoneal fluid, or tissue. For congenital cutaneous candidiasis, diagnosis requires a diffuse rash with identification of *Candida* or yeast from the skin, placenta, or umbilical cord [2]. These ICIs can disseminate directly or hematogenously throughout the body, even in spite of antifungal therapy. This can lead to end-organ abscesses and damage of the heart, kidneys, brain, liver, spleen, bone, and joints.

The majority of ICI in the neonatal intensive care unit (NICU) are due to *Candida albicans* (~ 50%), followed by *C. parapsilosis*, and to a lesser degree by *C. glabrata*. Infections due to *C. tropicalis*, *C. lusitania*, *C. krusei*, *C. guilliermondii*, and other species occur less frequently. *C. albicans* is the most pathogenic of the *Candida* species, with mortality rates two to three times higher compared with non-albicans candidemia [3].

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There is variation between rates of ICI in NICUs as well as the incidence reported in the literature due to the following factors:

- Many studies only include candidemia and/or meningitis, not all ICIs as defined above.
- Considerable variation exists due to gestational age or birth weight cutoffs for resuscitation of extremely preterm infants. NICUs that do not resuscitate infants <25 weeks, for example, would have a lower rate of ICI in infants <1000 g compared with centers caring for infants equal or less than 24-week gestation.
- Rates vary depending if infants with necrotizing enterocolitis (NEC), gastroschisis, and other complex gastrointestinal diseases are cared for or transferred to a tertiary center [4, 5].
- Infection control, medication practices, and use of antifungal prophylaxis are major factors effecting ICI rates. Antifungal prophylaxis is associated with lowest rates (nearly eliminating these infections) even in the highest-risk patients of the lowest gestational ages (<26 weeks) and birth weights (<750 g) [6–11].

Risk Factors

Prematurity. In the absence of antifungal prophylaxis, the incidence of ICI in extremely low birth weight (ELBW; <1000 g) infants, not including congenital cutaneous candidiasis, is around 10% [12]. The incidence decreases from >20% at 23 weeks gestation to 3% at 28 weeks gestation. Although bloodstream infections account for the majority of ICI, *Candida* UTIs account for an additional 3–4%, and meningitis and peritonitis (complicating any bowel perforation) contribute an additional 1–2% [6–11, 13]. The average candidemia rates are much lower in larger infants (1.32%, 0.36%, and 0.29% for birth weights of 1001–1500, 1501–2500, and > 2500 g, respectively) [14].

Medications. Proliferation is favorable under certain conditions such as when antibiotics eradicate competitive flora, H2 blockers or proton pump inhibitors (PPIs) reduce stomach acidity, which is an important defense against *Candida*, or when postnatal steroid exposure impairs granulocyte function. Longer antibiotic duration or exposure to multiple antibiotics, particularly third- and fourth-generation cephalosporins or carbapenems, is associated with increasing risk for ICI [12, 15, 16]. Dexamethasone and high-dose hydrocortisone (>1 mg/kg/day) are associated with increased incidence of ICI, but physiologic dosing of hydrocortisone (≤1 mg/kg/day) does not appear to increase risk [17–19].

Lines, Tubes, and Feedings. Central venous catheters, endotracheal tubes, and certain feeding practices increase the risk of ICI. Prospective epidemiologic studies have found an association with infants who do not receive enteral feedings by age 3 days and candidiasis, which may be related to patient factors or the effect of feeding [20]. Infants who receive increased amounts of fresh expressed human milk from their mothers have fewer bacterial infections, but studies have not demonstrated a decrease in ICI.

Gastrointestinal Pathology and Abdominal Surgery. Gastrointestinal pathology is associated with an increased risk for candidemia in patients with NEC, gastroschisis, Hirschsprung's disease, omphalocele, intestinal atresia, or tracheoesophageal fistula [4, 5].

Pathogenesis

Candida pathogenesis involves exposure, followed by colonization, infection, and dissemination (Fig. 1).

Exposure. As discussed above, prematurity is the greatest risk factor for ICI. This is due to an underdeveloped immune system and immature and often breeched (by central catheters and endotracheal tubes) defense barriers including the skin, gastrointestinal and respiratory tracts. *Candida* species are potential opportunistic pathogens for preterm infants as they are naturally present on the skin and oral and gastrointestinal mucosa primarily as saprophytes. *Candida* species can also lead to infections if the host is exposed to a large number of organisms (at birth or with poor infection control) or circumstances that allow *Candida* to proliferate easily.

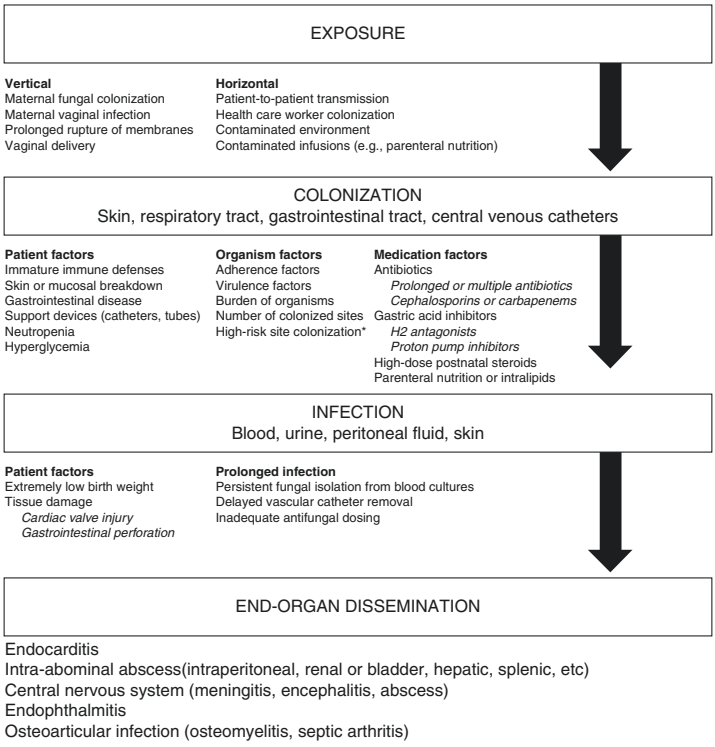


Fig. 1 Pathogenesis and risk factors of invasive *Candida* infections: exposure, colonization, infection, and dissemination. *High-risk colonization sites include the central venous catheter, endotracheal tube, and urine

Colonization. Colonization rates are inversely correlated with gestational age and birth weight similar to infection. In the first weeks of life, >50% of ELBW and 25–50% of very low birth weight (VLBW; <1500 g) infants may become colonized as compared with 5–10% of full-term infants [1]. Skin and gastrointestinal colonization occurs initially followed by respiratory tract colonization [21]. Approximately 25% of colonized infants will progress to infection; risk is influenced by the number and location of colonized sites [22]. Colonization of multiple sites or colonization at a single high-risk site (endotracheal tube, urine, catheter tips, drains, and surgical devices) is associated with higher ICI risk than colonization at a single low-risk site [6, 23–26].

Infection and dissemination. Colonized infants who progress to ICI can present with a variety of clinical syndromes, as discussed below. However, at onset of an ICI, *Candida* often has already disseminated to other tissues, organs, or body fluids and formed microabsesses. This is due to adherence properties of *Candida* and its slow growth prior to clinical signs and symptoms in an immunocompromised host. Additionally, central vascular catheters can cause local trauma to valvular, endocardial, or endothelial tissue followed by clot formation to which yeast can adhere. Among infants with ICI, the incidence of concomitant endocarditis is around 5%, kidney abscesses 5%, central nervous system abscesses 4%, and endophthalmitis 3% [27]. End-organ dissemination is higher in ELBW infants and any infant with candidemia lasting >5 days [28–30].

Morbidity and mortality. Mortality following any type of ICI is approximately 25–30% among ELBW infants. All-cause mortality rates are similar for candidemia (28%) and candiduria (26%) and increase to >50% for other sterile sites (meningitis and peritonitis) or if multiple sites are infected (blood, urine, CSF) [12]. Attributable mortality—the difference in mortality between ICI infected and non-infected infants—is 20%. In contrast, infants >1000 g with ICI have a much lower mortality risk of 2% compared to 0.4% in uninfected infants [31]. Survival is improved in candidemia cases with prompt removal of a central venous catheter, prompt empiric antifungal therapy, and in centers using antifungal prophylaxis [9, 32, 33]. Survivors of ICI are at increased risk for morbidity. Even with prompt treatment, neurodevelopmental impairment or delay exceeds 50% for both candidemia and *Candida* meningitis [20]. Compared with uninfected, age-matched controls, infants with candiduria (OR 2.5) or candidemia (OR 3) are at significantly increased risk for neurodevelopmental impairment [34].

Clinical Findings

Congenital Cutaneous Candidiasis (CCC)

Diagnosis of CCC is made by the presence of a diffuse CCC rash involving major skin areas of the body, extremities, face or scalp, and/or funisitis, presenting in the first week (≤7 days), with identification of *Candida* species or yeast from the (1) skin or mucous membrane cultures, (2) placenta staining or cultures, or (3) umbilical cord staining or cultures. CCC is usually evident at birth but can emerge during

the first week of life. Dermatologic findings include desquamation alone (scaling, peeling, flaking, or exfoliation); maculopapular, papulopustular, and erythematous rashes; or a combination of these skin manifestations (Fig. 2) [2]. CCC can occur with or without dissemination. There is a high burden of yeast with invasion into dermis, which brings *Candida* close to the dermal vasculature. Therefore, preterm and term infants need to be treated promptly at the time of rash presentation with systemic antifungal therapy and for a minimum of 14 days. Delaying systemic treatment, solitary use of topical therapy (nystatin), and treating for <10 days is associated with *Candida* dissemination to the bloodstream [2].

In evaluating a diffuse CCC rash in the first week life, aerobic skin cultures for both fungal and bacterial organisms need to be obtained to identify the source of infection. Specific fungal staining and aerobic culture of the umbilical cord and placenta also aid in the diagnosis. Additionally, blood culture, urine culture if older than 48 h, and CSF if no rash on the back is present should be performed. Lumbar puncture should not be performed or deferred if there is cutaneous involvement on the back due to invasion into the dermis and risk of introducing *Candida* into the CSF. Differential diagnosis includes staphylococcal as well as other bacterial and fungal skin infections. In certain cases when the rash appearance could be due to bacterial and fungal pathogens, empiric staphylococcal and fungal empiric coverage should be initiated pending culture results.

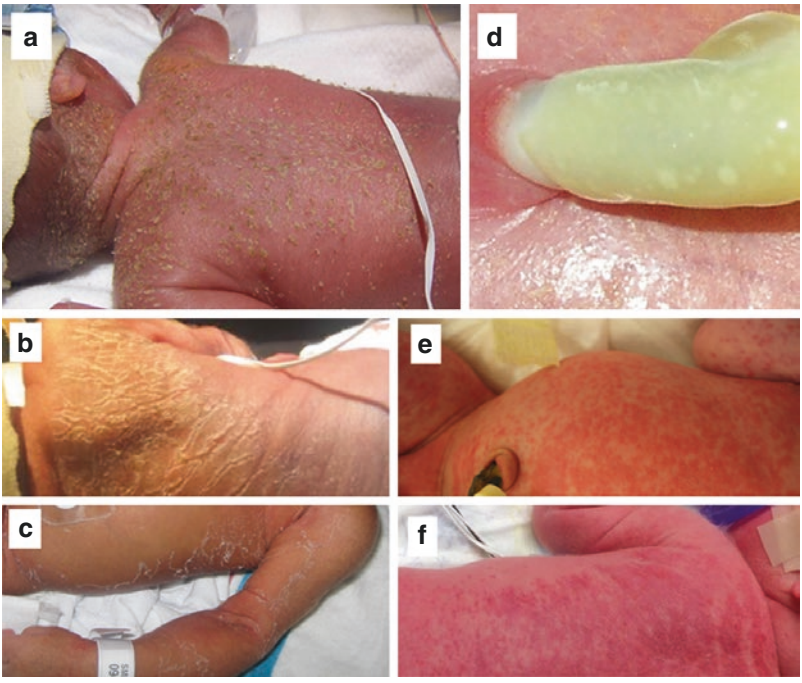


Fig. 2 Congenital cutaneous candidiasis presentation. (**a**) Dry, flaky skin. (**b**) Dry, cracking scaly skin with waxlike appearance. (**c**) Peeling skin with mild erythema. (**d**) White-yellow plaques of the umbilical cord. (**e** and **f**) Maculopapular rashes

Cutaneous Candidiasis (CC)

Cutaneous (or mucocutaneous) candidiasis presents as a diffuse rash with similar skin manifestations as CCC, but occurs later, at age ≥8 days [2]. Aerobic skin cultures to evaluate for both fungal and bacterial organisms need to be obtained to identify the source of infection. Additionally, blood and urine cultures plus a lumbar puncture if no rash on the back is present should be performed. Empiric systemic therapy should be started at the time of skin presentation and treatment for a minimum of 14 days in preterm infants. This is an invasive infection of the skin and will disseminate if not systemically treated. Similar to CCC, topical therapy is insufficient.

Candidemia

Signs and symptoms of *Candida* bloodstream infections (Table 1) are similar to bacteremia, with candidemia having some unique patterns related to thrombocytopenia. In VLBW infants, candidemia has lower initial platelet counts, lower platelet nadirs, and a greater duration of thrombocytopenia compared to gram-positive sepsis [35]. The percentage decrease from baseline at presentation is also greater with candidemia (50%) compared to gram-positive infections.

Candidemia is often associated with end-organ dissemination (Fig. 1). Initial screening for dissemination should include an echocardiogram, renal ultrasound, cranial ultrasound, and ophthalmologic exam. If there had been significant bowel pathology such as NEC or focal bowel perforation, a complete abdominal ultrasound should be performed to rule out peritoneal, liver, or splenic abscesses. This could be

Table 1 Presenting signs and symptoms of candidemia in very low birth weight infants [51]

Most common (>50%)
Thrombocytopenia <100,000/μl (>80%)
Immature-to-total neutrophil ratio ≥ 0.2 (>75%)
↑ C-reactive protein
↑ (1–3)-Beta-D-glucan >125 pg/dL
↑ Apnea and/or bradycardia
↑ Oxygen requirement
↑ Assisted ventilation
Frequent (~33%)
Lethargy/hypotonia
Gastrointestinal symptoms (e.g., gastric aspirates, distention, bloody stools)
Less frequent (<15%)
Hypotension
Hyperglycemia
Elevated white blood cell count >20,000/μl
Absolute neutrophil count <1500/μl
Metabolic acidosis

performed at presentation or a few days into treatment. Reevaluation for end-organ dissemination should occur with persistent candidemia (>7 days).

Studies in the era prior to antifungal prophylaxis have demonstrated candidemia complicating ~10% of cases of NEC due to candida translocation or bowel perforation. Evaluation of the gastrointestinal tract by culture of the rectum, stool, or oral flora in patients with the diagnosis of stage II NEC or greater for the presence of *Candida* species or yeast should be performed and if isolated prompt the addition of systemic antifungal therapy in addition to antibacterial treatment of NEC. This may not be needed if patients have been on antifungal prophylaxis since birth.

Prolonged positivity of blood cultures occurs with candidemia with a median of 3 days even in the absence of end-organ dissemination [20]. Documenting blood clearance could be done after 48 hours of systemic antifungal treatment with daily cultures until three negative cultures are obtained or waiting until 5–7 days into treatment and documenting two or more negative cultures. However, with persistent candidemia greater than 5 days, four key questions should be explored:

- *Does the patient still have a central venous catheter?* If so remove or replace at another site if central access critical to maintain.
- *Is antifungal dosing appropriate?* If not, adjust dosing with the assistance of a pediatric pharmacist or pediatric infectious disease specialist.
- *Is there end-organ dissemination?* Rescreen. If candidemia persists after 5–7 days, end-organ dissemination is even more likely, and initial screen should be repeated and expanded to include (1) ultrasound the location of the tip of any current or previous central catheter for an infected thrombus, (2) repeat complete abdominal ultrasound if history of NEC or bowel perforation for abscesses (laparotomy is sometimes considered if high clinical suspicion), and (3) cranial ultrasound/ magnetic resonance image (MRI) to detect brain dissemination. Abscesses that are amenable to removal should be managed with drainage or surgery.
- *What is the absolute neutrophil count?* Neutrophils are one of the most important components in the innate immune system's initial response to *Candida* infections, both through direct phagocytosis and other neutrophil functions. If neutropenia is present with candidemia (or another ICI) while on appropriate antifungal therapy for more than 2 days, correction of neutropenia with granulocyte colony-stimulating factor should be given.

Urinary Tract Infection

Late-onset sepsis evaluations should include a urine culture obtained via sterile catheterization as *Candida* UTIs and sepsis have similar presentations. *Candida* UTIs often occur in the absence of candidemia, emphasizing the need to obtain urine cultures. An elevated creatinine level without clear etiology may be another

sign of a UTI. In the absence of antifungal prophylaxis, candiduria can occur in up to 2.4% of VLBW and 6% of ELBW infants.

UTIs are most commonly defined as growth of ≥10,000 CFU/ml from a sterile catheterization or ≥1000 CFU/ml for bladder aspiration. Some experts consider the presence of any *Candida* in the urine a risk for significant infection and outcomes. Others consider a urine culture with lower CFUs representative of colonization at a high-risk site and may recommend preemptive treatment. Renal ultrasonography is warranted for all *Candida* UTIs to evaluate for abscess formation. Renal fungal abscess formation may occur with candiduria via an ascending infection or dissemination to the kidneys with candidemia. Prompt initial antifungal therapy with candiduria has decreased its incidence. Renal imaging should be performed at presentation and repeated in cases with persistent candiduria (as well as candidemia).

Central Nervous System (CNS) Infection

Meningitis, meningoencephalitis, or abscess formation may complicate candidemia or occur separately. Studies have found around 50% of meningitis cases occur in the absence of candidemia [20, 36]. Lumbar puncture at the time of sepsis evaluation prior to the initiation of antifungal therapy is important as CSF cell counts and chemistries may not be abnormal especially in preterm infants [37]. If lumbar puncture is unable to be performed at the time of presentation, it is important to obtain it as soon as possible in cases of candidemia or CNS disease. If meningitis is present, repeat lumbar puncture should be performed after several days or near the end of 21 days of treatment to document clearance in case antifungal therapy needs to be extended. Neuroimaging (ultrasonography or MRI) is needed to evaluate for abscess formation in cases of candidemia, meningitis, or infections with CNS symptoms.

Peritonitis

ICI can complicate patients presenting with stage III NEC or focal bowel perforation. If exploratory laparotomy or drains are placed, cultures should be obtained to determine what organisms may be present. Peritonitis may initially present with or without erythema as part of abdominal symptomatology. Identification of pathogens in the peritoneal cavity is critical to appropriate management of bowel perforation, peritonitis and preventing potential abscess formation. *Candida* species are the predominant organism causing peritonitis in 44% of focal bowel perforation and in 15% of the perforated NEC cases [13]. While radiographs can identify bowel perforation, complex fluid collects on ultrasound may indicate perforation or abscess formation. Some cases of perforation or abscess formation may be missed, and exploratory laparotomy may be needed if clinically indicated. All abscesses should be drained.

Pneumonia

Pneumonia remains a difficult diagnosis in ventilated neonates with chronic lung disease as radiologic findings of infection versus atelectasis, fluid, or scarring are often similar. Respiratory colonization is a high-risk site for infection especially in intubated patients [21]. Preemptive treatment has been shown to prevent dissemination when *Candida* is detected in a tracheal aspirate by culture, PCR, or *Candida* mannan antigen [38, 39].

Osteoarticular Infection

If an infant with candidemia also has signs of septic arthritis or osteomyelitis (swelling, immobility, erythema), a clinical diagnosis of osteoarticular infection can be made. Joint aspiration may be needed for diagnosis in the absence of candidemia. Evaluation with bone scan or MRI may help define the extent of involvement, but they cannot be used to rule out joint or bone involvement in neonates in the face of clinical symptoms. Treatment should be for 4–6 weeks.

Endocarditis or Infected Vascular Thrombi

Candida endocarditis or infected vascular thrombi are the most common complication of candidemia and associated with higher mortality than candidemia alone [29, 30]. When antifungal therapy alone is unsuccessful in resolution of the endocarditis or thrombus, thrombolytic or anticoagulation therapy has been used in some cases depending on infant's gestational age and associated conditions.

Endophthalmitis

Endophthalmitis presents most commonly as an intraocular dissemination from the bloodstream but also could be a rare complication of retinopathy of prematurity surgery or local trauma. Endophthalmitis progresses from a chorioretinal lesion that breaks free in the vitreous. Fundoscopy reveals one or more yellow-white, elevated lesions in the posterior retina or vitreous, generally appearing as a white fluffy ball. The clear cell-free vitreous can also become hazy due to an influx of inflammatory cells. More rapid diagnosis, treatment, and prevention of ICIs have made retinal endophthalmitis rare but still important to screen for with candidemia. Even in absence of visible retinal abscesses or chorioretinitis, *Candida* sepsis increases the risk for severe retinopathy of prematurity, and screening for retinal pathology is recommended even if not indicated by gestational age or birth weight criteria.

Diagnosis (Fig. 3)

Cultures

Cultures of blood, urine, CSF, or other sterile body fluids remain the best method for diagnosing ICIs. For infection evaluations, blood, urine (if age >48 h), and CSF cultures should be obtained and are critical to making a prompt diagnosis. When laparotomy is performed in cases of stage III NEC (see chapter "Necrotizing Enterocolitis") or focal bowel perforation, peritoneal cultures should always be obtained [13]. Collecting sufficient blood culture volumes (≥1 mL) is also key to detecting candidemia. *Candida* will grow on regular media; fungal-specific cultures are not required. For infants with ICI, >50% of cultures will be positive by 36 h and 97% by 72 h. Antifungal therapy for treatment or prophylaxis does not affect fungal detection or time to positivity [40].

Diagnosis of CCC and CC is a diffuse rash (±funisitis) with identification of *Candida* species or yeast from the (1) skin, (2) placenta, or (3) umbilical cord. See section on CCC and CC for more details.

Non-culture-Based Methods

Fungal cell wall polysaccharides such as (1–3)-beta-D-glucan (BDG) and mannan as well as polymerase chain reaction (PCR) can be extremely useful in identifying high-risk patients who would benefit from early empiric antifungal therapy while awaiting culture results, detecting non-bloodstream infections, or following response to antifungal therapy. However, they are not better than cultures in identifying true infections at this time.

The cutoff for BDG is higher (>125 pg/ml) for neonates than adults (>80 pg/ml) due to the effect fungal colonization, other infections such as gram-negative and coagulase-negative *Staphylococcus* (median 116 pg/ml [IQR 46–128]), and red blood cells or fresh frozen plasma transfusions (170 pg/mL, [IQR 65–317]) can have on BDG levels [41–43]. BDG levels in infants with ICI are 364 pg/mL (IQR 131–976) vs. 89 pg/mL (IQR 30–127) in non-infected neonates. Levels decrease significantly with antifungal therapy and can be used to follow a patient's response to treatment [41–43].

PCR to identify 18S ribosomal RNA (rRNA) in preterm infants can detect candidemia as well as non-bloodstream infections including *Candida* peritonitis, candiduria, previous candidal infections, and endotracheal colonization [44]. Similar to adjunctive tests, the question of whether PCR is detecting infection or only colonization has not been critically studied in neonates. Finally, another method that may help with the decision to start early empiric therapy is direct fluorescent assay of the buffy coat [45]. This test is a fluorescent stain that binds to structures containing cellulose and chitin yielding results in 1–2 h.

Treatment

Definitive Therapy

Antifungal dosing and duration are outlined in Table 2 and Fig. 3. Empiric antifungal therapy on the day cultures are sent or prompt antifungal therapy within 2 days of the blood culture decreases mortality and neurodevelopmental impairment [32, 46]. In addition to prompt appropriate antifungal dosing, immediate central catheter removal with candidemia is key to ICI clearance, decreasing risk for end-organ dissemination and improving survival and neurodevelopment.

Preemptive Treatment

Several studies have demonstrated when high-risk sites are colonized (e.g., the respiratory tract or urine), infants may benefit from treatment [39]. Studies have used endotracheal positive candida cultures or mannan levels ≥0.5 ng/mL to decide on preemptive treatment and significantly decreased ICI [39].

Table 2 Principles of invasive *Candida* infection treatment and clearance

Appropriate dosing
• Amphotericin (deoxycholate) 1 mg/kg/day
• Amphotericin (liposomal) 5–7 mg/kg/day
• Fluconazole 25 mg/kg load, followed by 12 mg/kg/day
• Micafungin 10 mg/kg/day
• Caspofungin 2.5 mg/kg (3 mg/kg if CNS disease)
Screen for end-organ dissemination
• Echocardiogram
• Renal ultrasound (or complete abdomen if GI pathology present)
• Head ultrasound
• Fundoscopy
Remove foci
• Promptly remove central venous catheter(s) when candidemia identified
• Consider removal of abscesses not responding to antifungal treatment and amenable to drainage or surgery
Appropriate duration
• 14 days for candidemia or cutaneous candidiasis (congenital or postnatal)
• 21 days for meningitis
• 4–6 weeks minimum if endocarditis, abscess, joint, or bone involvement

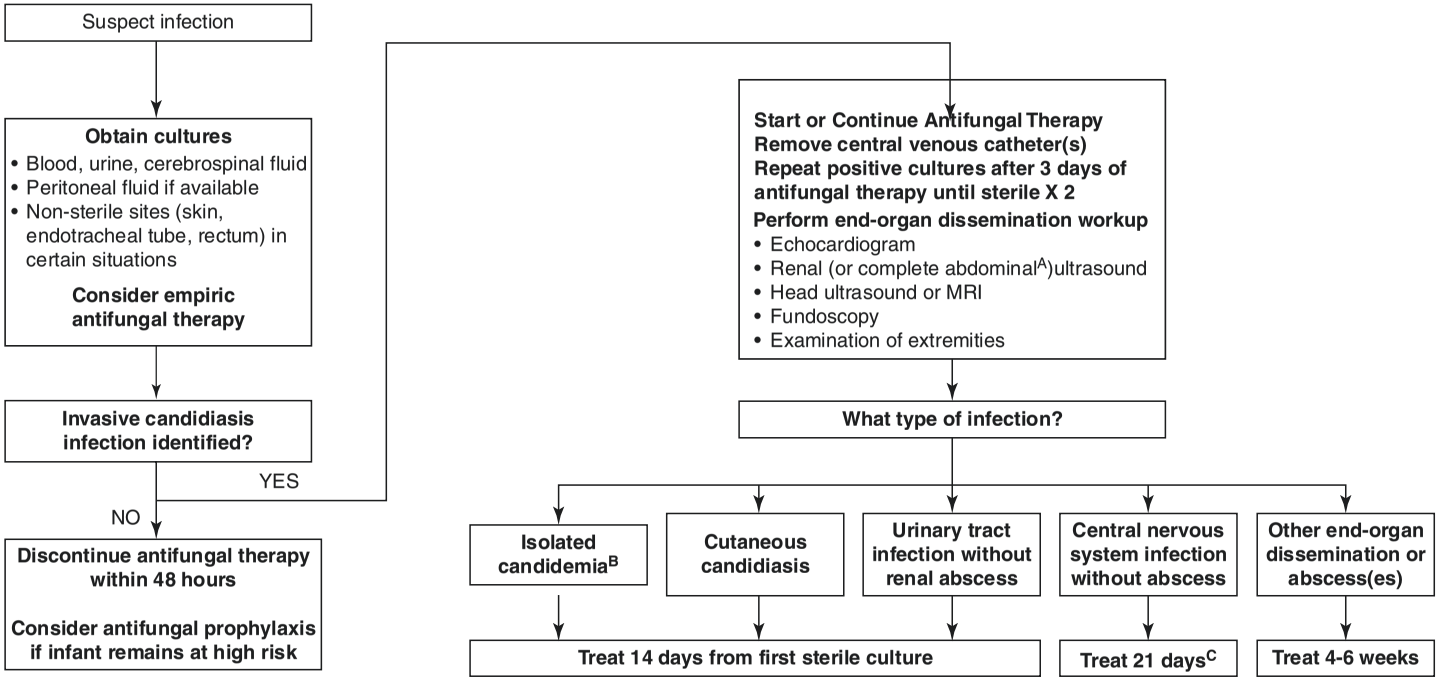


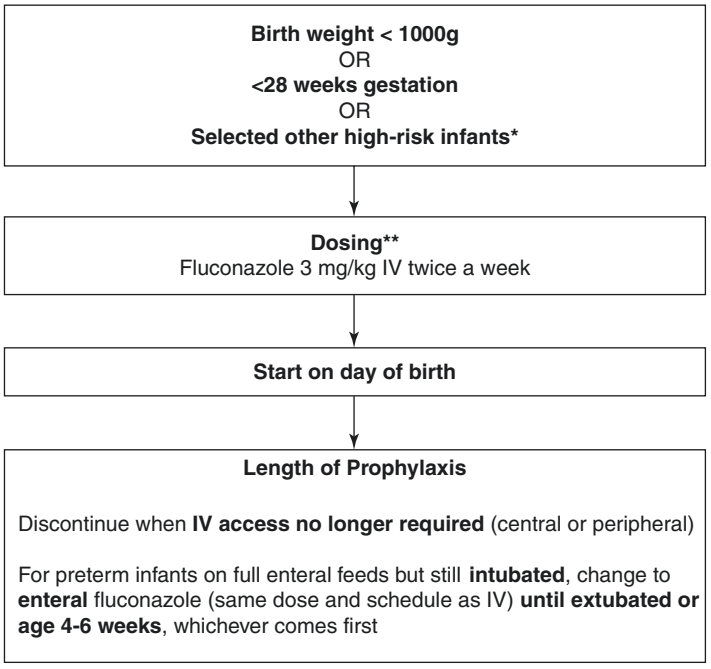
Fig. 3 Diagnosis, evaluation, and management of invasive *Candida* infections. Diagnosis of Congenital and Cutaneous Candidiasis is a diffuse rash (±funisitis) with identification of *Candida* species or yeast from the (1) skin, (2) placenta, or (3) umbilical cord. Non-sterile sites would involve skin when rash present, endotracheal tube if pneumonia suspected, and rectal/stool cultures if necrotizing enterocolitis. See text for more details. (A) If gastrointestinal disease (e.g., perforation, necrotizing enterocolitis) is present or recent, a complete abdominal ultrasound for abscess should be performed. (B) If blood cultures are positive after antifungal treatment for ≥5–7 days, the end-organ dissemination workup should be repeated including a complete abdominal ultrasound. (C) Repeat cerebrospinal fluid culture should be obtained near the end of therapy to ensure sterility

Prevention

Antifungal Prophylaxis

Targeted prophylaxis in extreme preterm infants (<1000 g or < 28 weeks, Fig. 4) during the period when they require intravenous access focuses on high-risk patients and individualizes each patient to the receive prophylaxis during their high-risk period based on individual risk factors. Linking the duration of prophylaxis to IV access correlates to the time period preterm infants are likely to have risks for ICI, such as significant immune immaturity, central lines, parenteral nutrition, antibiotic exposure, and lack of enteral feedings. By targeting prophylaxis to individual patients' risk factors limits exposure to the patient as well as fungi, which helps limit toxicity, costs, and the emergence of fungal resistance.

When antifungal prophylaxis is used, the recommendation is intravenous fluconazole starting shortly after birth at a dose of 3 mg/kg, twice a week, for 4–6 weeks,



*Other high-risk infants include:
1. Infants receiving a 3rd or 4th generation cephalosporin or carbapenem.
2. Infants with acute complicated gastrointestinal disease (*e.g.*, necrotizing enterocolitis or bowel perforation)
3. Infants with congenital gastrointestinal disease who require prolonged NPO periods or prolonged antibiotic exposure (*e.g.*, gastroschisis or Hirshsprung's disease).

**First dose on day of birth, then twice a week (*e.g.*, Tuesdays and Fridays at 10 AM). Give over 60 min. Give via central line if present.

Fig. 4 Targeted antifungal prophylaxis for high-risk neonates

or until intravenous access no longer is required for care [10]. This dosage and duration of chemoprophylaxis has not been associated with emergence of fluconazole-resistant *Candida* species [47]. Administering fluconazole prophylaxis twice weekly on the same days (e.g., Tuesdays and Fridays), at the same times, reduces pharmacy costs and may limit medication errors. Additionally, if antifungal prophylaxis is used, a different antifungal (amphotericin B or another non-azole) should be used for empiric therapy.

High-risk infants >1000 g in the NICU who also have rates ≥5% include infants with NEC, gastroschisis, and those with gram-negative infections being treated with third- or fourth-generation cephalosporins or carbapenems. For NICUs with significant rates of ICI in their infants 1000–1500 g, some retrospective studies have proposed either presence of a central venous catheter or treatment with antibiotics for >3 days as guidelines for the use of antifungal prophylaxis [9].

Infection Control Measures

In pregnancies complicated by preterm labor or prolonged rupture of membranes, screening and treatment of vaginal candidiasis may be beneficial in preventing *Candida* colonization and subsequent infection in the newborn [48, 49]. After delivery, standard NICU infection control including hand hygiene, environmental cleaning each shift, family education, and pharmacy preparation and handling of all infusions and medications remains a critical part of prevention. The use of medications that increase the risk for ICI (cephalosporins, carbapenems, gastric acid inhibitors, and postnatal steroids) should be monitored with stewardship and guidelines and avoided when possible. Feeding protocols and promoting use of human milk feedings may help decrease the risk for ICI. In addition, human milk feedings will lead to a decreased incidence of NEC and therefore the number of ICI that can complicate NEC. Finally, standardized protocols for insertion and management of central venous catheters, attention to sterile practices, hub and dressing care, and closed medication delivery systems have been shown to decrease CLABSIs, including those due to *Candida* [50]. A “bundled approach” including antifungal prophylaxis as part of CLABSI prevention is associated with near elimination of ICI.

References

1. Kaufman D, Fairchild KD. Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. Clin Microbiol Rev. 2004;17:638–80.
2. Kaufman DA, Coggins SA, Zanelli SA, Weitkamp JH. Congenital cutaneous candidiasis: prompt systemic treatment is associated with improved outcomes in neonates. Clin Infect Dis. 2017;64(10):1387–95.
3. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD neonatal research network. Pediatrics. 2002;110:285–91.
4. Feja KN, Wu F, Roberts K, et al. Risk factors for candidemia in critically ill infants: a matched case-control study. J Pediatr. 2005;147:156–61.

5. Barton M, O'Brien K, Robinson JL, et al. Invasive candidiasis in low birth weight preterm infants: risk factors, clinical course and outcome in a prospective multicenter study of cases and their matched controls. BMC Infect Dis. 2014;14:327.
6. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med. 2001;345:1660–6.
7. Kaufman DA, Morris A, Gurka MJ, Kapik B, Hetherington S. Fluconazole prophylaxis in preterm infants: a multicenter case-controlled analysis of efficacy and safety. Early Hum Dev. 2014;90(Suppl 1):S87–90.
8. Swanson JR, Gurka MJ, Kaufman DA. Risk factors for invasive fungal infection in premature infants: enhancing a targeted prevention approach. J Pediatric Infect Dis Soc. 2014;3:49–56.
9. Kaufman DA. Aiming for zero: preventing invasive candida infections in extremely preterm infants. NeoReviews. 2011;12:e381-e392.
10. Benjamin DK Jr, Hudak ML, Duara S, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized clinical trial. JAMA. 2014;311:1742–9.
11. Weitkamp JH, Ozdas A, Lafleur B, Potts AL. Fluconazole prophylaxis for prevention of invasive fungal infections in targeted highest risk preterm infants limits drug exposure. J Perinatol. 2008;28(6):405–11.
12. Benjamin DK Jr, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics. 2010;126:e865–73.
13. Coates EW, Karlowicz MG, Croitoru DP, Buescher ES. Distinctive distribution of pathogens associated with peritonitis in neonates with focal intestinal perforation compared with necrotizing enterocolitis. Pediatrics. 2005;116:e241–6.
14. Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T. Changing incidence of Candida bloodstream infections among NICU patients in the United States: 1995-2004. Pediatrics. 2006;117:1680–7.
15. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK Jr. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006;118:717–22.
16. Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in neonatal intensive care unit patients. The National Epidemiology of mycosis survey study group. Pediatr Infect Dis J. 2000;19:319–24.
17. Stoll BJ, Temprosa M, Tyson JE, et al. Dexamethasone therapy increases infection in very low birth weight infants. Pediatrics. 1999;104:e63.
18. Botas CM, Kurlat I, Young SM, Sola A. Disseminated candidal infections and intravenous hydrocortisone in preterm infants. Pediatrics. 1995;95:883–7.
19. Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics. 2004;114:1649–57.
20. Benjamin DK Jr, Stoll BJ, Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117:84–92.
21. Kaufman DA, Gurka MJ, Hazen KC, Boyle R, Robinson M, Grossman LB. Patterns of fungal colonization in preterm infants weighing less than 1000 grams at birth. Pediatr Infect Dis J. 2006;25:733–7.
22. Manzoni P, Stolfi I, Pugni L, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. N Engl J Med. 2007;356:2483–95.
23. Manzoni P, Farina D, Antonielli dE, Leonessa ML, Gomirato G, Arisio R. An association between anatomic site of Candida colonization and risk of invasive candidiasis exists also in preterm neonates in neonatal intensive care unit. Diagn Microbiol Infect Dis. 2006;56:459–60.
24. Manzoni P, Farina D, Leonessa M, et al. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. Pediatrics. 2006;118:2359–64.
25. Manzoni P, Farina D, Galletto P, et al. Type and number of sites colonized by fungi and risk of progression to invasive fungal infection in preterm neonates in neonatal intensive care unit. J Perinat Med. 2007;35:220–6.

26. Rowen JL, Rench MA, Kozinetz CA, Adams JM Jr, Baker CJ. Endotracheal colonization with Candida enhances risk of systemic candidiasis in very low birth weight neonates. J Pediatr. 1994;124:789–94.
27. Benjamin DK Jr, Poole C, Steinbach WJ, Rowen JL, Walsh TJ. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. Pediatrics. 2003;112:634–40.
28. Barton M, Shen A, O'Brien K, et al. Early-onset invasive candidiasis in extremely low birth weight infants: perinatal acquisition predicts poor outcome. Clin Infect Dis. 2017;64:921–7.
29. Chapman RL, Faix RG. Persistently positive cultures and outcome in invasive neonatal candidiasis. Pediatr Infect Dis J. 2000;19:822–7.
30. Noyola DE, Fernandez M, Moylett EH, Baker CJ. Ophthalmologic, visceral, and cardiac involvement in neonates with candidemia. Clin Infect Dis. 2001;32:1018–23.
31. Zaoutis TE, Heydon K, Localio R, Walsh TJ, Feudtner C. Outcomes attributable to neonatal candidiasis. Clin Infect Dis. 2007;44:1187–93.
32. Greenberg RG, Benjamin DK Jr, Gantz MG, et al. Empiric antifungal therapy and outcomes in extremely low birth weight infants with invasive candidiasis. J Pediatr. 2012;161:264–9.
33. Healy CM, Campbell JR, Zaccaria E, Baker CJ. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant Candida species. Pediatrics. 2008;121:703–10.
34. Wynn JL, Tan S, Gantz MG, et al. Outcomes following candiduria in extremely low birth weight infants. Clin Infect Dis. 2012;54:331–9.
35. Guida JD, Kunig AM, Leef KH, McKenzie SE, Paul DA. Platelet count and sepsis in very low birth weight neonates: is there an organism-specific response? Pediatrics. 2003;111:1411–5.
36. Cohen-Wolkowiez M, Smith PB, Mangum B, et al. Neonatal Candida meningitis: significance of cerebrospinal fluid parameters and blood cultures. J Perinatol. 2007;27:97–100.
37. Garges HP, Moody MA, Cotten CM, et al. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? Pediatrics. 2006;117:1094–100.
38. Vendettuoli V, Tana M, Tirone C, et al. The role of Candida surveillance cultures for identification of a preterm subpopulation at highest risk for invasive fungal infection. Pediatr Infect Dis J. 2008;27:1114–6.
39. Posteraro B, Sanguinetti M, Boccia S, et al. Early mannan detection in bronchoalveolar lavage fluid with preemptive treatment reduces the incidence of invasive Candida infections in preterm infants. Pediatr Infect Dis J. 2010;29:844–8.
40. Schelonka RL, Moser SA. Time to positive culture results in neonatal Candida septicemia. J Pediatr. 2003;142:564–5.
41. Goudjil S, Kongolo G, Dusol L, et al. (1-3)-beta-D-glucan levels in candidiasis infections in the critically ill neonate. J Matern Fetal Neonatal Med. 2013;26:44–8.
42. Cornu M, Goudjil S, Kongolo G, et al. Evaluation of the (1,3)-beta-D-glucan assay for the diagnosis of neonatal invasive yeast infections. Med Mycol. 2017;
43. Goudjil S, Chazal C, Moreau F, Leke A, Kongolo G, Chouaki T. Blood product transfusions are associated with an increase in serum (1-3)-beta-d-glucan in infants during the initial hospitalization in neonatal intensive care unit (NICU). J Matern Fetal Neonatal Med. 2016:1–5.
44. Tirodker UH, Nataro JP, Smith S, LasCasas L, Fairchild KD. Detection of fungemia by polymerase chain reaction in critically ill neonates and children. J Perinatol. 2003;23:117–22.
45. Higareda-Almaraz MA, Loza-Barajas H, Maldonado-Gonzalez JG, Higareda-Almaraz E, Benitez-Godinez V, Murillo-Zamora E. Usefulness of direct fluorescent in buffy coat in the diagnosis of Candida sepsis in neonates. J Perinatol. 2016;36:874–7.
46. Friedman S, Richardson SE, Jacobs SE, O'Brien K. Systemic Candida infection in extremely low birth weight infants: short term morbidity and long term neurodevelopmental outcome. Pediatr Infect Dis J. 2000;19:499–504.
47. Candidiasis. In: Kimberlin D, Brady M, Jackson M, Long SS, eds. Red Book: 2015 report of the committee on infectious diseases. 30th ed. Elk Grove Village, IL: American Academy of Pediatric; 2015, pp. 279–280.

48. Freydiere AM, Piens MA, Andre JM, Putet G, Picot S. Successful treatment of Candida glabrata peritonitis with fluconazole plus flucytosine in a premature infant following in vitro fertilization. Eur J Clin Microbiol Infect Dis. 2005;24:704–5.
49. Mendling W, Brasch J. Guideline vulvovaginal candidosis (2010) of the German Society for Gynecology and Obstetrics, the working Group for Infections and Infect immunology in Gynecology and obstetrics, the German Society of Dermatology, the Board of German Dermatologists and the German speaking mycological society. Mycoses. 2012;55(Suppl 3):1–13.
50. Chitnis AS, Magill SS, Edwards JR, Chiller TM, Fridkin SK, Lessa FC. Trends in Candida central line-associated bloodstream infections among NICUs, 1999-2009. Pediatrics. 2012;130(1):e46–52.
51. Fanaroff AA, Korones SB, Wright LL, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. The National Institute of Child Health and Human Development neonatal research network. Pediatr Infect Dis J. 1998;17:593–8.

Neonatal Conjunctivitis

Karli L. McCoy and Charlene R. Bultmann

Epidemiology

The most common causes of neonatal conjunctivitis include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and herpes simplex virus. Infected women can pass these infections to their newborns during the perinatal period. In 2016, there were approximately 1.6 million new chlamydial infections and 470,000 gonococcal infections; people of childbearing age (adolescents and young adults) account for the large majority of these [1]. As with syphilis (see chapter "Congenital Syphilis"), the incidence of both chlamydia and gonorrhea has continued to rise since the early 2000s [2].

Chlamydial and gonococcal conjunctivitis in neonates are a manifestation of failed antenatal screening (see Prevention, below). For infants born to mothers who were effectively screened and treated, other bacteria and viruses can also cause neonatal conjunctivitis. These include *Staphylococcus aureus*, *Moraxella catarrhalis* or non-typeable *Haemophilus influenzae*, rhinovirus, adenovirus, and bocavirus, to name a few [3, 4].

Pathogenesis

The conjunctiva is a transparent membrane of epithelial cells that lines the inner eyelids and the surface of the eye. In contrast, the cornea is part of the eye itself (the transparent membrane that covers the iris and pupil). The cornea and the conjunctiva are in the same plane and meet the limbus. Inflammation of the conjunctiva results in conjunctivitis; inflammation of the cornea is called keratitis (Table 1).

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Table 1 Clinical findings, diagnosis, and management of neonatal conjunctivitis by causative organism

Pathogen	Onset	Clinical signs	Diagnosis	Treatment
Neisseria gonorrhoeae	2–5 days	• Heavy purulence • Chemosis (swelling of conjunctiva) • Eyelid swelling	Gram stain and culture	Cefotaxime IV or IM
Chlamydia trachomatis	5–14 days	• Watery or mucopurulent drainage • Mild eyelid swelling • Conjunctival injection	DFA or PCR	Azithromycin or erythromycin PO
Other bacteria (*S. aureus*, *H. influenzae*, etc.)	Variable	• Mild to severe drainage • Mild to severe eyelid swelling • Conjunctival injection	Gram stain and culture	Topical antibiotic drops (systemic if severe)
Herpes simplex virus	5–21 days	• Periorbital vesicles or ulcerations • Keratitis	PCR	Acyclovir IV
Other viruses	Variable	• Mild to severe drainage • Mild to severe eyelid swelling • Conjunctival injection	Exclusion	None

Severe or untreated neonatal conjunctivitis may progress to involve either the cornea or the subconjunctival connective tissue of the eye, causing ulcerations, scarring, and ultimately permanent visual impairment.

Chlamydial and gonococcal conjunctivitis are perinatal infections that occur when infected maternal genital secretions come in contact with conjunctival epithelia during the birth process [5, 6]. In contrast, *S. aureus*, *M. catarrhalis*, *H. influenzae*, and the upper respiratory tract viruses such as adenovirus are generally transmitted postnatally on hands or contaminated equipment. Herpes simplex virus (HSV) keratoconjunctivitis can be acquired either perinatally or postnatally (see chapter "Neonatal Herpes Simplex Virus Infection").

Clinical Findings

The clinical presentation of neonatal conjunctivitis has significant overlap between pathogens (Table 1) [7–9]. Timing of onset and the presence of certain findings, such as vesicular disease for HSV or heavy purulence for gonococcal disease, may suggest a given diagnosis, but confirmation with specific testing is virtually always indicated (see Diagnosis, below).

Conjunctivitis presents with unilateral or bilateral eye injection, swollen eyelids, and drainage (which may be heavy or light, watery, or purulent). Severe or untreated disease, particularly due to *N. gonorrhoeae* or HSV, may lead to corneal scarring or ulceration and ultimately visual impairment.

Table 2 Diagnostic approach to the neonate with conjunctivitis

	N. gonorrhoeae	*C. trachomatis*	*S. aureus* and other bacteria	HSV	Other viruses
Gram stain	**Gram-negative diplococci**	Negative	**Often positive**	Negative	Negative
Culture	**Positive**	Negative	**Positive**	Negative	Negative
Chlamydia PCR (or DFA or EIA)	Negative	**Positive**	Negative	Negative	Negative
HSV PCR	Negative	Negative	Negative	**Positive**	Negative

DFA direct fluorescent antibody, *EIA* enzyme immunoassay, *HSV* herpes simplex virus
Expected positive findings in bold

Diagnosis

All infants with conjunctivitis require gram stain and culture of their conjunctival exudate (Table 2) [10]. Gram stain can provide immediate information about the morphology of bacteria, if present. For example, gonococcal disease is easily identifiable if gram-negative diplococci are seen in the gram stain. However, all gram stains should be confirmed with culture. Of note, nucleic acid-based testing is widely used for urogenital gonorrhea but is not recommended for the diagnosis of gonococcal conjunctivitis [11].

If chlamydial disease is suspected, the conjunctiva should be scraped to obtain conjunctival epithelial cells for either direct antigen testing (e.g., direct fluorescent antibody or enzyme immunoassay) or PCR [12]. Unlike gonococcus and other common bacterial causes of conjunctivitis, *Chlamydia* is an intracellular organism and is not present in the exudate itself—scrapings must be obtained. *Chlamydia* is also not visible on regular gram staining. If HSV disease is suspected, HSV-specific PCR testing should be obtained from the conjunctiva as well as other surface sites (pharynx, rectum), blood, and cerebrospinal fluid (see chapter "Neonatal Herpes Simplex Virus Infection") [13].

Treatment

The treatment of neonatal conjunctivitis depends on the causative agent. Identifying an etiology is critical as the therapy for one pathogen is likely to be ineffective against the others.

Neisseria gonorrhoeae: A single dose of third-generation cephalosporin therapy, given either IV or IM, is generally a sufficient therapy. Ceftriaxone (50 mg/kg/dose up to 125 mg) and cefotaxime (100 mg/kg/dose) are equally effective, although cefotaxime is generally used due to concerns about ceftriaxone displacing bilirubin in a jaundiced neonate [11].

Chlamydia trachomatis: Historically, oral erythromycin at 50 mg/kg/day divided four times per day for 14 days has been recommended. However, the failure rate

approaches 25%. Recently, oral azithromycin at 10 mg/kg/day given once followed by 5 mg/kg/day for 4 days has been shown to be effective [12].

Herpes simplex virus: If HSV disease is confirmed and limited to the eye, skin, and mucous membranes (skin/eye/mouth disease; see chapter "Neonatal Herpes Simplex Virus Infection"), then intravenous acyclovir at 60 mg/kg/day divided q8 hours for 14 days is generally sufficient. If keratitis is present, topical therapy with trifluridine or a similar antiviral agent is often added [13].

Other bacteria: Other bacteria, such as *S. aureus*, *M. catarrhalis*, or *H. influenzae*, may be treated with topical antibacterial drops or systemic therapy depending on the severity of illness and whether or not concomitant systemic disease (e.g., sepsis, urinary tract infection) is present.

Prevention

The single most effective way to prevent neonatal conjunctivitis is to identify and treat gonococcal or chlamydial disease in pregnant women. Current recommendations are to screen all pregnant women age < 25 years for gonorrhea and chlamydia; women age ≥ 25 years should be screened if they have new or multiple partners or if their partner has multiple partners. For at-risk women, screening should be at the first prenatal visit and again in the third trimester. Any women who test positive should have a test of cure 3–4 weeks after treatment and should be rescreened in 3 months [14]. Reinfection by an untreated sexual partner is frustratingly common, and the American College of Obstetricians and Gynecologists has endorsed expedited partner therapy (i.e., treating sexual partners of a woman diagnosed with gonorrhea or chlamydia without waiting to examine or test those partners) [15].

All infants, regardless of maternal screening results, should receive prophylactic eye ointment after delivery. This may be erythromycin, tetracycline, or silver nitrate; erythromycin is the only one currently available in the United States [16]. Notably, erythromycin ointment is only protective against gonococcal conjunctivitis; it does not prevent chlamydia or HSV [17].

References

1. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2015. Available at https://www.cdc.gov/std/stats15/std-surveillance-2015-print.pdf. Accessed on February 8, 2018.
2. LeFevre ML, U.S. Preventive Services Task Force. Screening for chlamydia and gonorrhea: U.S. Preventive Services Task Force recommendations statement. Ann Intern Med. 2014;161:902–10.
3. Honkila M, Renko M, Ikaheimo I, et al. Aetiology of neonatal conjunctivitis evaluated in a population-based setting. Acta Paediatr. 2018; Available online January 18, 2018.
4. Pak KY, Kim SI, Lee JS. Neonatal bacterial conjunctivitis in Korea in the 21st century. Cornea. 2017;36:415–8.
5. Comkornruecha M. Gonococcal infections. Pediatr Rev. 2013;34:228–34.
6. Siqueria LM. Chlamydia infections in children and adolescents. Pediatr Rev. 2014;35:145–52.

7. Rapoza PA, Quinn TC, Kiessling LA, Taylor HR. Epidemiology of neonatal conjunctivitis. Ophthalmology. 1986;93:456–61.
8. Sandström I. Etiology and diagnosis of neonatal conjunctivitis. Acta Paediatr Scand. 1987;76:221–7.
9. Rees E, Tait IA, Hobson D, Byng RE, Johnson FW. Neonatal conjunctivitis caused by Neisseria gonorrhoeae and Chlamydia trachomatis. Br J Vener Dis. 1977;53:173–9.
10. Drew RJ, Cole TS, Newman W. How to use… eye swabs. Arch Dis Child Educ Pract Ed. 2015;100:155–61.
11. Woods CR. Gonococcal infections in neonates and young children. Semin Pediatr Infect Dis. 2005;16:258–70.
12. Darville T. Chlamydia trachomatis infections in neonates and young children. Semin Pediatr Infect Dis. 2005;16:235–44.
13. James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. Clin Perinatol. 2015;42:47–59.
14. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1–137.
15. American College of Obstetricians and Gynecologists. Committee opinion no. 632: expedited partner therapy in the management of gonorrhea and chlamydial infection. Obstet Gynecol. 2015;125:1526–8.
16. U.S. Preventive Services Task Force. Ocular prophylaxis for gonococcal ophthalmia neonatorum: reaffirmation recommendation statement. Am Fam Physician. 2012;85:195–8.
17. Hammerschlag MR, Cummings C, Roblin PM, Williams TH, Delke I. Efficacy of neonatal ocular prophylaxis for the prevention of chlamydial and gonococcal conjunctivitis. N Engl J Med. 1989;320:769–72.

Respiratory Viruses in the Neonatal Intensive Care Unit

Phillip S. Wozniak

Epidemiology

The "usual suspects" causing RVI are well-known and include the following pathogens: human rhinovirus, influenza A and B, adenovirus, human metapneumovirus, parainfluenza, coronavirus, and—most importantly—RSV [1, 2]. In countries with temperate climates, such as the United States and Western Europe, late autumn until spring represents the "epidemic season" in which patients are most likely to acquire an RVI [1]. The introduction of reliable and fast polymerase chain reaction (PCR) assays in the recent years has allowed for rapid detection of viruses in the NICU, which has in turn challenged the previously held assumption that infants within NICUs are protected from community pathogens [3]. These findings highlight the importance of hand hygiene and other preventive strategies during the epidemic season.

The clinical presentation of patients with RVI—typically rhinorrhea, cough, cackles, wheezing, retractions, or respiratory distress—can prompt diagnoses of "culture-negative sepsis" and initiation of antibiotic therapy [1, 2]. Prospective studies in which respiratory viral testing has been performed during late-onset sepsis evaluations demonstrate that 5–10% of suspected late-onset sepsis is actually due to RVI infection [2, 4, 5]. These findings support the use RVI screening by PCR when sepsis is suspected to bolster antimicrobial stewardship efforts in the NICU.

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Pathogenesis

While the exact cause of preterm infants' increased susceptibility to RVI remains unknown, the current literature points to a combination of inflammatory conditions, both in utero and after birth, immaturity and dysfunction of the immune system, and genetic and epigenetic factors [6, 7]. RVI in the first year of life has been associated with recurrent respiratory morbidity, including asthma and wheezing, though it remains to be determined if respiratory viruses cause these morbidities or exacerbate an underlying genetic predisposition in these children [1].

RSV, in particular, has been strongly associated with the development of respiratory sequelae, though rhinovirus and human metapneumovirus have been implicated as well [1, 8]. For patients with RSV infection, the normal immune response follows a three-step pattern: the innate epithelial response at the nasal mucosa, the antibody response (specifically, IgG) at the upper airway for protection against infection of the lower respiratory tract, and the T cell response, which is responsible for viral clearance [1, 6]. Preterm neonates have deficient immune responses to some pathogens and overly aggressive, unregulated responses to others [1, 6, 8].

Along with preterm infants, those with congenital heart disease, Down syndrome, congenital neuromuscular diseases, cystic fibrosis, or congenital immunological deficiencies are at particularly high risk for severe RVI, particularly RSV [1]. In infants with congenital heart disease, RSV infection of the lower respiratory tract may cause a variety of potentially fatal complications including sinoatrial block, tachyarrhythmias, atrioventricular block of varying entity, pericarditis, and myocarditis [1, 9]. The importance of palivizumab prophylaxis in this population has been well documented (see chapter "Immunizations in the Nursery") [10, 11]. Similarly, children with Down syndrome are considered to be high risk for severe RSV infection due to the underlying heart disease that frequently accompanies the condition [1]. Infants with congenital neuromuscular disease are also at high risk from RVI due to reduced vital capacity in the lungs, weak cough and dysphagia inhibiting clearance of respiratory excretions, compromised ability to comply with physiotherapeutic interventions, and recurrent aspiration due to gastroesophageal reflux disease or vomiting due to coughing [12].

Preterm infants with cystic fibrosis are also at risk of accelerated decline in respiratory function over the course of their lives due to RSV infection. These patients are extremely susceptible to recurrent wheezing and bacterial superinfections, most commonly *Pseudomonas aeruginosa*, secondary to RSV infection. RSV is a known facilitator of *Pseudomonas aeruginosa* infection and proliferation in this population [13, 14]. Finally, patients with severe immunocompromise—either due to transplantation, HIV, DiGeorge syndrome, severe combined immunodeficiency, etc.—have a deficient T cell lymphocyte response, which inhibits viral clearance causing greater virulence and persistently higher viral loads [15–17].

In addition to RSV, human metapneumovirus poses its own set of challenges for NICU clinicians. In contrast to RSV hospitalizations, which peak around age 2–3 months, metapneumovirus hospitalizations peak between age 6 and 12 months [18–21]. Human metapneumovirus is the second most commonly

detected viral pathogen after RSV and may have a greater predilection for preterm infants. When compared to children infected with RSV, Anderson et al. [21] found that infants with human metapneumovirus infection were more premature (mean 27 vs. 33 weeks' gestation) and more likely to have bronchopulmonary dysplasia (59% vs. 22%). Similar to RSV, the increased risk for human metapneumovirus for patients with bronchopulmonary dysplasia persists into the second year of life [21].

For immunocompromised patients, adenovirus can be particularly dangerous with disseminated disease or localized severe infection of the respiratory tract infection [4, 22]. While adenovirus infections in neonates are rare, mortality exceeds 50% for adenovirus pneumonia and 85% for disseminated adenovirus disease [22]. Disseminated disease may present with pneumonia and hepatitis with hypothermia, apnea, nasal congestion, tachypnea, cyanosis, poor feeding with emesis, hypotension, neutropenia, hematuria, and hypotonia [4, 22].

Clinical Findings

In general, clinical findings of RVI in the nursery setting have significant overlap between pathogens (Table 1). Signs include upper respiratory (rhinorrhea, cough, stridor) and lower respiratory (tachypnea, desaturations, crackles, wheezing, retractions) findings [23]. For preterm infants, respiratory deterioration or apnea is common. Nonspecific findings (e.g., feeding intolerance,

Table 1 Respiratory viral infections (RVI) in the nursery setting

Epidemiology	RVI can be detected in ~5–10% of infants with suspected late-onset sepsis
Etiology	Rhinovirus (most common) Parainfluenza Respiratory syncytial virus Human metapneumovirus Influenza Coronavirus
Clinical findings	*Nonspecific* • Temperature instability • Apnea/bradycardia • Feeding intolerance • Respiratory distress *Specific* • Rhinorrhea/congestion • Cough • Crackles/wheezing
Diagnosis	Multiplex respiratory viral PCR (preferred) Direct fluorescent antibody testing Rapid antigen testing
Treatment	Supportive Droplet precautions Consider antiviral therapy for influenza

temperature instability) are also seen. New or evolving radiographic changes are sensitive for lower respiratory tract involvement, but in preterm infants, it is difficult to differentiate viral from bacterial pneumonia in the absence of testing. As mentioned above, extrapulmonary findings such as hepatitis or myocarditis in the setting of RVI are particularly concerning for adenoviral infection or severe RSV disease.

Diagnosis

The diagnosis of RVI in the NICU occurs in two distinct phases: the clinical diagnosis and the etiological diagnosis [1]. The clinical diagnosis should be derived from physical examination and the medical history. Infants with RVI who present with nonspecific findings such as temperature instability, apnea, or respiratory deterioration may be difficult to differentiate from infants with late-onset sepsis (see chapter "Late-Onset Sepsis"). Viral testing can differentiate RVI from bacterial infection. When RVI is suspected, determining the etiology is still useful as it may assist antimicrobial stewardship efforts, identify ongoing horizontal transmission within the unit, and identify infants who could benefit from antiviral therapy (i.e., those with influenza).

Serologic testing or viral culture is rarely used any longer to diagnose RVI. Instead, the nasopharynx or, rarely, bronchoscopy fluid can be directly tested for viral material:

Rapid antigen detection tests collected by nasal lavage or swab offer results in ≤60 min with 80–90% sensitivity, though false negatives have been reported in children aged less than 3 months.

Polymerase chain reaction is the gold standard test for respiratory viruses, offering 93–100% sensitivity and 64–100% specificity [1]. The BioFire® FilmArray respiratory panel (Salt Lake City, Utah, USA) currently allows for testing of up to 17 respiratory viruses and 3 bacteria from a single sample. Rogers et al. [24] found that implementation of rapid respiratory panel testing significantly reduced the duration of antibiotic use, the length of inpatient stay, and the patient's time in isolation. These findings support the use of PCR testing when indicated and where available.

Treatment

With the exception of oseltamivir for influenza infection, there are no specific antiviral therapies available for treatment of RVI in infants. Treatment is instead limited to supportive care with supplemental oxygen and intravenous hydration [1, 6]. Nebulized 3% hypertonic saline has also shown to be a safe and effective respiratory support. There is insufficient evidence for the efficacy of bronchodilators, steroids, antibiotics, or respiratory physical therapy in the treatment of bronchiolitis, and international guidelines for bronchiolitis treatment remain limited to supplemental oxygen and intravenous fluids [1].

For influenza, dosing recommendations are available for term and preterm infants. However, safety data is limited for infants younger than 3 months, so treatment should be reserved for high-risk cases such as infants with acute respiratory decompensation or extreme prematurity [25].

Prevention

Prevention is the best medicine for RVI in preterm infants. In the absence of antiviral therapies or vaccines against most RVIs, environmental prophylaxis is most effective means of prevention. Compliance with hand hygiene protocols and the decontamination of objects and surfaces in the NICU have been shown to be effective in reducing preterm infants' exposure to RVI [26].) For especially devastating infections such as RSV, additional preventative measures include active surveillance with testing, cohorting infected infants away from those testing negative, use of pathogen-specific precautions (see chapter "Principles of Infection Prevention in the Nursery"), and limiting patient contact with visitors [27–30]. For eligible patients, palivizumab is a safe and effective means of pharmacological prophylaxis against RSV [31]. In 2014, the American Academy of Pediatrics' Committee on Infectious Diseases and Bronchiolitis Guidelines Committee issued new recommendations for infants eligible to receive palivizumab prophylaxis (see chapter "Immunizations in the Nursery").

Finally, recent research has focused on the effects of restrictions on sibling visits to patients in the NICU for the prevention of RVIs. Peluso et al. [32] demonstrated a significant reduction in RSV infections after implementing restrictions on all visitors under the age of 13 years. Similarly, Caserta et al. [33] found that visitor restrictions on children less than 14 years in combination with other hand hygiene protocols were associated with a significantly lower rate of infection than in term infants living in the community and in preterm infants once discharged from the hospital. These findings highlight the need for additional research to develop improved protocols for the prevention of RVI in the NICU.

References

1. Baraldi E, Lanari M, Manzoni P, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. *Ital J Pediatr*. 2014;40:65.
2. Ronchi A, Michelow IC, Chapin KC, et al. Viral respiratory tract infections in the neonatal intensive care unit: the VIRIoN-I study. *J Pediatr*. 2014;165:690–6.
3. Bennett NJ, Tabarani CM, Bartholoma NM, et al. Unrecognized viral respiratory tract infections in premature infants during their birth hospitalization: a prospective surveillance study in two neonatal intensive care units. *J Pediatr*. 2012;161:814–8.
4. Kidszun A, Hansmann A, Winter J, et al. Detection of respiratory viral infections in neonates treated for suspicion of nosocomial bacterial sepsis: a feasibility study. *Pediatr Infect Dis J*. 2014;33:102–4.
5. Bennett NJ, Tabarani CM, Bartholoma NM, et al. Unrecognized viral respiratory tract infections in premature infants during their birth hospitalization: a prospective surveillance study in two neonatal care units. *J Pediatr*. 2012;161:814–8.

6. Maitre NL, Williams JV. Human metapneumovirus in the preterm neonate: current perspectives. *Res Rep Neonatol*. 2016;6:41–9.
7. Drysdale SB, Lo J, Prendergast M, et al. Lung function of preterm infants before and after viral infections. *Eur J Pediatr*. 2014;173:1497–504.
8. Weisman L. Populations at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. *Pediatr Infect Dis J*. 2003;22:S33–9.
9. Willson DF, Landrigan CP, Horn SD, Smout RJ. Complications in infants hospitalized for bronchiolitis or respiratory syncytial virus pneumonia. *J Pediatr*. 2003;143:S142–9.
10. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143:532–40.
11. Anderson EJ, Carosone-Link P, Yogev R, Yi J, Simoes EAF. Effectiveness of palivizumab in high-risk infants and children: a propensity score weighted regression analysis. *Pediatr Infect Dis J*. 2017;36:699–704.
12. Wilkesmann A, Ammann RA, Schildgen O, et al. Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course. *Pediatr Infect Dis J*. 2007;26:485–91.
13. Manzoni P, Paes B, Resch B, Carbonell-Estrany X, Bont L. High risk for RSV bronchiolitis in late preterms and selected infants affected by rare disorders: a dilemma of specific prevention. *Early Hum Dev*. 2012;88:S34–41.
14. Giebels K, Marcotte JE, Podoba J, et al. Prophylaxis against respiratory syncytial virus in young children with cystic fibrosis. *Pediatr Pulmonol*. 2008;43:169–74.
15. Hall CB, Powell KR, MacDonald NE, et al. Respiratory syncytial viral infection in children with compromised immune function. *N Engl J Med*. 1986;315:77–81.
16. El Saleeby CM, Somes GW, DeVincenzo JP, Gaur AH. Risk factors for severe respiratory syncytial virus disease in children with cancer: the importance of lymphopenia and young age. *Pediatrics*. 2008;121:235–43.
17. Sung L, Alonzo TA, Gerbing RB, et al. Respiratory syncytial virus infections in children with acute myeloid leukemia: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2008;51(6):784.
18. Edwards KM, Zhu Y, Griffin MR, et al. Burden of human metapneumovirus infection in young children. *N Engl J Med*. 2013;368:633–43.
19. Bosis S, Esposito S, Niesters HG, Crovari P, Osterhaus AD, Principi N. Impact of human metapneumovirus in childhood: comparison with respiratory syncytial virus and influenza viruses. *J Med Virol*. 2005;75:101–4.
20. van den Hoogen BG, van Doornum GJ, Fockens JC, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. *J Infect Dis*. 2003;188:1571–7.
21. Anderson EJ, Simoes EA, Buttery JP, et al. Prevalence and characteristics of human metapneumovirus infection among hospitalized children at high risk for severe lower respiratory tract infection. *J Pediatric Infect Dis Soc*. 2012;1(3):212–22.
22. Ronchi A, Doern C, Brock E, Pugni L, Sanchez PJ. Neonatal adenoviral infection: a seventeen year experience and review of the literature. *J Pediatr*. 2014;164:529–35.
23. Friedman JN, Rieder MJ, Walton JM. Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age. *Paediatr Child Health*. 2014;19:485–98.
24. Rogers BB, Shankar P, Jerris RC, et al. Impact of a rapid respiratory panel test on patient outcomes. *Arch Pathol Lab Med*. 2015;139:636–41.
25. Centers for Disease Control and Prevention. Recommended dosage and duration of influenza antiviral medications for treatment or chemoprophylaxis. Available at https://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-dosage-duration.pdf. Accessed 17 Jan 2018.
26. Sattar SA, Springthorpe VS, Tetro J, Vashon R, Keswick B. Hygienic hand antiseptics: should they not have activity and label claims against viruses? *Am J Infect Control*. 2002;30:355–72.

27. Groothuis J, Bauman J, Malinoski F, Eggleston M. Strategies for prevention of RSV nosocomial infection. *J Perinatol*. 2008;28:319–23.
28. Bont L. Nosocomial RSV infection control and outbreak management. *Paediatr Respir Rev*. 2009;10:S16–7.
29. Karanfil LV, Conlon M, Lykens K, et al. Reducing the rate of nosocomially transmitted respiratory syncytial virus. *Am J Infect Control*. 1999;27:91–6.
30. Macartney KK, Gorelick MH, Manning ML, Hodinka RL, Bell LM. Nosocomial respiratory syncytial virus infections: the cost-effectiveness and cost-benefit of infection control. *Pediatrics*. 2000;106:520–6.
31. Subramanian KN, Weisman LE, Rhodes T, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. *Pediatr Infect Dis J*. 1998;17:110–5.
32. Peluso AM, Harnish BA, Miller NS, Cooper ER, Fujii AM. Effect of young sibling visitation on respiratory syncytial virus activity in a NICU. *J Perinatol*. 2015;35:627–30.
33. Caserta MT, Yang H, Gill SR, Holden-Wiltse J, Pryhuber G. Viral respiratory infections in preterm infants during and after hospitalization. *J Pediatr*. 2017;182:53–8.

Part II

Congenital Infections

Pathogenesis of Congenital Infections

Joseph B. Cantey

Terminology

A variety of terms are used to refer to infections of the fetus and newborn (Table 1). For the purposes of this book, the following mutually exclusive terms will be used preferentially:

Congenital infection: Transmission of a pathogen from the mother to the fetus via the placenta

Perinatal infection: Transmission of a pathogen from the mother to the infant via contact with an infected birth canal during the birth process

Postnatal infection: Transmission of a pathogen from any individual to the infant after delivery

Epidemiology

The incidence of specific infections can be found in their respective chapters. The incidence of congenital infection varies geographically, but overall incidence is approximately 1–2% of live births [1]. The majority of these infections are due to cytomegalovirus, but a tremendous variety of pathogens are capable of causing congenital infection (Table 2). Notably, the percentage of infants who require additional observation or evaluation due to suspected congenital (or perinatal) infection is substantially higher, but many of these infants ultimately are determined to be uninfected.

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Table 1 Selected terms for infection of the fetus and newborn and their definitions

Congenital infection	Transmission of a pathogen from the mother's bloodstream to the fetus via the placenta	Preferred term
In utero infection	Transmission of a pathogen from the mother to the fetus before delivery	Not preferred; does not distinguish between true congenital infection and ascending perinatal infection that occurs before delivery (e.g., group B streptococcal disease apparent at birth due to prolonged rupture of membranes or chorioamnionitis)
Perinatal infection	Transmission of a pathogen from the mother to the newborn during delivery due to organisms from the genital tract	Preferred term
Vertical infection	Transmission of a pathogen from the mother to the fetus or newborn	Not preferred, does not distinguish between either congenital or perinatal infections or postnatal infections whose source is the mother
Horizontal infection	Transmission of a pathogen from an individual other than the mother to the infant	Not preferred; often used synonymously with postnatal infection
Postnatal infection	Transmission of a pathogen from an individual to the infant after delivery	Preferred term

Table 2 Pathogens capable of causing congenital infection

Viral	Bacterial	Protozoan	Fungal
Cytomegalovirus (most common) Adenovirus Enteroviruses Hepatitis B Hepatitis C Herpes simplex virus Human immunodeficiency virus Lymphocytic choriomeningitis virus Parvovirus Rubella Smallpox Varicella-zoster Zika	*Borrelia burgdorferi* *Brucella* sp. *Campylobacter fetus* *Listeria monocytogenes* *Mycobacterium tuberculosis* *Salmonella typhi* *Treponema pallidum* (syphilis)	*Babesia microti* *Plasmodium sp.* (malaria) *Toxoplasma gondii* *Trypanosoma cruzi*	*Candida* sp.

Pathogenesis

The immune system of a pregnant woman is in a delicate balance between protecting the mother from infection while remaining tolerant of allogenic fetal antigens. This state of tolerance is achieved in part by a relative reduction in CD8+ T cell

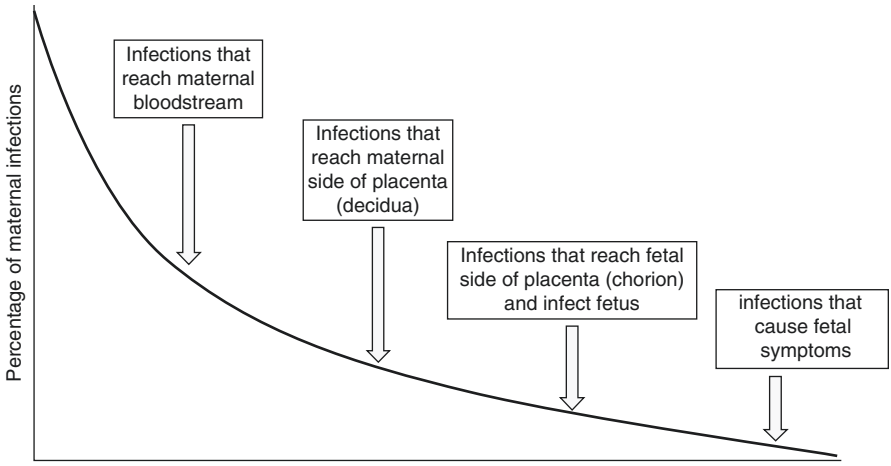

Fig. 1 Only a small fraction of maternal infections reach the fetus, due to the extensive physical and immunologic barriers designed to protect the fetus from maternal pathogens

function, the main driver of cell-mediated immunity [2]. Therefore, certain infections that require effective cytotoxic T cells for control may be more common or more severe in pregnancy (e.g., listeriosis, toxoplasmosis). Additionally, infections may trigger an increased cytotoxic T cell response that can disrupt the immune tolerance of the fetus and lead to fetal loss or premature delivery [3]. Unsurprisingly, many maternal infections are associated with higher rates of spontaneous abortion, stillbirth, and premature labor.

Fortunately, the incidence of fetal infection is markedly lower than maternal infection. There are several physical and immunologic barriers in place to protect the fetus from maternal pathogens (Fig. 1).

Maternal Infection

Maternal immunity: Preexisting immunity will prevent maternal infection in the first place and therefore decrease the risk of fetal infection. For example, preconceptional immunity to rubella eliminates the risk of congenital rubella syndrome in the fetus.

Maternal control of infection: The majority of infections in pregnant women are contained by their innate and adaptive immune systems and with appropriate antimicrobial therapy when indicated. Infections that do not reach the bloodstream do not have the opportunity to cross the placenta. In addition, some of the infections that do reach the maternal bloodstream are effectively controlled there by antibody and complement before the pathogen is able to reach the placenta.

Placental Control of Infection

When organisms evade maternal control and reach the bloodstream, they are carried to the maternal side of the placenta (the decidua) via the uterine arteries. Infection of the placenta is necessary—but not sufficient—for fetal infection. Histopathologic studies estimate the proportion of infections that are controlled by the placenta before fetal infection can occur at ~50% [4]. Two different factors account for the placental control of infection:

Immunologic control: The decidua has its own unique immunologic milieu that includes natural killer cells, toll-like receptors, phagocytes, and distinct cytokines that moderate the transmission of infection between the decidua and the fetal side of the placenta (the chorion) [5].

Physical barrier: Although maternal blood comes into very close approximation with fetal blood in the intervillous space, there is no direct communication between the two circulations under normal circumstances. Pathogens have to navigate this intervillous space either directly (e.g., cell-to-cell spread) or indirectly (e.g., by hijacking pinocytosis or active transport mechanisms) [6]. However, abnormal placentation, microhemorrhages, or overt maternal-fetal hemorrhage can lead to maternal-fetal mixing and increased risk for transplacental transmission of pathogens.

As a result, the placenta is a relatively effective barrier even in the setting of maternal bloodstream infection.

Fetal Infection

Pathogens that successfully cross the placenta and reach fetal circulation cause fetal infection. The effects of fetal infection vary widely and depend on several factors, the most important of which is the timing of fetal infection (Fig. 2). In general, fetal infection early in pregnancy is less common (since immature placental development means larger distances between the maternal and fetal circulation) but significantly more severe (due to disruption of early organogenesis by the infecting organism). In contrast, fetal infection late in pregnancy is more common, but signs of infection may be mild or absent. Signs of fetal infection include:

Pregnancy loss: Severe infection can result in spontaneous pregnancy loss or stillbirth. For example, untreated congenital syphilis is associated with fetal loss in up to 20% of cases [7]. Additionally, congenital infection may lead to elective abortion in situations when a prenatal diagnosis is made and ultrasonography suggests severe fetal malformations (e.g., congenital Zika infection or cytomegalovirus). Finally, very early fetal infection (i.e., <6 weeks) may cause embryonic death and reabsorption, although this incidence has not been determined as embryonic death generally occurs before the pregnancy is recognized [8].

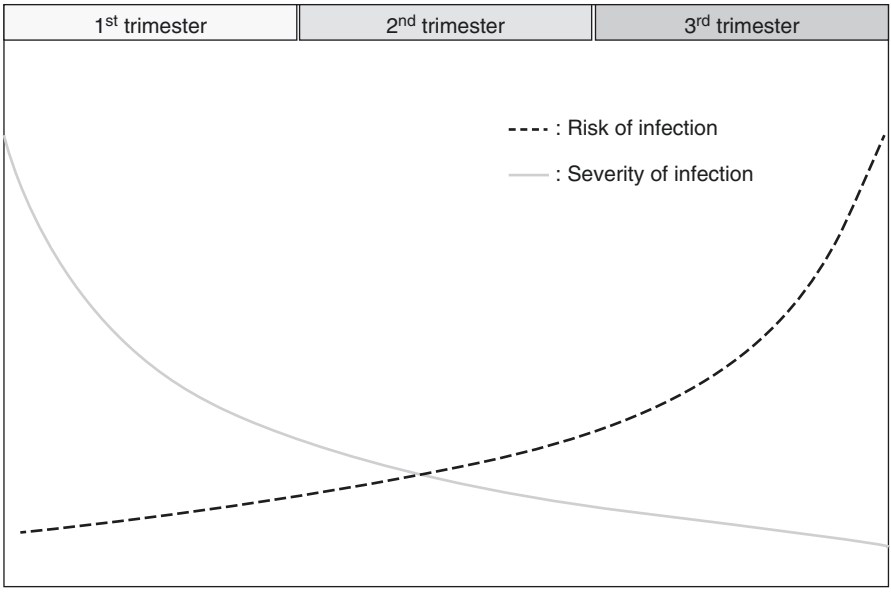

Fig. 2 Early in pregnancy, the severity of fetal infection (gray line) is significantly greater as it can disrupt organogenesis or cause pregnancy loss. However, the risk of fetal infection (black dashed line) is lower due to immature placental development. Later in pregnancy, as the maternal and fetal circulations grow closer, fetal infection is easier to achieve but less likely to result in overt clinical signs. This graph demonstrates why the majority of infants with congenital infections are asymptomatic in the newborn period

Premature delivery: In addition to the clinical signs listed below, fetal inflammation can trigger premature delivery. An increase in fetal interleukin production is hypothesized to be an important trigger of normal labor; presumably, increased cytokine production by the infected fetus triggers preterm labor [9].

Fetal signs: Disseminated infection of the fetus leads to a common final pathway of systemic inflammation, reticuloendothelial activation, and impaired hematopoiesis. This results in a nonspecific phenotype shared by many congenital infections (Box 1).

Box 1 Common Signs of Congenital Infection in the Fetus and Newborn
Intrauterine growth restriction
Small for gestational age
Maculopapular exanthems
Hepatosplenomegaly
Jaundice
Purpura or petechiae
Anemia
Chorioretinitis
Meningoencephalitis

Certain signs are more specific to certain pathogens, and these are discussed in detail in pathogen-specific chapters (e.g., cataracts in congenital rubella syndrome or periventricular calcifications in congenital cytomegalovirus infection.) However, other signs are common to virtually all congenital infections:

Growth restriction: Intrauterine growth restriction can result from impaired transfer of nutrients to the fetus across the infected placenta as well as increased consumption of nutrients due to unchecked fetal infection. Infected infants may have intrauterine growth restriction and/or be small for gestational age [10].

Reticuloendothelial activation: The fetal immune response to infection includes activation of macrophages, which leads to enlargement of the lymph nodes, spleen, and liver. Hepatosplenomegaly is a common, nonspecific sign of congenital infection.

Impaired hematopoiesis: Congenital infection involves the bone marrow, and the resulting inflammation suppresses hematopoiesis and leads to anemia and thrombocytopenia. In an effort to produce blood cells, the fetus will revert to sites of extramedullary hematopoiesis from earlier in fetal life, including the liver and spleen (which contributes to hepatosplenomegaly) and the skin (causing the classic "blueberry muffin" rash of blue hematopoietic cells within jaundiced skin). Purpura, petechiae, and pallor are other common findings.

Jaundice: Increased stress on the fetal liver from reticuloendothelial activation, extramedullary hematopoiesis, and the infection itself results in decreased bilirubin conjugation and transport. Affected infants are at higher risk for jaundice, often due to a combination of direct and indirect bilirubin.

The asymptomatic infant: Although all of the above-listed outcomes and findings are seen with fetal infection, it is important to remember that the majority of newborns with congenital infection are asymptomatic [1]. As a result, many congenital infections go undiagnosed during the newborn period. However, even clinically silent congenital infection can have a major impact on long-term morbidity. To name just a few examples, undiagnosed congenital cytomegalovirus infection can cause late-onset hearing loss, undiagnosed congenital toxoplasmosis can cause chorioretinitis in adulthood, and undiagnosed congenital syphilis can result in marked bone destruction and deformity [11–13].

References

1. Cantey JB, Sanchez PJ. Overview of congenital infections: the prominence of cytomegalovirus. Infect Disord Drug Targets. 2011;11:426–31.
2. Bonney EA. Immune regulation in pregnancy: a matter of perspective? Obstet Gynecol Clin N Am. 2016;43:679–98.
3. Rowe JH, Ertelt JM, Xin L, Way SS. Regulatory T cells and the immune pathogenesis of prenatal infection. Reproduction. 2013;146:R191–203.
4. Arora N, Sadovsky Y, Dermody TS, Coyne CB. Microbial vertical transmission during human pregnancy. Cell Host Microbe. 2017;21:561–7.

5. Zhang J, Dunk C, Croy AB, Lye SJ. To serve and protect: the role of decidual innate immune cells on human pregnancy. Cell Tissue Res. 2016;363:249–65.
6. Robbins JR, Bakardjiev AI. Pathogens and the placental fortress. Curr Opin Microbiol. 2012;15:36–43.
7. Qin J, Yang T, Xiao S, et al. Reported estimates of adverse pregnancy outcomes among women with and without syphilis: a systematic review and meta-analysis. PLoS One. 2014;9:e102203.
8. Robertson SA, Chin PY, Femia JG, Brown HM. Embryotoxic cytokines – potential roles in embryo loss and fetal programming. J Reprod Immunol. 2017;124:80–8.
9. Boyle AK, Rinaldi SF, Norman JE, Stock SJ. Preterm birth: inflammation, fetal injury and treatment strategies. J Reprod Immunol. 2017;119:62–6.
10. Resnik R. Intrauterine growth restriction. Obstet Gynecol. 2002;99:490–6.
11. Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. Clin Infect Dis. 2013;57:S178–81.
12. Braccio S, Sharland M, Ladhani SN. Prevention and treatment of mother-to-child transmission of syphilis. Curr Opin Infect Dis. 2016;29:268–74.
13. Mets MB. Eye manifestations of intrauterine infections. Ophthalmol Clin N Am. 2001;14:521–31.

Chagas Disease

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and Susan P. Montgomery

Epidemiology

Chagas disease is an infection caused by the protozoan parasite, *Trypanosoma cruzi* (*T. cruzi*). Chagas disease is an emerging health concern in the United States [1]. It is estimated that 300,000 persons living in the United States have chronic Chagas disease, including approximately 40,000 women of childbearing age [2]. An estimated 63–315 infants are born each year with congenital Chagas disease [2, 3].

Identifying women who have lived in regions where Chagas disease is endemic is important for determining those for whom diagnostic testing during pregnancy should be considered. Most women in the childbearing years who have Chagas disease acquired the infection while living in Mexico, Central America, or South America. The country of origin for approximately 85% of *T. cruzi*-infected women living in the United States is Mexico, El Salvador, Guatemala, Honduras, or Nicaragua. Among the remainder, many acquired infection in endemic regions in Argentina, Ecuador, Colombia, Brazil, or Bolivia [2].

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Pathogenesis

Chagas disease is a vector-borne infection. The usual mode of transmission is through exposure to bloodsucking triatomine insects, known as kissing bugs, which carry *T. cruzi* in their intestinal tracts. Triatomines defecate when they bite, and feces of infected insects containing *T. cruzi* trypomastigotes enter the human body through a bite wound, intact mucous membranes, or conjunctivae. Risk of infection among persons living in Chagas disease-endemic regions is greater for those with repeated and prolonged exposure to triatomine bugs, for example, through residence in a rural setting or living in adobe or thatched-roofed dwellings.

The vector of *T. cruzi* or a mammalian reservoir, or both, has been documented in at least 28 states in the southern half of the United States. Vector-borne Chagas disease acquired in the United States can occur but has been documented, to date, in fewer than 50 persons. These individuals have lived in locales in which the vector or an infected mammalian reservoir was identified, and they have had potential for exposure through working outdoors or participating in outdoor leisure activities [4]. Blood transfusion and organ transplantation are potential modes of transmission, but donor screening for *T. cruzi* has rendered these modes of transmission rare in the United States [5]. Breast milk-associated transmission has not been reported.

Newborn infants are at risk for congenital infection if their mothers have acute or chronic *T. cruzi* infection. Acute Chagas disease in children or adults usually manifests as a mild and self-limited influenza-like illness that lasts 4–8 weeks; parasitemia is present during acute phase infection. Infection then enters a chronic phase that, without treatment, persists for life. In chronic phase infection, the parasite is found in tissues of the body and is undetectable in peripheral blood. After years or decades, 20–40% of people with untreated infection develop Chagas cardiomyopathy or gastrointestinal disease. Features of cardiomyopathy can include arrhythmias, left ventricular dysfunction, congestive heart failure, apical rupture, and death. Gastrointestinal disease, including megaesophagus or megacolon, occurs less commonly but can cause substantial morbidity. Most women in the childbearing years who are living in the United States have chronic Chagas disease without symptoms and are unaware that they are infected.

Congenital transmission of *T. cruzi* occurs during the second or third trimesters of pregnancy [6]. Congenital infection is not thought to lead to congenital malformation, presumably because transmission occurs only after organogenesis is complete. The risk of transmission from a mother with chronic Chagas disease to her infant is 1–5% [2]. Factors thought to influence the likelihood of transmission include parasite strain, as there may be differences in strain virulence and invasiveness, level of parasites in the blood, and advancing maternal age, as this can impact integrity of the placental barrier. The risk is further increased for mothers with untreated human immunodeficiency virus coinfection.

Clinical Findings

Approximately 10–40% of *T. cruzi* congenitally infected infants have clinical findings at birth [7, 8]. Congenital Chagas disease can be associated with premature rupture of the membranes and preterm delivery [9]. Congenitally infected infants can present with low birth weight for gestational age, low Apgar scores, and findings such as hepatosplenomegaly, jaundice, anemia, or thrombocytopenia. Less common manifestations of congenital Chagas disease include hydrops fetalis, hepatitis, pneumonitis, cardiac failure, and meningoencephalitis. There are no pathognomonic clinical features of congenital Chagas disease. The diagnosis should also be considered when the maternal history is consistent with exposure to triatomines. There have been two confirmed cases reported in the United States, both to mothers who had immigrated from a country endemic for Chagas disease. Each infant presented with hydrops fetalis. There are no reports of congenital Chagas disease in the US birth cohort [10, 11].

Healthy-appearing, congenitally infected infants generally do well in infancy. However, 20–30% of children with untreated congenital Chagas disease, with or without signs of infection at birth, will develop irreversible life-threatening and often fatal heart disease after years or decades of silent infection [12]. Conduction system abnormalities are an early manifestation of Chagas heart involvement. Cardiac arrhythmias, apical or ventricular aneurysms, and progressive dilated cardiomyopathy with congestive heart failure carry a high risk of sudden death [13]. Gastrointestinal tract manifestations, which include megaesophagus and megacolon, are a debilitating but usually nonfatal late manifestation of untreated infection. Reactivation of infection, potentially causing severe disease, can occur in people who have suppressed immune systems in association with chemotherapy, organ transplantation, or human immunodeficiency virus infection.

Diagnosis

The diagnosis of Chagas disease in chronically infected pregnant women is established by serologic testing (Fig. 1) [14]. Pregnant women who have lived in a Chagas disease-endemic region should undergo screening for *T. cruzi* IgG antibodies through a commercial laboratory. Most commercial laboratories employ enzyme-linked immunoassay (ELISA)-based tests. Because no single serologic test is sufficiently sensitive and specific to establish the diagnosis, women who screen positive for *T. cruzi* antibody require confirmatory testing at a reference laboratory, such as the Parasitic Diseases Branch Laboratory at the Centers for Disease Control and Prevention (CDC). The standard approach for confirmation of the diagnosis is to perform at least two tests that use different techniques and different antigen preparations to detect antibodies to *T. cruzi* antigens. Testing at CDC is performed at no charge to the patient. The state health department should be contacted regarding

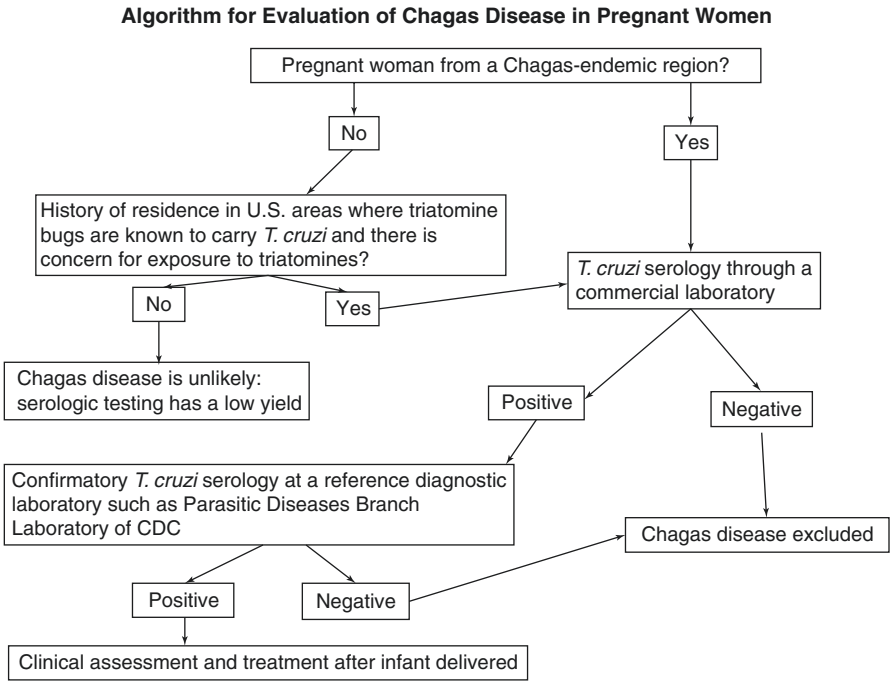

Fig. 1 Algorithm for the evaluation of Chagas disease in pregnant women

requests for testing at CDC; in many states, including those in which Chagas disease is a reportable infection, routing of specimens to CDC through the state public health laboratory is required. As of 2018, Chagas disease is a reportable infection in Arizona, Arkansas, Louisiana, Mississippi, Tennessee, and Texas. Women identified as having Chagas disease should be referred for clinical evaluation and, after the infant is delivered, treatment.

Infants born to women identified as positive for acute or chronic *T. cruzi* infection should undergo testing as soon as possible after birth (Fig. 2) [14]. Serologic testing is appropriate to determine infant risk if the mother was not tested during pregnancy. The only method to establish the diagnosis of congenital Chagas disease conclusively in a neonate is by detection of trypomastigotes, either by microscopic examination of fresh anticoagulated blood specimens or by PCR testing of whole blood through the Parasitic Diseases Branch Laboratory at CDC. The CDC reference laboratory employs a multi-targeted PCR testing algorithm using *T. cruzi* minicircle TaqMan real-time PCR and nuclear *T. cruzi* minisatellite TaqMan real-time PCR assays to detect circulating parasite DNA [10, 15]. Results of testing are usually available within 1 week.

A positive initial PCR result requires confirmation by testing a second blood specimen, because low levels of maternal DNA can, on occasion, be detected in uninfected infants born to infected mothers (Fig. 2). Detection of maternal DNA is

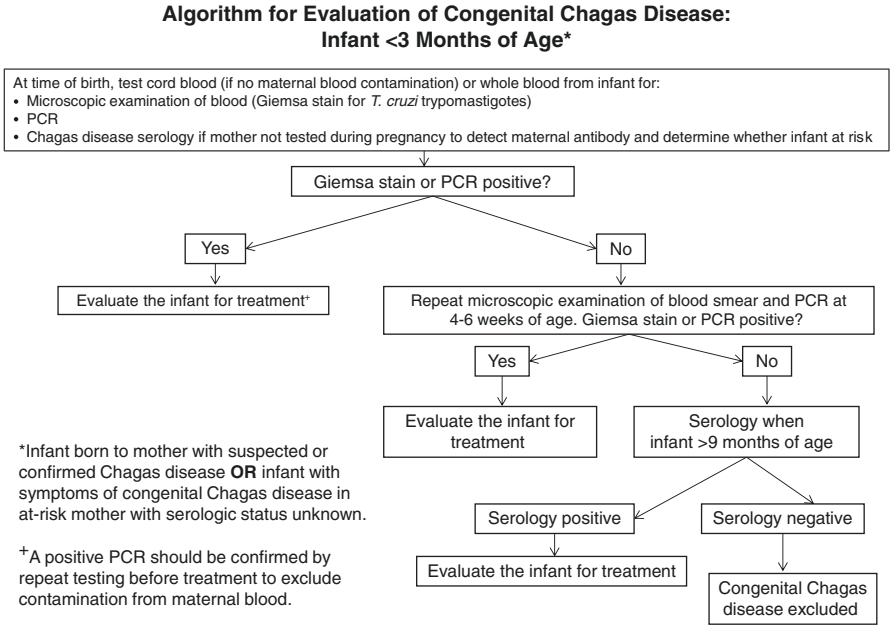

Fig. 2 Algorithm for evaluation of congenital Chagas disease in infants age <3 months

unlikely after the first week or two of life. If a second PCR is positive, the diagnosis of congenital Chagas disease is confirmed, and the infant should be evaluated clinically for signs of infection and treated. A negative initial PCR result should be followed by repeat testing when the infant is age 4–6 weeks to confirm absence of infection because the level of parasitemia increases after birth and is not always detectable in the first weeks of life [16]. If PCR testing at age 4–6 weeks is positive in an infant born to a mother with *T. cruzi* infection, the diagnosis of congenital Chagas disease is confirmed, and the infant should be evaluated clinically and treated.

If an infant born to a mother with chronic Chagas disease has no detectable parasitemia by molecular testing, the infant's serologic status should be monitored. Passively acquired maternal antibody wanes to undetectable levels by 9 months after birth. Infants who are uninfected should be antibody negative when tested at age 9–12 months. Similarly, if an infant born to a mother with chronic Chagas disease is first evaluated at age >3 months, serologic testing at age 9–12 months is the appropriate approach to document or exclude congenital infection (Fig. 3) [14].

Serologic testing through a commercial laboratory is indicated for all siblings of an infant exposed to maternal Chagas disease. Maternal relatives, including the grandmother, should also undergo screening serologic testing. Other family or household members who share the same risk history should also be screened for infection.

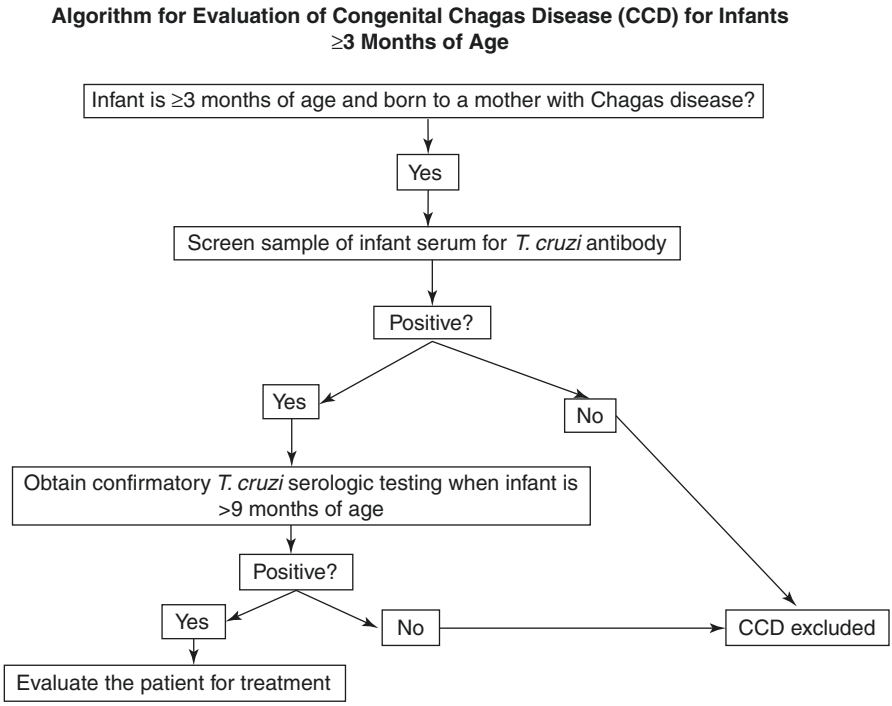

Fig. 3 Algorithm for evaluation of congenital Chagas disease for infants age ≥3 months

Treatment

The American Academy of Pediatrics recommends treatment for all cases of acute or congenital Chagas disease as well as chronic *T. cruzi* infection in children age <18 years [17]. The two medications employed for treatment of Chagas disease, including congenital infection, are benznidazole and nifurtimox. The dosing for both medications is age-specific. Benznidazole is administered at a dose of 10 mg/kg/day orally in two divided doses for 60 days in infants and children age <12 years. Nifurtimox is administered at a dose of 15–20 mg/kg/day orally in three or four divided doses for 90 days in infants and children age <10 years. Benznidazole is considered first-line treatment based upon the accumulated clinical experience and a more favorable side effect profile. The medications are generally well tolerated in neonates and infants [18]. In 2017, the US Food and Drug Administration granted accelerated approval to benznidazole for use in children ages 2–12 years with Chagas disease [19]. Information regarding treatment of *T. cruzi* infection for neonates or young infants with confirmed congenital Chagas disease can be obtained by contacting CDC's Parasitic Diseases Inquiries Service at (404) 718–4745 or parasites@cdc.gov, including assistance with release of nifurtimox under an investigational protocol.

Mothers identified as having chronic Chagas disease should receive treatment after delivery for their own well-being and because untreated infection can be transmitted during subsequent pregnancies. Treatment is contraindicated during pregnancy. Safety for infants exposed to antitrypanosomal medications through breastfeeding has not been evaluated; withholding maternal treatment until cessation of breastfeeding is recommended. Breastfeeding by mothers with chronic Chagas disease should be withheld only if there is bleeding around the nipples and then only until bleeding has resolved.

Prevention

There are important challenges to providing optimal care for infants with congenital Chagas disease. Enhanced awareness of Chagas disease as a health concern for women and infants born in the United States is needed to prompt diagnostic evaluation of at-risk infants and improve long-term outcomes from congenital Chagas disease. Substantial knowledge gaps regarding Chagas disease awareness and knowledge have been identified among healthcare providers, including obstetrician-gynecologists [20, 21]. In particular, education to promote targeted screening of at-risk pregnant women is needed.

Data are needed to better understand the extent and distribution of Chagas disease in the United States in the ~40,000 women of childbearing age with chronic *T. cruzi* infection so that efforts to identify and treat infants with congenital infection can be expanded. Diagnostic tests with improved specificity and sensitivity as well as validated rapid screening tests are needed to simplify the process of identification of *T. cruzi*-infected adults and infants. Safe, effective, and easily accessible drugs for treatment are needed. As these advances are underway, caregivers of neonates have an unparalleled opportunity to initiate evaluation of infants at risk for congenital Chagas disease so that those with confirmed *T. cruzi* infection can receive curative treatment early in life.

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References

1. Centers for Disease Control and Prevention. Parasites-Neglected parasitic infections. Available from: http://www.cdc.gov/parasites/npi.index.html. Accessed 27 Jul 2017.
2. Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. *Clin Infect Dis*. 2009;49:e52–4.
3. Montgomery SP, Starr MC, Cantey PT, Edwards MS, Meymandi SK. Neglected parasitic diseases in the United States: Chagas disease. *Am J Trop Med Hyg*. 2014;90:814–8.

4. Cantey PT, Stramer SL, Townsend RL, et al. The United States *Trypanosoma cruzi* infection study: evidence for vector-borne transmission of the parasite that causes Chagas disease among United States blood donors. *Transfusion*. 2012;52:1922–30.
5. AABB. Chagas Biovigilance Network. Available from: http://www.aabb.org/research/hemovigilence/Pages/chagas.aspx. Accessed 2 Sep 2018.
6. Carlier Y, Truyens C. Maternal-fetal transmission of *Trypanosoma cruzi*. In: Telleria J, Tibayrenc M, editors. *American trypanosomiasis-Chagas disease: One hundred years of research*. New York: Elsevier; 2010. p. 539–81.
7. Oliveira I, Torrico F, Muñoz J, Gascon J. Congenital transmission of Chagas disease: a clinical approach. *Expert Rev Anti Infect Ther*. 2010;8:945–56.
8. Freilij H, Altcheh J. Congenital Chagas' disease: Diagnostic and clinical aspects. *Clin Infect Dis*. 1995;21:551–5.
9. Gebrekristos HT, Buekens P. Mother-to-child transmission of *Trypanosoma cruzi*. *J Pediatr Infect Dis Soc*. 2014;3:S36–40.
10. Centers for Disease Control and Prevention. Congenital transmission of Chagas disease-Virginia, 2010. MMWR Morb Mortal Wkly Rep. 2012;61:477–9.
11. Alarcón A, Morgan M, Montgomery SP, et al. Diagnosis and treatment of congenital Chagas disease in a premature infant. *J Pediatr Infect Dis Soc*. 2016;5:e28–31.
12. Bern C, Martin DL, Gilman RH. Acute and congenital Chagas disease. *Adv Parasitol*. 2011;75:19–47.
13. Rassi A Jr, Rassi A, Martin-Neto JA. Chagas disease. *Lancet*. 2010;375:1388–402.
14. Congenital Chagas disease. Available from: https://www.cdc.gov/parasites/chagas/health_professionals/congenital_chagas.html. Accessed 8 Aug 2017.
15. Qvarnstrom Y, Schijman AG, Veron V, Aznar C, Steurer F, da Silva AJ. Sensitive and specific detection of *Trypanosoma cruzi* DNA in clinical specimens using a multi-target real-time PCR approach. *PLoS Negl Trop Dis*. 2012;6:e1689.
16. Bern C, Verastegui M, Gilman RH, et al. Congenital *Trypanosoma cruzi* transmission in Santa Cruz, Bolivia. *Clin Infect Dis*. 2009;49:1667–74.
17. American Academy of Pediatrics. American trypanosomiasis (Chagas disease). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015. p. 803–5.
18. Altcheh J, Moscatelli G, Moroni S, Garcie-Bournissen F, Freilij H. Adverse events after the use of benznidazole in infants and children with Chagas disease. *Pediatrics*. 2011;127:e212–8.
19. FDA News Release. FDA approves first U.S. treatment for Chagas disease. Available from: https://www.fda.gov/NewsEvents/Newsroon/PressAnnouncements/ucm573942.htm. Accessed 4 Sep 2017.
20. Stimpert KK, Montgomery SP. Physician awareness of Chagas disease, USA. *Emerg Infect Dis*. 2010;16:871–2.
21. Verani JR, Montgomery SP, Schulkin J, Anderson B, Jones JL. Survey of obstetrician-gynecologists in the United States about Chagas disease. *Am J Trop Med Hyg*. 2010;83:891–5.

Cytomegalovirus Infection

Andrea Ronchi, Lorenza Pugni, and Fabio Mosca

Epidemiology

Adult infection. Human cytomegalovirus (CMV) is an ubiquitous double-stranded DNA herpesvirus [1]. CMV is found only in humans; primary infection is followed by lifelong persistence of the virus in a latent phase and periodic reactivations. Reinfection with other strains of CMV may occur and can cause congenital infection in seropositive women [2]. The virus spreads from person to person via contact with infected bodily fluids, most notably saliva. CMV infection is very common; seropositivity ranges from 50 to 70% in the United States and Western Europe and is >90% in developing countries [3–5]. Low socioeconomic status, non-white race, sexual activity, and child care (either personally or professionally) are associated with CMV infection. This is because young children who acquire CMV infection in the first few years of life shed the virus in urine and saliva for an average of 18 months [6]. The annual rate of infection in seronegative individuals is approximately 1–2%, but seronegative women caring for young children acquire CMV at rates 10–25 times higher [7].

Congenital infection. Congenital CMV infection is the most common congenital infection by an order of magnitude [8]. Congenital CMV constitutes a major public health problem because of its frequency and its role as a cause of sensorineural hearing loss (SNHL) and central nervous system damage in children. In the United States, large prospective cohort studies suggest that approximately 0.5–0.7% (1 in 140–200) infants have congenital cytomegalovirus, which equates to approximately 25,000 infected infants annually [9]. Of these, more than 3500 will develop SNHL

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at some point during childhood. In developing countries, the incidence of congenital CMV is higher; rates as high as 5% have been reported in sub-Saharan Africa [10]. This may be due in part to concomitant infection with HIV; risk for congenital CMV infection is increased sixfold in infants who are also HIV-exposed. Immunosuppression is associated with increased CMV shedding in the genital tract and with a higher rate of CMV reactivation.

Postnatal infection. Postnatal infection is most commonly acquired by ingestion of CMV-positive breast milk. Blood transfusions are a theoretical route of infection, but CMV-safe transfusion practices have virtually eliminated infection of infants via blood transfusion [11]. The rate of infection among newborns fed CMV-positive breast milk varies from 15 to 70%.

Pathogenesis

CMV can be transmitted to the fetus following (1) a primary maternal infection during pregnancy, (2) reactivation of latent virus, or (3) reinfection with a new strain.

Primary infection. Primary CMV infection is reported in 1–4% of seronegative women during pregnancy, and the risk of viral transmission to the fetus is much higher in primary infected mothers than in mothers with preconceptional immunity (30–35% versus 1–2%) [7, 12].

Reactivation or reinfection. Preconceptional immunity to CMV provides substantial protection against intrauterine transmission, newborn disease, and sequelae. The relatively benign course in the infants of mothers with recurrent infection is presumably due to the modulating effect of preexisting maternal antibody. However, this protection is incomplete as intrauterine transmission and symptomatic congenital infections do occur in infants born to women who were seropositive before pregnancy. Therefore, considering the high seroprevalence in adults, congenital CMV infection occurs as a result of non-primary maternal infection in approximately two-thirds of infected infants [2].

The risk of congenital CMV infection increases with increasing gestational age, from 30 to 40% in the first trimester to 70–90% at the end of pregnancy. However, the risk of fetal damage is much higher when the fetus is infected in the early stages of pregnancy (see chapter “Pathogenesis of congenital infections”).

Clinical Findings

Older children and adults. Manifestations of primary infection in adults and children vary with the age and the immunocompetence of the host. Asymptomatic infections are the most common, particularly in young children. In contrast, nonspecific “influenza-like” illness, prolonged fever, fatigue, and malaise mimicking infectious mononucleosis or even overt hepatitis can occur in older children and adults. Immunocompromised hosts are at risk for end-organ dysfunction including retinitis and pneumonia [1].

Symptomatic congenital infection. Approximately 10–15% of congenitally infected infants have symptoms at birth. The clinical picture varies widely, ranging from mild findings to a severe disease with multiple organ system involvement, especially reticuloendothelial system and central nervous system (Table 1) [13]. The most common findings are petechiae, jaundice, hepatomegaly, splenomegaly, intrauterine growth restriction, and neurological signs or symptoms such as microcephaly, seizures, hypotonia, and lethargy [14]. Laboratory findings include thrombocytopenia, conjugated hyperbilirubinemia, high level of transaminases, and elevated cerebrospinal fluid protein level. Ocular and auditory damage, especially chorioretinitis and SNHL, may be present at birth. Brain abnormalities include congenital malformations (e.g., ventriculomegaly, polymicrogyria, cerebellar hypoplasia) and destructive lesions (e.g., impaired myelination, calcifications, frontal/temporal/germinolytic cysts), depending on the timing of infection.

It should be highlighted that the diagnostic criteria of symptomatic infection vary widely in the literature. For example, some authors have considered neonates with isolated intrauterine growth restriction as symptomatic, whereas other authors have not. In addition, neonates with isolated SNHL are not classified as symptomatic by all authors. In 2017, a consensus recommendation from a panel of experts suggested definitions of congenital CMV infection and disease previously published, with minor adjustments (Table 2) [15]. The mortality rate in symptomatic infants is about 5–10%; approximately 50% of survivors develop sequelae, including SNHL, visual deficits, and cognitive and motor deficits [13–15].

Asymptomatic congenital infection. The remaining 85–90% of infants with congenital CMV are asymptomatic at birth. The risk for long-term sequelae is reduced,

Table 1 Clinical and laboratory findings in infants with symptomatic congenital cytomegalovirus infection

Clinical findings	Infants with abnormality %
Petechiae	70–80
Jaundice	70
Hepatosplenomegaly	60
Microcephaly	50
Intrauterine growth retardation	50
Chorioretinitis/optic atrophy	20
Purpura	10
Seizures	<10
Laboratory findings	
Elevated aspartate aminotransferase (AST, >80 U/L)	80
Conjugated hyperbilirubinemia (direct bilirubin >4 mg/dL)	80
Thrombocytopenia (<100,000/mm^3)	75
Elevated cerebrospinal fluid protein (>120 mg/dL)	50

Adapted from references [13, 14]

Table 2 Definitions of congenital cytomegalovirus infection and disease among infants with confirmed infection, adapted from [15]

Classification	Recommendation
Moderate-severe	
Multiple manifestations attributable to congenital cytomegalovirus infection, including: • Thrombocytopenia • Petechiae • Hepatosplenomegaly • Intrauterine growth restriction • Hepatitis (elevated transaminases or direct bilirubin) or Central nervous system involvement, including[a]: • Microcephaly • Ventriculomegaly • Periventricular calcifications or echogenicity • Cortical or cerebellar dysplasia • Abnormal cerebrospinal fluid indices	Antiviral treatment for 6 months Multidisciplinary follow-up
Mild	
1–2 isolated, noncentral nervous system manifestations (e.g., mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase)	No treatment[b] Multidisciplinary follow-up
Asymptomatic infection with isolated sensorineural hearing loss • Sensorineural hearing loss (≥ 21 decibels) without other clinical findings of congenital CMV infection	
Asymptomatic without hearing loss • No apparent abnormalities to suggest congenital cytomegalovirus disease and normal hearing	No treatment Multidisciplinary follow-up

[a]No consensus on whether isolated lenticulostriate vasculopathy is considered evidence of central nervous system involvement [37]

[b]No evidence or formal recommendation to treat infants with mild disease or those who have isolated hearing loss, but some providers would offer treatment

but not eliminated, with asymptomatic infection. Approximately 10–15% will develop sequelae, particularly SNHL and learning disorders [16]. Notably, some infants initially classified as "asymptomatic" actually have signs of infection once a thorough evaluation is performed; the distinction has important prognostic implications. Although individual risk is greater for symptomatic infants, asymptomatic infants account for the majority of CMV-associated SNHL (Fig. 1).

Sensorineural hearing loss. SNHL is the most common sequela of congenital CMV infection, affecting about 50% of symptomatic and 10% of asymptomatic infants [17]. Congenital CMV infection is the most common cause of nongenetic hearing loss worldwide [18]. SNHL is bilateral in most cases and can vary from mild loss to profound impairment. SNHL may be present in the newborn period or appear as late as adolescence; the median age at onset is 33 months for symptomatic and 44 months for asymptomatic infants. Approximately 50% of congenitally infected infants with SNHL will have further deterioration of their hearing. The rate of progression seems to be similar regardless of whether the infant had a

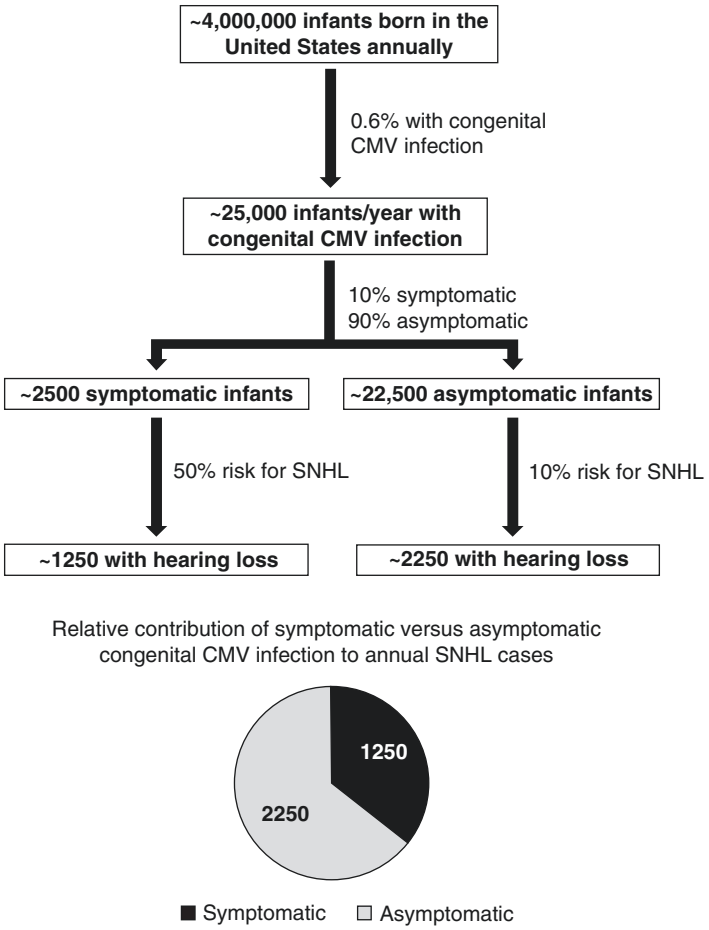

Fig. 1 Although case-by-case risk for sensorineural hearing loss (SNHL) is higher for infants with symptomatic congenital cytomegalovirus (CMV) infection, the preponderance of CMV-associated SNHL annually is actually due to asymptomatic infants due to their greater numbers. As a result, there is significant interest in research toward a universal screening program for congenital CMV infection, which would allow earlier identification, targeted screening, and prompt audiological correction of CMV-associated SNHL

symptomatic or an asymptomatic infection. CMV-related hearing loss can also fluctuate from mild to profound over time, but the overall pattern is one of deterioration [19].

Postnatal infection. In extremely premature infants, postnatal CMV infection may be asymptomatic or can present with nonspecific sepsis-like illness or with focal disease (e.g., hepatitis, pneumonitis) [11]. However, in contrast to congenital CMV infection, there is no compelling evidence that risk for long-term neurologic sequelae or SNHL is increased following postnatal CMV infection [20].

Diagnosis

Diagnosis of CMV infection can be based on serology or by detection of CMV in bodily fluids by PCR or culture. Serology is most often used for screening purposes, whereas PCR or culture is favored for confirmation of congenital CMV in neonates [15].

Diagnosis of Maternal Infection During Pregnancy

CMV screening during pregnancy remains a topic of intense interest and research, but still no consensus has been reached [21]. Therefore, universal CMV screening of pregnant women is not currently recommended as part of routine antenatal screening in any country. However, some providers view routine CMV screening at the beginning of pregnancy as useful as it can identify seronegative women that may benefit from education and preventive measures. "Serial" screening for primary infection during pregnancy in seronegative women is even more controversial, since there is no evidence-based prenatal treatment option (see Treatment, below).

Maternal primary infection is defined as detection of IgG antibody to CMV in a previously seronegative woman (seroconversion). Unfortunately, seroconversion during pregnancy is not easily documented, since maternal immunity status just before conception is often unknown. In addition, IgM antibodies to CMV may persist for months after primary infection and can reappear during reactivation or reinfection. When the exact timing of seroconversion is unknown, avidity testing can be useful [22]. The avidity test is a measure of the binding capacity of CMV-IgG antibodies. Low to moderate avidity is observed for 16–18 weeks following a primary infection. Therefore, a low-moderate IgG avidity in combination with detection of specific IgM antibodies supports a diagnosis of primary CMV infection within the preceding 3 months. There are currently no tests for diagnosing a recurrent infection during pregnancy.

If screening is not performed, serologic specific tests (IgG, IgM, IgG avidity) should be done when a pregnant woman has flu-like symptoms not attributable to another specific infection or if signs suggestive of fetal CMV infection are detected by ultrasound or MRI (e.g., cerebral ventriculomegaly, intracranial calcifications, cerebral cysts, microcephaly, fetal growth restriction, echogenic fetal bowel).

Diagnosis of Fetal Infection

Fetal infection can be confirmed by detection of virus or viral DNA from amniotic fluid. Although viral culture is 100% specific, it can be falsely negative; CMV DNA PCR is both sensitive and specific, especially when the amniotic fluid is sampled after 21 weeks gestation and at least 6 weeks after the onset of infection in the mother [23]. Cordocentesis may be performed to ascertain the presence of virus, viral DNA, and anti-CMV IgM in fetal blood. However, amniotic fluid sampling is

usually sufficient, so the benefit of deriving additional information from cordocentesis must be weighed against the risk of cord injury or pregnancy loss. Targeted ultrasonography is used to identify fetal abnormalities compatible with CMV disease; fetal MRI can reveal dysgenesis or injury to the central nervous system.

Diagnosis of Neonatal Infection

Congenital CMV infection should be suspected in neonates with any of the signs described in Tables 1 and 2 or those who had fetal ultrasound findings consistent with CMV infection. Asymptomatic infants often go undetected, but testing should be considered in certain situations:

1. Infants who refer their newborn hearing screen [24]
2. Infants born to HIV-positive mothers [25]
3. Infants with intrauterine growth restriction

Detection of CMV in urine or saliva by either real-time PCR or viral culture is the gold standard for diagnosis, with sensitivity and specificity both approaching 100% [9]. Testing should be performed within the first 3 weeks of life in order to distinguish congenital infection from postnatal infection [15]. Since most CMV-seropositive women shed CMV in breast milk, saliva samples should be obtained >1 h after feeding, and positive saliva tests in breastfeeding infants should be confirmed with a urine sample. The utility of blood or cerebrospinal fluid testing is uncertain as there is no clear association between viral load and prognosis.

For infants with confirmed congenital CMV infection, additional testing includes laboratory testing (complete cell blood count, platelet count, liver function tests), ophthalmological evaluation, and audiological evaluation by using auditory brainstem response [15]. Neuroimaging is also recommended: cerebral ultrasound is very reliable in detecting findings associated with congenital CMV infection such as ventriculomegaly, calcifications, periventricular pseudocysts, and lenticulostriate vasculopathy; MRI is better suited to identify cortical, white matter, and cerebellar dysplasia. CT is useful to detect ventriculomegaly and calcifications but is rarely performed today due the excessive radiation exposure.

Treatment

Maternal infection. There is no consensus currently regarding treatment of primary CMV infection in pregnant women. In 2005, a nonrandomized study by Nigro et al. [26] suggested that treatment of pregnant women who seroconvert in pregnancy with intravenous CMV-specific immune globulin may be effective in the prevention and treatment of congenital CMV infection. However, a randomized, placebo-controlled, double-blind study in 2014 did not demonstrate a significant reduction in congenital infection with immune globulin therapy (30% in the immune globulin

group, 44% in the placebo group, $P = 0.13$) [27]. Currently, two randomized, placebo-controlled trials are ongoing in the United States and in Europe to confirm this result. In the interim, experts recommend that hyperimmune globulin should not be administered to pregnant women who seroconvert during pregnancy.

Congenital infection. Infants with confirmed symptomatic congenital CMV infection should be treated with 6 months of antiviral therapy [28]. Options include oral valganciclovir or intravenous ganciclovir for infants who cannot be fed enterally [28, 29]. At present, there is no recommendation to treat asymptomatic or mildly symptomatic infants (Table 2), as this group has not been extensively studied. However, some providers prefer treatment for neonates with an abnormal hearing assessment, regardless of the presence or absence of other signs or symptoms [30]. Ultimately, treatment of congenital CMV is a prolonged process that requires significant caregiver effort, laboratory monitoring, and follow-up, and therefore decisions regarding treatment in borderline cases should be made in consultation with the family and a pediatric infectious disease specialist.

All infants with congenital CMV infection, whether symptomatic or asymptomatic at birth, require close, multidisciplinary follow-up. This includes the primary care physician, audiology, ophthalmology, and developmental surveillance at a minimum. Since hearing loss can present later in life, hearing screening is recommended every 6 months until the child is in school, then annually. Ophthalmologic examinations should occur annually. Close attention to speech delay, impaired socialization, motor delays, or other signs of abnormal neurodevelopment should be investigated promptly.

Postnatal CMV infection. Data on treatment of postnatal CMV infection is limited to case reports. Expert opinion varies, but some providers would recommend a short course (e.g., 2–3 weeks) of antiviral therapy for preterm infants with pneumonitis, hepatitis, or sepsis-like syndrome secondary to postnatal CMV [31]. In reality, it is often difficult to differentiate postnatal from congenital CMV infection if the infant does not have a negative test during the first 3 weeks of life.

Prevention

Congenital CMV prevention. Given the burden of congenital CMV infection following primary maternal infection, the development of an effective CMV vaccine likely would markedly reduce the burden of congenital CMV infection. Unfortunately, despite continued advances in CMV vaccine research, no product is yet under consideration for licensure [32]. Therefore, the most effective current prevention strategy is education of pregnant women (Table 3). This includes education regarding CMV awareness, modes of transmission, and preventive measures (e.g., handwashing after contact with urine or saliva from young children). Unfortunately, despite being by far the most common congenital infection, knowledge of congenital CMV among women of childbearing age is extremely low. A survey by Jeon et al. [33] demonstrated that few women of childbearing age (22%) had heard of congenital CMV, and even fewer were aware of prevention strategies. CMV education is

Table 3 Hygienic precautions to prevent CMV seroconversion during pregnancy among seronegative women

Washing hands often with water and soap for 15–20 s, especially after:
• Changing diapers
• Feeding a young child
• Wiping a young child's nose or drool
• Handling children's toys
Don't share food, drinks, or eating utensils used by young children
Don't put a child's pacifier in your mouth
Don't share a toothbrush with a young child
Avoid contact with saliva when kissing a child
Clean toys and other surfaces that come into contact with children's urine or saliva

viewed favorably by pregnant women and has been shown to reduce the risk for primary infection during pregnancy [34].

Postnatal CMV prevention. Preterm infants requiring transfusion should receive CMV-safe packed red blood cells. CMV-safe techniques, including irradiation and leukoreduction, minimize the risk of transfusion-associated postnatal CMV. Currently, there is no technique that eliminates CMV from breast milk without also interfering with its immunologic and nutritional value [35]. Since the short- and long-term risks of postnatal CMV are thought to be minimal, there is no recommendation to withhold fresh human milk from preterm infants [36].

References

1. Plosa EJ, Esbenshade JC, Fuller MP, Weitkamp JH. Cytomegalovirus infection. Pediatr Rev. 2012;33:156–63.
2. Ross SA, Arora N, Novak Z, Fowler KB, Britt WJ, Boppana SB. Cytomegalovirus reinfections in healthy seroimmune women. J Infect Dis. 2010;201:386–9.
3. Lanzieri TM, Kruszon-Moran D, Gambhir M, Bialek SR. Influence of parity and sexual history on cytomegalovirus seroprevalence among women aged 20-49 years in the USA. Int J Gynaecol Obstet. 2016;135:82–5.
4. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. Clin Infect Dis. 2010;50:1439–47.
5. Lanzieri TM, Dollard SC, Bialek SR, Grosse SD. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. Int J Infect Dis. 2014;22:44–8.
6. Cannon MJ, Stowell JD, Clark R, et al. Repeated measures study of weekly and daily cytomegalovirus shedding patterns in saliva and urine of healthy cytomegalovirus-seropositive children. BMC Infect Dis. 2014;14:569.
7. Hyde TB, Schmid DS, Cannon MJ. Cytomegalovirus seroconversion rates and risk factors: implications for congenital CMV. Rev Med Virol. 2010;20:311–26.
8. Cantey JB, Sanchez PJ. Overview of congenital infections: the prominence of cytomegalovirus. Infect Disord Drug Targets. 2011;11:426–31.
9. Boppana SB, Ross SA, Shimamura M, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. N Engl J Med. 2011;364:2111–8.

10. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013;26:86–102.
11. Josephson CD, Caliendo AM, Easley KA, et al. Blood transfusion and breast milk transmission of cytomegalovirus in very low-birth-weight infants: a prospective cohort study. JAMA Pediatr. 2014;168:1054–62.
12. Kagan KO, Hamprecht K. Cytomegalovirus infection in pregnancy. Arch Gynecol Obstet. 2017;296:15–26.
13. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. Clin Infect Dis. 2013;57:S178–81.
14. Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J. 1992;11:93–9.
15. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis. 2017;17:177–88.
16. Fowler KB, McCollister FP, Dahle AJ, et al. Progressive and fluctuating sensorineural hearing loss in infants with asymptomatic congenital cytomegalovirus infection. J Pediatr. 1997;130:624–30.
17. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. Pediatrics. 2014;134:972–82.
18. Kenna MA. Acquired hearing loss in children. Otolaryngol Clin N Am. 2015;48:933–53.
19. Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. Clin Infect Dis. 2013;57:S182–4.
20. Gunkel J, de Vries LS, Johngmans M, et al. Outcome of preterm infants with postnatal cytomegalovirus infection. Pediatrics. 2018;141:e20170635.
21. Mosca F, Pugni L. Cytomegalovirus infection: the state of the art. J Chemother. 2007;19:46–8.
22. Kaneko M, Ohhashi M, Minematsu T, Muraoka J, Kusumoto K, Sameshima H. Maternal immunoglobulin G avidity as a diagnostic tool to identify pregnant women at risk of congenital cytomegalovirus infection. J Infect Chemother. 2017;23:173–6.
23. Goegebuer T, Van Meensel B, Beuselinck K, et al. Clinical predictive value of real-time PCR quantification of human cytomegalovirus DNA in amniotic fluid samples. J Clin Microbiol. 2009;47:660–5.
24. Stehel EK, Shoup AG, Owen KE, et al. Newborn hearing screening and detection of congenital cytomegalovirus infection. Pediatrics. 2008;121(5):970.
25. Duryea EL, Sanchez PJ, Sheffield JS, et al. Maternal human immunodeficiency virus infection and congenital transmission of cytomegalovirus. Pediatr Infect Dis J. 2010;29:915–8.
26. Nigro G, Adler SP, La Torre R, Best AM. Passive immunization during pregnancy for congenital cytomegalovirus infection. N Engl J Med. 2005;353:1350–62.
27. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. N Engl J Med. 2014;370:1316–26.
28. Kimberlin DW, Jester PM, Sánchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015;372:933–43.
29. Kimberlin DW, Lin CY, Sánchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr. 2003;143:16–25.
30. Lim Y, Lyall H. Congenital cytomegalovirus – who, when, what-with, and why to treat? J Infect. 2017;74:S89–94.
31. Gunkel J, Wolfs TF, de Vries LS, Nijman J. Predictors of severity for postnatal cytomegalovirus infection in preterm infants and implications for treatment. Expert Rev Anti-Infect Ther. 2014;12:1345–55.
32. Schleiss MR, Permar SR, Plotkin SA. Progress toward development of a vaccine against congenital cytomegalovirus infection. Clin Vaccine Immunol. 2017;24:e00268-17.
33. Jeon J, Victor M, Adler SP, et al. Knowledge and awareness of congenital cytomegalovirus among women. Infect Dis Obstet Gynecol. 2006;2006:80383.

34. Vauloup-Fellous C, Picone O, Cordier AG, et al. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. J Clin Virol. 2009;46:S49–53.
35. Hamprecht K, Goelz R. Postnatal cytomegalovirus infection through human milk in preterm infants: transmission, clinical presentation, and prevention. Clin Perinatol. 2017;44:121–30.
36. American Academy of Pediatrics, Policy Statement. Breastfeeding and the use of human milk. Pediatrics. 2012;129:827–41.
37. Amir J, Schwarz M, Levy I, Haimi-Cohen Y, Pardo J. Is lenticulostriated vasculopathy a sign of central nervous system insult in infants with congenital CMV infection? Arch Dis Child. 2011;96:846–50.

Enteroviruses

Emily Carroll

Epidemiology

Genus *Enterovirus* is single-stranded RNA virus belonging to the *Picornaviridae* family [1]. Historically, enteroviruses were classified as polio and non-polio, but classification has been restructured in recent years to better accommodate new viral strains. *Enterovirus* species are now grouped by shared molecular serotypes of their viral polypeptide capsid (Table 1). However, since diagnosis of suspected enterovirus infection has moved to PCR-based testing, serologic typing is rarely available to the clinician.

Neonatal infection accounts for about 10% of all enterovirus infections in the United States annually [1]. While enterovirus typically demonstrates increased incidence in summer and fall seasons with peak incidence in August, infections may occur any time of the year [2].

Pathogenesis

Enteroviruses are transmitted through both fecal-oral route and respiratory secretions [3, 4]. The virus first replicates in the patient's upper respiratory tract or mesenteric lymphoid tissue for 1–3 days then disseminates hematogenously ("primary viremia," Fig. 1). This primary viremia may lead to end-organ infection and the overt clinical manifestations of neonatal enterovirus infection. A secondary viremia follows end-organ infection and lasts approximately 1 week until the emergence of enterovirus-specific antibody. In congenital enterovirus infection, maternal viremia leads to transplacental passage of enterovirus, and the fetus begins their infection with the primary viremia [5].

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Table 1 Reclassification of enteroviruses from the traditional "polio" and "non-polio" groups to groups based on viral capsid serology

Traditional classification	Current classification
Non-polio viruses • Echovirus (*e*nteric *c*ytopathogenic *h*uman *o*rphan) • Coxsackie A viruses • Coxsackie B viruses • Numbered enteroviruses Polioviruses	Human enterovirus (HEV) • HEV-A • HEV-B (includes Coxsackie B viruses) • HEV-C (includes polio) • HEV-D (includes enterovirus D68)

Congenital Infection

Neonatal enteroviral infections that present with signs of infection within 24–48 h of delivery are presumed to have been acquired in utero. In these congenital cases, the virus can be isolated from amniotic fluid and cord blood suggesting either congenital transmission or—rarely—ascending infection. It is most commonly seen when maternal infection is acquired late in pregnancy. In contrast to most other congenital infections, enterovirus has not been clearly associated with increased risk for abortion, prematurity, or congenital malformations.

Perinatal and Postnatal Infection

Enterovirus can also be transmitted during the perinatal or postnatal period through infant contact with maternal blood, stool, or genital secretions. Maternal illness within 1 week of delivery is associated with greatest risk of transmission. Infection due to perinatal transmission generally presents around age 3–5 days; if signs appear later, postnatal transmission through contact with secretions of infected persons is the most likely route of infection. Cohort studies suggest that transmission from family members, including parents and siblings, is relatively common [6]. Nosocomial transmission can be seen in NICU and nursery settings through shared providers of an infected neonate or spread from an infected provider to a neonate [7].

Clinical Findings

Enterovirus is capable of causing both extremely diverse clinical presentations and a wide spectrum of severity of illness. The majority of neonatal infections are asymptomatic (~80%) [8]. As neonates are at greatest risk for disseminated disease, the most common clinically apparent presentation is a nonspecific febrile illness with irritability, poor feeding, and lethargy which mimics bacterial sepsis. Table 2 summarizes the multitude of ways neonatal enteroviral infection can manifest in each organ system.

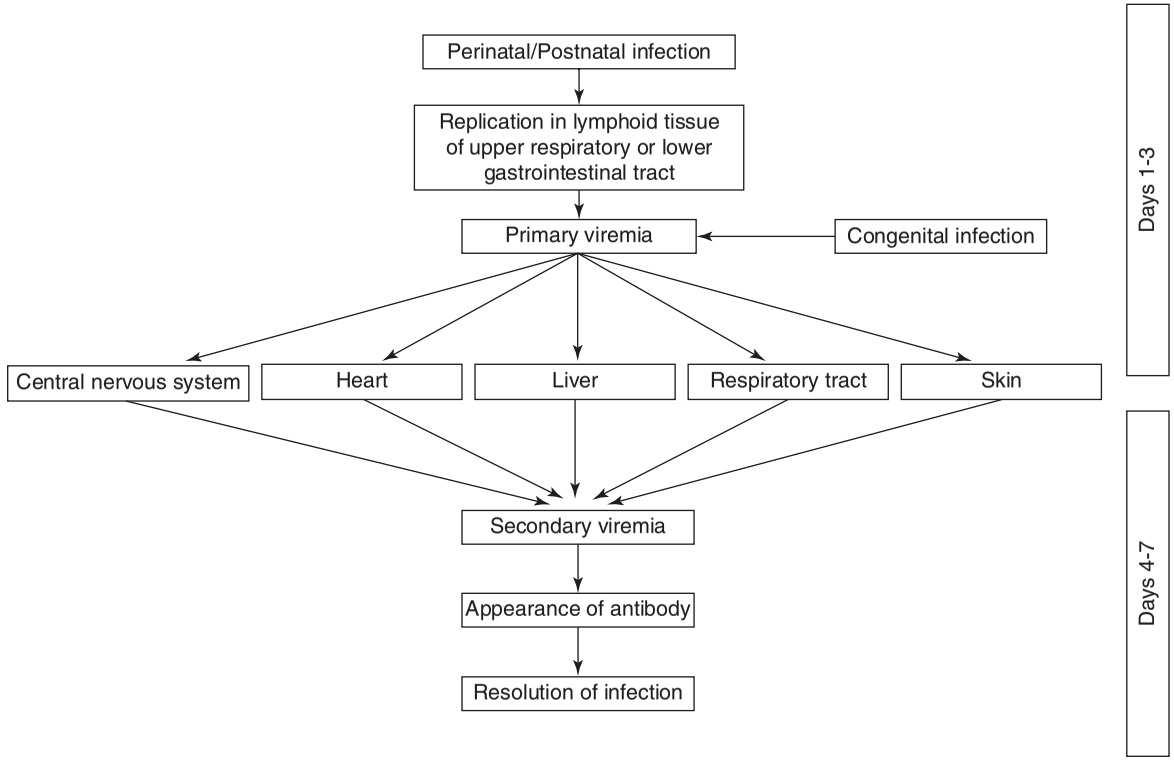

Fig. 1 Pathogenesis of neonatal enterovirus infection. Initial infection, either by entry through the gastrointestinal or upper respiratory tract or by transplacental spread, leads to a primary viremia which may in turn result in end-organ infection including the central nervous system (meningitis, encephalitis), heart (myocarditis), or other organs. Viremia is generally present, although there are periods where viral replication is limited to tissue and PCR testing of blood may be negative. Eventually, the appearance of type-specific antibody heralds the resolution of the infection; intravenous immunoglobulin may speed resolution if the aliquot contains the appropriate type-specific antibody

Table 2 Clinical presentations of neonatal enterovirus infections

System	Diagnosis	Clinical findings
Multisystem (most common, rarely diagnosed)	• Mild, nonspecific illness • Enteroviral sepsis	Fever, irritability, poor feeding, lethargy
CNS (>50% of diagnosed cases)	• Aseptic meningitis • Encephalitis	Irritability, poor feeding, fullness of anterior fontanel, seizure, altered mental status CSF: mild to moderate lymphocytic pleocytosis, elevated protein, and normal glucose
Cardiovascular	• Myocarditis	Arrhythmia, cardiomegaly, ventricular dilatation, heart failure, hypotension, myocardial ischemia
Gastrointestinal	• Hepatitis • Gastroenteritis • Pancreatitis	Jaundice, hepatomegaly, hepatic necrosis and failure, abdominal distention, vomiting, diarrhea
Integument	• Viral exanthem	Nonspecific maculopapular rash, hand-foot-mouth disease
Respiratory	• Upper or lower respiratory tract infection	Rhinorrhea, apnea, tachypnea, increased work of breathing, cough

Central Nervous System Infection

Aseptic meningitis or, rarely, true encephalitis is the most commonly identified presentation of neonatal enterovirus infection, accounting for >50% of cases [6, 9]. Clinical findings are indistinguishable from bacterial meningitis, including lethargy, apnea, or seizures. CSF analysis may be normal or may show pleocytosis and proteinosis, but CSF glucose levels are generally normal. In most cases, infection is limited to the meninges but encephalitis may occur, especially among preterm infants [10, 11].

Myocarditis

Neonatal enterovirus infections, particularly those due to Coxsackievirus B, are capable of infecting the heart during primary viremia. The resulting myocarditis generally presents with signs of acute heart failure, including feeding difficulty, listlessness, new gallop or murmur on auscultation, and respiratory distress. Most infants have concomitant fever. Although less common than central nervous system infection, myocarditis is a more specific manifestation of enterovirus infection due to the narrow range of pathogens capable of causing neonatal myocarditis [12]. Infants who survive the initial period of cardiovascular collapse have good prognoses.

Most neonatal enterovirus infections typically follow a benign course with resolution of symptoms 4–7 days after onset. A more severe disease course is associated with prematurity, maternal symptoms at time of delivery, neonatal symptom onset within the first week of life, and absence of passive maternal immunity with serotype-specific antibodies.

Mortality ranges from 0 to approximately 40% and is largely determined by clinical presentation. Myocarditis, hepatitis, and enteroviral sepsis increase risk of mortality and morbidity [6]. In contrast, mortality is lower with nonspecific febrile illnesses or central nervous system infection. However, the subset of infants with enteroviral encephalitis is at risk for persistent neurologic deficits including epilepsy, cerebral palsy, and learning difficulties.

Diagnosis

PCR is currently the cornerstone of diagnosis. However, other modalities are available including viral culture and serology.

PCR

Molecular studies detect enteroviral RNA in blood, CSF, stool, and respiratory secretions. PCR is the most specific and sensitive means of detection of enterovirus, and since results may be available within hours, PCR has become the gold standard for clinical diagnosis, and blood should be included when CSF is being tested [13, 14]. The use of routine enterovirus PCR testing of blood and CSF in febrile young infants is cost-effective [15].

It is important to remember that since enterovirus is common, often asymptomatic, and shed for weeks after infection from the upper respiratory and lower gastrointestinal tract [16]. Therefore, detection of enterovirus by PCR from a mucosal site does not necessarily equate to causation. Other etiologies for the clinical presentation should not be overlooked. Additionally, most PCR assays cannot distinguish between different types of enteroviruses and may report enterovirus and rhinovirus together as they both belong to the *Picornaviridae* family, and the detection of "rhino-/enterovirus" from the nasopharynx should not preclude additional workup if other conditions are suspected.

Viral Culture

Enterovirus can be isolated in cell culture from a variety of specimens including nasopharyngeal or oropharyngeal swabs, stool, CSF, pericardial fluid, and blood. The virus is then identified through immunofluorescence staining, typing with antisera, or RNA sequencing. Low sensitivity and comparatively long turnaround times (3–8 days) limit the clinical utility of viral culture.

Serology

Serology takes weeks to result and has limited use in the diagnosis of acute infection as titers must be compared between acute and convalescent stages. Absence of common antigen among serotypes prevents development of a universal assay and limits sensitivity.

Histology

In contrast to other viral pathogens (e.g., cytomegalovirus, herpes simplex virus), enterovirus does not have specific histopathologic features, which prevents definitive diagnosis through histopathology. However, tissue can be tested with PCR or immunofluorescence as per above. In cases where blood PCR is negative but enteroviral disease is strongly suspected (e.g., myocarditis or hepatitis), tissue-based testing can be useful.

Treatment

The majority of neonatal enterovirus infections are self-limiting and require only supportive therapy. For severe infections or high-risk patients, limited treatment options are available:

- Intravenous immunoglobulin (IVIG) may shorten the duration of viremia or mitigate disease severity when used prophylactically. It has been used in chronic meningoencephalitis and severe neonatal infections, but studies to date are inconclusive and use remains investigational. The effectiveness of IVIG is determined by the presence or absence of type-specific neutralizing antibody; some experts recommend multiple small aliquots of IVIG from different products or preparations (rather than a single large dose from one product) to increase the chance of at least one dose containing neutralizing antibody [17, 18].
- Pleconaril is an antiviral agent that has activity against enterovirus. Data regarding efficacy in neonates is very limited, and pleconaril is not currently available for clinical use in the United States [19, 20].

Prevention

Viral shedding in respiratory secretions can persist for up to 3 weeks and in feces for up to 8 weeks following primary infection [16]. Hospitalized neonates should be placed in contact precautions and cohorted for duration of illness. Appropriate handwashing and careful disposal following diaper changes are also essential to prevent spread and outbreaks in hospital and home settings [21].

References

1. Tebruegge M, Curtis N. Enterovirus infections in neonates. Semin Fetal Neonatal Med. 2009;14:222–7.
2. Piralla A, Mariani B, Stronati M, Marone P, Baldanti F. Human enterovirus and parechovirus infections in newborns with sepsis-like illness and neurological disorders. Early Hum Dev. 2014;90(S1):S75–7.
3. Grist NR, Bell EJ, Assaad F. Enterovirus in human disease. Prog Med Virol. 1978;24:114–57.
4. Cherry JD, Krogstad P. Enteroviruses, parechoviruses, and scaffold viruses. In: Cherry JD, Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PT, editors. Textbook of pediatric infectious diseases. 7th ed. Saunders: Philadelphia; 2014.
5. Kibrick S, Bernirschke K. Acute aseptic myocarditis and meningoencephalitis in the newborn child infected with Coxsackie virus group B, type 3. N Engl J Med. 1956;255:883–9.
6. Abzug MJ, Levin MJ, Rotbart HA. Profile of enterovirus disease in the first two weeks of life. Pediatr Infect Dis J. 1993;12:820–4.
7. Huang FL, Chen CH, Chen PY. An outbreak of enterovirus 71 in a nursery. Scand J Infect Dis. 2010;42:609–12.
8. Jenista JA, Powell KR, Menegus MA. Epidemiology of neonatal enterovirus infection. J Pediatr. 1984;104:685–90.
9. Morens DM. Enteroviral disease in early infancy. J Pediatr. 1978;92:374–7.
10. Verboon-Maciolek MA, Groenendaal F, Cowan F, et al. White matter damage in neonatal enterovirus meningoencephalitis. Neurology. 2006;66:1267–9.
11. Cantey JB, Hanners N, Mittal V. A persistently fussy, febrile infant. Clin Pediatr. 2012;51:93–5.
12. Schlapbach LJ, Ersch J, Balmer C, et al. Enteroviral myocarditis in neonates. J Paediatr Child Health. 2013;49:451–4.
13. Simpson KE, Storch GA, Lee CK, et al. High frequency of detection by PCR of viral nucleic acid in the blood of infants presenting with clinical myocarditis. Pediatr Cardiol. 2016;37:399–404.
14. Dagan R, Jenista JA, Prather SL, Powell KR, Menegus MA. Viremia in hospitalized children with enterovirus infections. J Pediatr. 1985;106:397–401.
15. Wallace SS, Lopez MA, Caviness AC. Impact of enterovirus testing on resource use in febrile young infants: a systemic review. Hosp Pediatr. 2017;7:96–102.
16. Chung PW, Huang YC, Chang LY, Lin TY, Ning HC. Duration of enterovirus shedding in stool. J Microbiol Immunol Infect. 2001;34:167–70.
17. Abzug MJ, Keyserling HL, Lee ML, Levin MJ, Rotbart HA. Neonatal enterovirus infection: virology, serology, and effects of intravenous immune globulin. Clin Infect Dis. 1995;20:1201–6.
18. Dagan R, Prather SL, Powell KR, et al. Neutralizing antibodies to non-polio enteroviruses in human immune serum globulin. Pediatr Infect Dis. 1983;2(6):454.
19. Abzug MJ, Cloud G, Bradley J, et al. Double blind placebo-controlled trial of pleconaril in infants with enterovirus meningitis. Pediatr Infect Dis J. 2003;22:335–41.
20. Abzug MJ, Michaels MG, Wald E, et al. A randomized, double-blind, placebo-controlled trial of pleconaril for the treatment of neonates with enterovirus sepsis. J Pediatric Infect Dis Soc. 2016;5:53–62.
21. Fuchs I, Golan A, Borer A, et al. Proactive approach to containment of enterovirus infection in the nursery. Clin Pediatr. 2013;52:639–44.

Hepatitis B in the Perinatal Period

Rebecca A. M. Pierce-Williams and Jeanne S. Sheffield

Epidemiology

The prevalence of chronic HBV varies globally, from <2% in low-prevalence areas such as North America, Australia, and Western Europe to 5–10% in East Asia and sub-Saharan Africa [3]. The variation in prevalence is predominantly due to age of infection, and in high-prevalence areas, the most common mode of transmission is mother-to-child, or transmission in early childhood [1, 4]. This is in contrast to low-prevalence areas, where the common modes of transmission are through sexual contact and intravenous drug use [1, 5]. The risk of developing chronic HBV depends on the age of infection, with rates of 80–90% in individuals infected in the first year of life, 30–50% in children <6 years of age, and <5% in healthy adults [1, 2, 6].

Since implementation of the HBV vaccine in the 1980s, new cases of HBV have drastically decreased. The vaccine is 95% effective in preventing new infection with HBV [1]. In 2014 in the United States, the incidence of HBV was 0.9 cases per 100,000 persons—an 82% decline in new infections since 1991, when childhood vaccination started [7]. The World Health Organization promotes universal immunization programs beginning at birth. As of 2015, 185 countries have adopted vaccine programs for infants, and global coverage with the recommended three-dose HBV vaccine is approximately 83% [8]. Ninety-six countries are now vaccinating newborns within 24 h of life. Even with these improvements, only 39% of newborns worldwide are receiving the first dose of the vaccine in the recommended timeframe [8].

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Pathogenesis

Hepatitis B virus is a member of the *Hepadnaviridae* family and a double-stranded DNA virus that mainly infects cells in the liver but has also been found in bile duct epithelium, pancreas, kidneys, and lymphoid tissues [9, 10]. HBV is spread through exposure to blood and bodily fluids including saliva, semen, and vaginal secretions [1, 7]. It can be contracted percutaneously, or through mucous membranes [1, 7]. Our focus here is on mother-to-child transmission, where the primary route is through mucous membranes during passage through the birth canal [7]. Only a small percentage of cases are acquired intrauterine, likely from transplacental "leakage" of maternal blood during a threatened abortion or preterm labor [11, 12].

A maternal HBV DNA level of >100,000 IU/mL is the most important independent risk factor for MTCT; transmission rates are reportedly 90% if the viral load is greater than 10^5 copies/mL [13, 14]. These rates are decreased with infant immunoprophylaxis (see Prevention, below). However, even with immunoprophylaxis, transmission rates of 8–30% have been reported from women with high viral loads [13, 15, 16]. In a retrospective study by Zou et al. [16], immunoprophylaxis failure rates for HBV DNA levels of <6, 6–6.99, 7–7.99, and ≥8 $\log_{10}$ copies/mL were 0%, 3.2%, 6.7%, and 7.6%, respectively. Rates of transmission also vary depending on the presence of the hepatitis B e antigen (HBeAg), a marker of infectivity. Without measures to prevent transmission, the rates of MTCT from mothers who are HBeAg positive are 70–90% [4, 17]. In mothers without HBeAg, rates of MTCT are 10–40% [4]. Timing of maternal acquisition of acute HBV also affects the risk of vertical transmission, with the highest risk in the third trimester or near the time of delivery [18].

Data surrounding the risk of MTCT with invasive tests such as amniocentesis and chorionic villus sampling are limited. A case-control study in 2014 showed a significant increase in rates of vertical transmission in women undergoing

Box 1 Risk Factors for Mother-to-Child Transmission of Hepatitis B Virus

Maternal
- High maternal viremia
- HBeAg positive
- Maternal infection near time of delivery

Neonatal
- Failure to receive appropriate passive-active immunoprophylaxis (hepatitis B vaccine and immune globulin)

Other
- Invasive testing (i.e., chorionic villi sampling, amniocentesis) when viral load is high
- Preterm labor
- Threatened abortion

amniocentesis versus controls when stratified by HBV DNA levels ≥7 $\log_{10}$ copies/mL (50% vs. 4.5%, respectively) [19]. Women considering invasive testing should be counseled about the possible increased risk of transmission with high viral loads, but if genetic testing is indicated, it can be offered [20]. These women should be counseled on available noninvasive screening options [21].

Clinical Findings

Acute infection in adults. After an incubation period of approximately 75 days (range, 30–180 days), symptoms of acute HBV may present in 30–50% of infected individuals; however, most people with acute HBV, including pregnant women, are asymptomatic [1]. Of those who do exhibit symptoms, they include nausea, vomiting, abdominal pain, fatigue, jaundice, loss of appetite, and joint pain [1, 7]. Extrahepatic signs such as a cutaneous rash may also occur [22]. The duration of these signs and symptoms ranges from only a few weeks up to 6 months [7]. The risk of an acute infection causing liver failure (acute fulminant hepatitis) is low, but when this occurs, it can lead to death, with fatality rates of 0.5–1.5% [22].

Acute infection in children. Infants and young children infected with HBV typically have no signs or symptoms [22]. This highlights the importance of serologic follow-up testing after perinatal HBV exposure (see Prevention, below).

Chronic infection. Adults and children with chronic HBV are usually asymptomatic, until development of liver cirrhosis, hepatocellular carcinoma, or liver failure [1, 7, 22].

Diagnosis

Diagnosis of HBV starts with a thorough history and physical exam. Both the American College of Obstetricians and Gynecologists and the US Preventive Services Task Force recommend universal testing for hepatitis B virus in pregnancy [21, 23]. Screening is based on detection of hepatitis B surface antigen (HBsAg). HBsAg can be detected beginning 30–60 days after infection [1]. A positive test requires further testing to evaluate for acute versus chronic infection (Table 1). Testing includes hepatitis B surface antibody (anti-HBs), total hepatitis B core antibody (anti-HBc), and hepatitis B core IgM antibody (IgM anti-HBc). Presence of the IgM anti-HBC indicates acute infection. Positive results for the HBsAg must be reported to the state health department, based on state reporting requirements [21, 24].

Once a diagnosis of HBV is made, additional laboratory testing includes evaluation of HBV viral load and HBeAg, liver function testing (i.e., aminotransferases, alkaline phosphatase, coagulation studies), and a complete blood count. These women should also be screened for coinfection with hepatitis C virus, hepatitis delta virus, and human immunodeficiency virus. Hepatitis A testing can also be done to evaluate for a need for vaccination. Imaging studies, such as a liver ultrasound, should also be performed in all patients [25].

Table 1 Interpretation of hepatitis B virus (HBV) serologic markers

Serologic test	Result	Interpretation
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible to HBV
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune due past infection
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to vaccination
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acute infection
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronic infection
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Negative Positive Negative Negative	1. False positive—susceptible to HBV 2. Resolved infection 3. Chronic infection—"low level" of infectivity 4. Passive transfer to infant of HBV infected mother

Adapted from [22]

Treatment

All pregnant women should be screened for HBsAg at their first prenatal visit. In women who engage in high-risk behaviors (i.e., injection drug use, HBsAg-positive sexual partner), testing should also be done when admitted for delivery [22]. A positive test requires follow-up, as noted in the section on "Diagnosis."

Women who have not previously been vaccinated for HBV should receive the vaccine if they are at high risk of infection. High-risk individuals include injection drug users, HIV-positive persons, household contacts of persons with chronic HBV, health-care workers, those with >1 sexual partner in the past 3 months, recent diagnosis of a sexually transmitted infection, developmentally delayed persons in a long-term care facility, hemodialysis patients, and those traveling to high-prevalence regions [21, 26]. Currently available adult vaccines include two single-antigen vaccines (Engerix-B® and Recombivax HB®) and one combination hepatitis A and B vaccine (Twinrix®) [21, 26]. Each of these is to be administered as a three-dose vaccine series, by intramuscular injection.

In the third trimester, women with known HBV infection should have repeat viral load testing completed in order to determine if they would benefit from antiviral therapy. The American Association for the Study of Liver Diseases and the Society for Maternal-Fetal Medicine propose antiviral therapy in pregnant women with >6 log10 copies/mL (1 million copies/mL, or 200,000 IU/mL) [20, 25]. Due to

its safety in pregnancy and the low risk of resistance, the first-line antiviral therapy is tenofovir [20, 25]. Alternative therapies include telbivudine and lamivudine. Timing of initiation of therapy has not been well studied, but many suggest starting at 28–32 weeks gestation [25]. Upon discontinuation of therapy, women must be monitored closely for aminotransferase flares [25].

Several studies have been performed to evaluate the benefit of HBIG administration to pregnant women infected with HBV. A Cochrane review determined that because of the low quality of the studies, no benefit could be shown [27].

While there have been studies to evaluate the benefit of elective cesarean delivery in reducing the risk of HBV transmission, the data are conflicting and the quality is low. Cesarean delivery solely for prevention of HBV transmission is not recommended [20, 25]. In addition, there is not enough data to make recommendations on the use of internal fetal monitoring during the intrapartum course [21].

Prevention

In order to prevent MTCT, it is recommended that children born to mothers with HBV infection receive passive-active immunoprophylaxis. This is a combination of HBIG (the passive component) and the single-antigen hepatitis B vaccine (Recombivax HB® or Engerix-B®) (the active component) [21, 22]. When given as soon as possible (no later than 12 h of life), followed by completion of the three- or four-dose vaccine series, immunoprophylaxis is 85–95% effective in preventing transmission from mothers with HBsAg and HBeAg positivity [4, 28]. Passive-active prophylaxis should also be given to newborns of mothers with unknown HBsAg status (Table 2) [20].

Women with HBV, but with no other contraindications to breastfeeding, should be encouraged to do so, as long as the infant receives passive-active immunoprophylaxis at birth [20, 21, 29]. Women on antiviral therapy should be counseled that although drug labels may recommend against breastfeeding while on these

Table 2 Passive-active immunoprophylaxis against hepatitis B infection for infants by maternal hepatitis B surface antigen status

Maternal HBsAg status at delivery	Hepatitis B vaccine	Hepatitis B immune globulin
Positive	Within 12 h	Within 12 h
Negative	≥*2 kg*: Within 24 h	Not indicated
	<*2 kg*: At 1 month of age or discharge, whichever comes first	
Unknown/ pending	Within 12 h	≥*2 kg*: If mother's HBsAg test is positive *OR* at age 7 days or hospital discharge if mother's HBsAg status still unknown
		<*2 kg*: Within 12 h unless mother's HBsAg testing is negative by then

medications, the American Association for the Study of Liver Diseases reports that there is minimal excretion of the drugs in breast milk. The overall risk of exposure is unknown [25].

Follow-up of neonates born to mothers with HBV involves completion of the vaccine series and postvaccination testing (see chapter "Immunizations in the Nursery"). The recommended schedule for the vaccine series with the single-antigen vaccine is dose #1 within 12–24 h of life, dose #2 at 1–2 months of age, and dose #3 at 6 months of age (not sooner than 24 weeks of age) [22]. If the series is completed with a combination vaccine, an "extra" dose is often given at 4 months but does not preclude the need for the 6-month dose. For HBV-exposed infants with a birth weight of <2 kg who receive HBV vaccine at birth, the immune response to the first dose may not be adequate; those infants should receive three more doses, starting after 1 month of age [22].

At 9–12 months of age, postvaccination testing for HBsAg and anti-HBs can be completed to rule out infection and to evaluate for protective titers [22]. If positive for HBsAg, the proper testing and follow-up should be done in a timely manner. If HBsAg is negative and anti-HBs is ≥10 mIU/mL, the infant is considered protected and no intervention is needed. If anti-HBs is <10 mIU/mL, additional immunization and follow-up testing should be completed (see chapter "Immunizations in the Nursery") [22].

References

1. World Health Organization. Media Centre. Hepatitis B. Fact sheet. Updated July 2016. http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed 6 Apr 2017.
2. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the global burden of disease study 2013. Lancet. 2015;385:117–71.
3. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30:2212.
4. Tran TT. Hepatitis B in pregnancy. Clin Infect Dis. 2016;62:S314–7.
5. Goldstein ST, Alter MJ, Williams IT, et al. Incidence and risk factors for acute hepatitis B in the United States, 1982–1998: implications for vaccination programs. J Infect Dis. 2002;185:713–9.
6. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis. 1995;20:992–1000.
7. Centers for Disease Control and Prevention. Hepatitis B FAQs for health professionals. Updated August 4, 2016. https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm. Accessed 6 Apr 2017.
8. World Health Organization. Media Centre. Immunization coverage. Fact sheet. Reviewed March 2017. http://www.who.int/mediacentre/factsheets/fs378/en/. Accessed 6 Apr 2017.
9. Pontisso P, Poon MC, Tiollais P, Brechot C. Detection of hepatitis B virus DNA in mononuclear blood cells. Br Med J Clin Res. 1984;288:1563–6.
10. Halpern MS, England JM, Deery DT, et al. Viral nucleic acid synthesis and antigen accumulation in pancreas and kidney of Pekin ducks infected with duck hepatitis B virus. Proc Natl Acad Sci U S A. 1983;80:4865–9.
11. Xu DZ, Yan YP, Choi BC, et al. Risk factors and mechanism of transplacental transmission of hepatitis B virus: a case-control study. J Med Virol. 2002;67:20–6.

12. Lin HH, Lee TY, Chen DS, et al. Transplacental leakage of HBeAg-positive maternal blood as the most likely route in causing intrauterine infection with hepatitis B virus. J Pediatr. 1987;111:877.
13. Pan CQ, Duan ZP, Bhamidimarri KR, et al. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. Clin Gastroenterol Hepatol. 2012;10:452–9.
14. Pawlowska M, Pniewska A, Pilarczyk M, Kozielewicz D, Domagalski K. Prophylaxis of vertical HBV infection. Expert Opin Drug Saf. 2016;15:1361–8.
15. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust. 2009;109:489–92.
16. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat. 2012;19:e18–25.
17. Chang M-H. Hepatitis B virus infection. Semin Fetal Neonatal Med. 2007;12:160–7.
18. Jonas MM. Hepatitis B and pregnancy: an underestimated issue. Liver Int. 2009;29:133.
19. Yi W, Pan CQ, Hao J, Hu Y, Liu M, Liang D. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. J Hepatol. 2014;60:523–9.
20. Dionne-Odom J, Tita A, Silverman N. Society for Maternal-Fetal Medicine (SMFM) consult series: #38: hepatitis B in pregnancy screening, treatment, ,and prevention of vertical transmission. Am J Obstet Gynecol. 2016;214:6–14.
21. American College of Obstetricians and Gynecologists. ACOG practice bulletin no 86. Viral hepatitis in pregnancy. Obstet Gynecol. 2007;110:941–55.
22. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices (ACIP) part 1: immunization of infants, children, and adolescents. Advisory committee on immunization practices (ACIP). MMWR Recomm Rep. 2005;54:1–31.
23. Lin K, Vickery J. Screening for hepatitis B virus injection in pregnancy women: evidence for the US preventive services task force reaffirmation recommendation statement. Ann Intern Med. 2009;150:874–6.
24. Centers for Disease Control and Prevention. 2017 nationally notifiable infectious diseases. https://wwwncdcgov/nndss/conditions/notifiable/2017/infectious-diseases/ Accessed 12 Apr 2017.
25. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261–83.
26. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices (ACIP) part 2: immunization of adults. MMWR Recomm Rep. 2006;55:1–33.
27. Eke AC, Eleje GU, Eke UA, Xia Y, Liu J. Hepatitis B immunoglobulin during pregnancy for prevention of mother-to-child transmission of hepatitis B virus. Cochrane Database Syst Rev. 2017;(2):CD008545.
28. Andre FE, Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. J Med Virol. 1994;44:144–51.
29. American Academy of Pediatrics. Transmission of infectious agents via human milk. In: Pickering LK, editor. Red book: 2003 report of the committee on infectious diseases. 26th ed. Elk Grove Village: American Academy of Pediatrics; 2003. p. 118–21.

Hepatitis C and Pregnancy

Rebecca A. M. Pierce-Williams and Jeanne S. Sheffield

Epidemiology

In the USA, the highest incidence of HCV is in the 20–29-year-old age group, and while new cases are likely under-reported, more than 30,000 new cases were estimated for 2014 [1–3]. Fifteen to twenty-five percent of persons with an acute infection will clear the virus, while the remaining 75–85% develop chronic infection [3]. Approximately 2.7–3.9 million people in the USA are living with chronic HCV, with the highest prevalence in those with repeated or large percutaneous blood exposures (i.e., injection drug users) [3, 4].

Consequences of chronic HCV include chronic liver disease (60–70%), cirrhosis (5–20%), and death from associated complications (1–5%) [3]. In the USA, chronic HCV is the primary reason for liver transplantation [3]. According to the Centers for Disease Control and Prevention (CDC) surveillance for 2010–2014, US mortality rates secondary to HCV have increased from 4.7 deaths per 100,000 to 5 deaths per 100,000 [2]. Globally, in 2013 there were an estimated 704,000 deaths due to HCV and associated morbidities, increased from 333,000 in 1990; however, the incidence of HCV has decreased [1, 5, 6]. This discordance is due to the idle period between infection and complications such as cirrhosis and hepatocellular carcinoma (HCC) [4].

The true prevalence of HCV in pregnant women or women of childbearing age in the USA is not known due to challenges capturing high-risk groups. The National Health and Nutrition Examination Survey provides estimates on the prevalence of

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hepatitis in the USA, but the data do not include populations such as the homeless, prisoners, or institutionalized persons [7]. Based on the existing data, prevalence rates in women of childbearing age have been reported at 1–1.6% [7, 8]. Among women with HCV and the presence of HCV RNA, rates of vertical transmission range from approximately 3 to 7% (median, 5%) [4, 9–11]. Among HCV-positive women with undetectable HCV RNA, vertical transmission is rare [9, 11, 12]. HIV coinfection increases HCV transmission several folds, up to 15% [3, 12]. Clearance rates among vertically infected children have been reported to be approximately 20–40% [13].

Pathogenesis

Hepatitis C virus is an RNA virus from the Flaviviridae family. There are 6 genotypes and more than 90 subtypes, and knowledge of these genotypes guides the choice of antiviral therapy [4]. Approximately 74% of cases in the USA are caused by genotype 1 [4]. In the USA, HCV is most commonly transmitted through injection drug use, but prior to 1992 when routine screening was implemented, blood transfusion was a leading cause. With the implementation of screening of blood and blood products, the risk of HCV from a transfusion is now less than 1 in 2 million units [3]. Since the virus is transmitted through infected blood and blood products, risk factors for transmission also include chronic hemodialysis, having received donated organs or tissues before 1992, occupational exposure, sexual contact with an HCV-infected partner, and being born to an HCV-infected mother [1, 3, 4, 14]. In contrast to hepatitis B virus (HBV), sexual transmission and vertical transmission are less efficient means of transmission of HCV [3].

Risk factors for vertical transmission: High maternal viremia is associated with vertical transmission; however, a critical titer has not yet been defined. In a cohort study of 190 infants born to HCV RNA-positive and human immunodeficiency (HIV)-negative women, mean RNA levels in those who transmitted HCV versus those who did not transmit were 8.9×10^6 genome copies/mL and 2.2×10^6 genome copies/mL, respectively [15]. A systematic review of 77 studies reported increased vertical transmission at HCV RNA titers greater than 10^5 to 10^6 copies/mL [11].

Maternal coinfection with HIV increases the risk of vertical transmission of HCV. A recent meta-analysis of the risk of vertical transmission of HCV showed transmission rates of 5.8% in HIV-negative mothers, versus 10.8% in HIV-positive mothers [12]. This is thought to be secondary to higher HCV viral loads in HIV-positive women [12, 16]. Additionally, one study showed that infants who are infected with HIV are at a 3.2-fold greater risk of acquiring HCV from co-infected mothers [17].

A cohort study by Mast et al. [9] identified prolonged rupture of membranes (>6 h) and the use of internal fetal monitoring devices as risk factors for transmission of HCV. Infection of peripheral blood mononuclear cells (PBMCs) by HCV has also been shown to increase the risk of transmission. This may be due to the

PBMCs serving as an HCV vector or because HCV variants that are able to infect PBMCs can more easily pass the placental barrier [18].

Factors not found to be associated with an increased risk of transmission of HCV include amniocentesis, route of delivery, and breastfeeding [19–22]. While amniocentesis has not been shown to be associated with vertical transmission, the American College of Obstetricians and Gynecologists (ACOG) suggest that noninvasive prenatal screening options be discussed with these patients [20]. According to ACOG and the American Academy of Pediatrics, breastfeeding is not contraindicated in pregnancy, and although HCV RNA and antibody have been detected in breast milk, no cases of HCV transmission through breast milk have been reported [19, 20].

Box 1 Risk Factors for Vertical Transmission of Hepatitis C Virus

Maternal

- High HCV viral load
- HIV coinfection
- Injection drug use
- Peripheral blood mononuclear cell infection
- Prolonged rupture of membranes
- Internal fetal monitoring (i.e., fetal scalp electrode)

Neonatal

- HIV coinfection

Risks of hepatitis C in pregnancy: Several pregnancy complications are associated with HCV infection. A recent meta-analysis showed that the risk of intrahepatic cholestasis of pregnancy is higher in women infected with HCV than in those without HCV (OR 20.4, 95% CI, 9.39–44.33) [23]. There is also a significant association with HCV and intrauterine fetal growth restriction and low birth weight [24]. Additional studies report associations with HCV and gestational diabetes and preterm labor as well as congenital anomalies, need for assisted ventilation, and neonatal intensive care unit (NICU) admission for the infant [25–27].

Clinical Findings

Acute infection in adults: After an incubation period of approximately 4–12 weeks (range, 2–24 weeks), symptoms of HCV may present in 20–30% of infected individuals; however, most people with HCV are asymptomatic [3]. Common symptoms include fever, nausea, vomiting, abdominal pain, fatigue, jaundice, and loss of appetite [1, 3].

Acute infection in infants: Infected infants are usually asymptomatic at birth and during childhood [3].

Chronic infection: Chronic HCV progresses in a slow and subtle manner, often without any signs for two decades, until complications arise, usually from

developing hepatic fibrosis [4]. Some may also develop conditions such as glomerulonephritis, cryoglobulinemia, and porphyria cutanea tarda, likely due to the immunologic response to infection [3, 4, 14].

Diagnosis

The diagnosis of HCV in pregnancy begins with a thorough history and physical exam, including screening for risk factors, such as injection drug use, family history, and coinfection with HIV. Although routine screening for HCV in pregnancy is currently not recommended, the CDC and ACOG recommend screening for women with significant risk factors [3, 20]. Testing of pregnant women is recommended in the following cases:

- All persons born between 1945 and 1965
- History of injection drug use
- Recipients of clotting factor concentrates prior to 1987
- Recipients of donated blood or organs prior to 1992
- Persons with HIV infection
- Persons with evidence of liver disease
- Persons on chronic hemodialysis

Maternal (and children age > 18 months) testing for HCV infection starts with identification of antibodies to HCV (anti-HCV) with enzyme immunoassays; however, antibody may not yet be positive if exposure was in the past 6–10 weeks [20]. If the test is positive, it should be followed with quantitative HCV RNA reverse-transcriptase polymerase chain reaction (RT-PCR), to confirm ongoing infection [4, 14]. HCV RNA can be detected within 1–2 weeks of exposure, making it an option for follow-up of a negative anti-HCV serologic test after a recent exposure to HCV [4, 28]. Table 1 provides an interpretation of the tests.

Table 1 Interpretation of hepatitis C serologic markers

Serologic test	Result	Interpretation
HCV antibody	Nonreactive	No HCV antibody, no further testing[a]
HCV antibody	Reactive	Past or current infection[b]
HCV antibody HCV RNA	Reactive Detected	Current HCV infection
HCV antibody HCV RNA	Reactive Not detected	No current infection[c]

Adapted from [28]

[a]If there has been a recent exposure to HCV, consider HCV RNA testing or follow-up antibody testing

[b]The possibility of a false-positive antibody test exists

[c]If there is a need to differentiate between a true- versus false-positive antibody test, another antibody assay (i.e. RIBA) can be done

Once a diagnosis of HCV is made, additional laboratory studies should include testing for genotype to guide treatment when appropriate, liver function testing (e.g., alanine aminotransferase and coagulation studies including fibrinogen), and a complete blood count. All pregnant women should be tested for HBV and HIV as part of routine prenatal screening. All susceptible HCV-positive patients should be vaccinated against hepatitis A and B [14]. Injection drug users should be screened for tuberculosis [29]. Imaging studies, such as ultrasound, should also be completed to evaluate for liver fibrosis [14]. These individuals ultimately should be referred to a practitioner experienced in the management of chronic liver disease [14, 20].

Treatment

Pregnant women with acute HCV can often be managed in the outpatient setting, with inpatient treatment reserved for those with severe illnesses such as encephalopathy or coagulopathy [20]. Treatment of chronic HCV in pregnancy is not available, as none of the available antiviral therapies have been tested on pregnant women [29]. A commonly used antiviral medication, ribavirin, is teratogenic and has been shown to cause termination of pregnancy. It is contraindicated in pregnancy, and women who have used ribavirin should avoid becoming pregnant for 6 months after cessation of use [14, 29]. With the advent of new antiviral regimens that do not include ribavirin or pegylated interferon, treatment during pregnancy may be possible in the near future. If HCV is diagnosed before pregnancy, therapy should be initiated in combination with effective contraception, in order to optimally treat the infection and decrease the risk of vertical transmission in a future pregnancy [29].

Prevention

No immunoprophylaxis exists to prevent the transmission of HCV. Intrapartum considerations include limited use of internal monitoring devices, and if possible, avoidance of prolonged rupture of membranes, as these may increase the risk of transmission [15]. Infected mothers should be educated on methods to reduce the risk of transmission to household contacts. Breast milk is not a mode of transmission, and women should be encouraged to breastfeed unless they develop cracked or bleeding nipples, which may allow blood-borne transmission to the infant [19].

Infants born to HCV-positive mothers must be followed closely to evaluate for possible infection (Fig. 1). Anti-HCV testing should not be done sooner than 18 months of age, due to the possible persistence of maternal antibodies [3, 16]. However, studies suggest that antibody-based testing results in the detection of significantly less HCV-infected children than would be expected. For example,

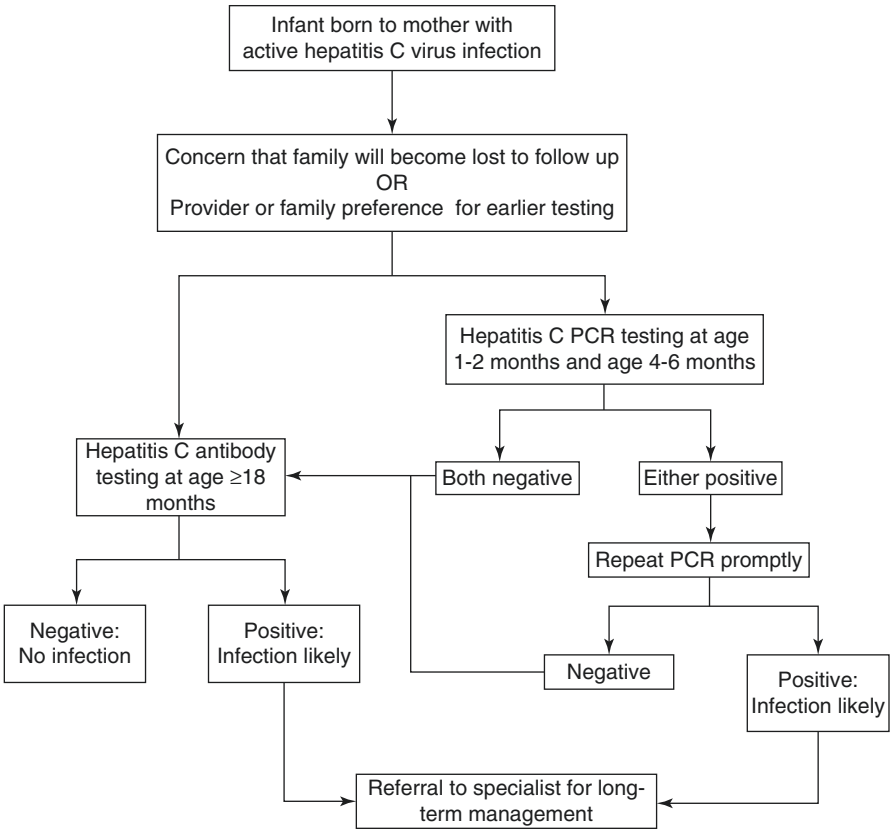

Fig. 1 Follow-up testing of infants born to mothers with active hepatitis C virus infection. *PCR* polymerase chain reaction

using Philadelphia public health registries, Kuncio et al. [30] identified only 4 HCV infections among 537 HCV-exposed infants, markedly less than the 27 (range, 15–38) infected infants that would be expected based on a mother-to-child transmission rate of 5% (range, 3–7%). As a result, some centers are increasingly moving to a PCR-based approach similar to the follow-up of HIV-exposed infants (see chapter "Management of HIV-Exposed Infants"). If PCR testing is performed, it should be done at age 1–2 months and again at age 4–6 months. Positive tests should be repeated at the next visit before confirming infection [4, 16]. Infants with negative PCR testing should still have confirmatory antibody testing after age 18 months.

Infected infants should be referred to a specialist in pediatric liver disease for long-term monitoring and consideration of antiviral therapy. Approximately 20–40% of infants will resolve acute HCV infection without progressing to chronic infection [13].

References

1. World Health Organization. Media Centre. Hepatitis C. Fact Sheet. Updated July 2016. http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed 19 Apr 2017.
2. Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis—United States, 2014. Updated June 22, 2016. https://www.cdc.gov/hepatitis/statistics/2014surveillance/commentary.htm#hepatitisC. Accessed 19 Apr 2017.
3. Centers for Disease Control and Prevention. Hepatitis C FAQs for Health Professionals. Updated January 27, 2017. https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed 18 Apr 2017.
4. CDC Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease. MMWR. 1998;47:1–39.
5. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–128.
6. GBD Mortality and Causes of Death Collaborators. Global, regional, and national age-specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117–71.
7. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705–14.
8. Prasad M, Honegger J. Hepatitis C virus in pregnancy. Am J Perinatol. 2013;30:149–60.
9. Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis. 2005;192:1880–9.
10. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. N Engl J Med. 1994;330:744–50.
11. Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. Hepatology. 2001;34:223–9.
12. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis. 2014;59:765–73.
13. European Paediatric Hepatitis C Virus Network. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. Clin Infect Dis. 2005;41:45.
14. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 18 Apr 2017.
15. Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, Alter MJ. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis. 2005;192:1880–9.
16. Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. Lancet. 1995;345:289–91.
17. Thomas DL, Villano SA, Riester KA, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and Infants Transmission Study. J Infect Dis. 1998;177:1480–8.
18. Azzari C, Moriondo M, Indolfi G, et al. Higher risk of hepatitis C virus perinatal transmission from drug user mothers is mediated by peripheral blood mononuclear cell infection. J Med Virol. 2008;80:65–71.
19. American Academy of Pediatrics. Transmission of infectious agents via human milk. In: Pickering LK, editor. Red book: 2012 report of the committee on infectious diseases. 29th ed. American Academy of Pediatrics: Elk Grove Village, IL; 2012. p. 128.
20. American College of Obstetricians and Gynecologists. Viral hepatitis in pregnancy. ACOG Practice bulletin no 86. Obstet Gynecol. 2007;110:941–55.
21. Delamare C, Carbonne B, Heim N, et al. Detection of hepatitis C virus RNA (HCV RNA) in amniotic fluid: a prospective study. J Hepatol. 1999;31:416–20.

22. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. BJOG. 2001;108:371–7.
23. Wijarnpreecha K, Thongprayoon C, Sanguankeo A, et al. Hepatitis C infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2017;41:39–45.
24. Huang QT, Li-lin H, Zhong M, et al. Maternal HCV infection is associated with intrauterine fetal growth disturbance: a meta-analysis of observational studies. Medicine. 2016;e4777:95.
25. Connell L, Salihu HM, Salemi JL, et al. Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. Liver Int. 2011;31:1163–70.
26. Pergam SA, Wang CC, Gardella CM, et al. Pregnancy complications associated with hepatitis C: data from a 2003–2005 Washington state birth cohort. Am J Obstet Gynecol. 2008;199:e1–9.
27. Reddick KL, Jhaveri R, Gandhi M, James AH, Swamy GK. Pregnancy outcomes associated with viral hepatitis. J Viral Hepat. 2011;18:e394–8.
28. Centers for Disease Control and Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR. 2013;62(18):362–5.
29. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. 2016. http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf. Accessed 18 Apr 2017.
30. Kuncio DE, Newbern EC, Johnson CC, Viner KM. Failure to test and identify perinatally infected children born to hepatitis C-infected women. Clin Infect Dis. 2016;62:980–5.

Neonatal Herpes Simplex Virus Infection

Nazia Kabani and David Kimberlin

Epidemiology

Neonatal HSV is acquired during one of three distinct periods: intrauterine, peripartum, or postpartum. A majority of infants (~85%) acquire the infection perinatally or in the peripartum period [1]. Approximately 10% of infants with neonatal HSV disease are infected postnatally, while 5% acquire the infection during the intrauterine period [1].

The incidence of neonatal HSV infection is approximately 1 per 2000–5000 live births [1]. However, neonatal HSV can be challenging to diagnose, so this may be an underestimate. Risk factors that increase the likelihood of HSV transmission to the neonate from a mother who is shedding HSV genitally at the time of delivery include:

1. Type of maternal infection (primary versus recurrent) [2–6]
2. Maternal antibody status [6–9]
3. Duration of rupture of membranes [5]
4. Integrity of mucocutaneous barriers (using fetal scalp probe, incisions, etc.) [6, 10, 11]
5. Mode of delivery (cesarean section versus vaginal delivery) [6]

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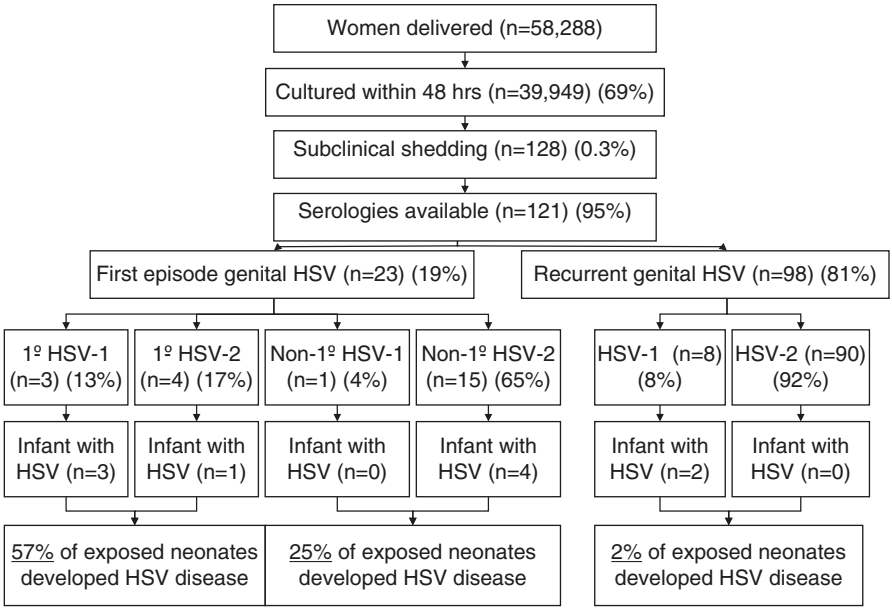

Fig. 1 Risk of neonatal herpes simplex virus (HSV) disease as a function of type of maternal infection. Adapted from [6]

Pathogenesis

Babies born to mothers with primary genital HSV infection near term (a first episode of genital HSV infection, with no preexisting antibody to either HSV type 1 [HSV-1] or HSV type 2 [HSV-2]) are at much greater risk of developing neonatal herpes than are babies who are born to mothers with recurrent genital HSV infection (i.e., who are shedding HSV-2 in the genital tract and who have preexisting HSV-2 antibody from infection earlier in life). This increased risk is due to two factors [2–6]. First, there is a lower concentration of transplacentally passaged HSV-specific antibodies present in babies born to women with primary infections [8]. In addition, these antibodies tend to be less reactive to the expressed peptides. Secondly, there is a larger load burden of the virus being shed vaginally, and for a longer period of time, in the maternal genital tract of women with primary infection compared with women with recurrent HSV infection [12]. This was demonstrated most effectively in a landmark study of approximately 60,000 women in labor who did not have any symptoms of genital HSV infection at the time of delivery. Of these women, approximately 40,000 had a vaginal swab obtained within 48 h of delivery for HSV detection (Fig. 1) [6]. Of these ~40,000 women, 121 had no visible evidence of genital HSV lesions but had HSV detected from their swab and also had sera available for HSV serologic testing, thereby allowing

for determination of first episode versus recurrent maternal infection classification. The trial found that 57% of babies born to moms with primary infection developed neonatal HSV, 25% of babies born to women with first episode non-primary infection developed neonatal HSV, and only 2% of babies born to women with recurrent HSV developed neonatal HSV. This same large study also confirmed that cesarean delivery effectively decreased transmission of HSV to the neonate when mothers are shedding in their genital tracts, affirming the results of a small study published in 1971 [5]. Despite this degree of protection, however, the risk of HSV transmission is not completely eliminated by cesarean delivery, and cases of neonatal HSV disease are well documented in babies delivered by cesarean delivery [13–15].

Clinical Findings

Neonatal HSV infection is classified based upon extent of involvement into one of three categories: (1) disseminated disease, (2) central nervous system infection, and (3) skin, eyes, and mouth infection. Disseminated disease involves multiple organs including but not limited to the lung, liver, adrenal glands, brain, and skin. Central nervous system (CNS) disease involves the brain and can have skin or mouth lesions as well. Skin, eyes, and mouth (SEM) disease is limited to only those areas. This classification is predictive of morbidity and mortality, with disseminated disease having the most significant mortality and CNS disease having the most significant morbidity [16–22].

Disseminated infection can manifest as severe hepatitis, disseminated intravascular coagulopathy, pneumonitis, and CNS involvement (seen in 60–75% of cases) [17, 21]. The mean age at presentation is around 11 days. Over 40% of disseminated HSV disease do not develop skin findings during the course of illness, which can delay diagnosis [14, 17, 22, 23].

Neonatal HSV CNS disease can present as seizures (focal or generalized), lethargy, poor feeding, irritability, or increased fussiness, tremors, temperature instability, and bulging fontanelle. The mean age of presentation is around 16 days [17]. Approximately 60–70% of babies with CNS disease will also have skin manifestations at some point in the disease course [17, 22]. Mortality is usually due to devastating brain destruction and atrophy, causing neurologic and autonomic dysfunction.

Skin, eyes, and mouth disease (SEM) has the best outcomes, with virtually no mortality and with morbidity associated solely with cutaneous recurrences but no neurologic sequelae (Table 1). Additionally, babies with SEM disease are most likely to have skin lesions (>80% of SEM patients), which facilitates diagnosis and allows prompt initiation of antiviral treatment before disease progresses. Presenting signs and symptoms of SEM disease include skin vesicles, fever, lethargy, and conjunctivitis [17]. Mean age of presentation is around 12 days. If SEM disease is not treated, it is likely to progress to CNS or disseminated disease [14].

Table 1 Mortality and morbidity outcomes among 295 infants with neonatal HSV infection, evaluated by the National Institutes of Allergy and Infectious Diseases' Collaborative Antiviral Study Group between 1974 and 1997

	Treatment			
Extent of disease	Placebo	Vidarabine	Acyclovir 30 mg/kg/day	Acyclovir 60 mg/kg/day
Disseminated disease	*n = 13*	*n = 28*	*n = 18*	*n = 34*
Dead	11 (85%)	14 (50%)	11 (61%)	10 (29%)
Alive	2 (15%)	14 (50%)	7 (39%)	24 (71%)
Normal	1 (50%)	7 (50%)	3 (43%)	15 (63%)
Abnormal	1 (50%)	5 (36%)	2 (29%)	3 (13%)
Unknown	0 (0%)	2 (14%)	2 (29%)	6 (25%)
Central nervous system infection	*n = 6*	*n = 36*	*n = 35*	*n = 23*
Dead	3 (50%)	5 (14%)	5 (14%)	1 (4%)
Alive	3 (50%)	31 (86%)	30 (86%)	22 (96%)
Normal	1 (33%)	13 (42%)	8 (27%)	4 (18%)
Abnormal	2 (67%)	17 (55%)	20 (67%)	9 (41%)
Unknown	0 (0%)	1 (3%)	2 (7%)	9 (41%)
Skin, eye, or mouth infection	*n = 8*	*n = 31*	*n = 54*	*n = 9*
Dead	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alive	8 (100%)	31 (100%)	54 (100%)	9 (100%)
Normal	5 (62%)	22 (71%)	45 (83%)	2 (22%)
Abnormal	3 (38%)	3 (10%)	1 (2%)	0 (0%)
Unknown	0 (0%)	6 (19%)	8 (15%)	7 (78%)

Diagnosis

HSV can be identified in clinical samples using either polymerase chain reaction (PCR) testing or viral culture. The diagnosis of neonatal HSV infections requires sampling of multiple sites:

1. Swabs of mouth, nasopharynx, conjunctivae, and rectum should be obtained for HSV surface cultures (if available) or PCR.
2. Specimens of skin vesicles should be obtained for culture (if available) or PCR.
3. CSF should be obtained for HSV PCR.
4. Whole blood should be obtained for HSV PCR.
5. Alanine aminotransferase (ALT) should be obtained as an indicator of hepatic involvement [25].

In past decades, the presence of red blood cells in CSF was suggestive of HSV CNS infection, likely due to relatively advanced disease due to diagnostic limitations; however, with development of more advanced imaging and diagnostic capabilities, hemorrhagic HSV encephalitis is less commonly seen now, and as such most HSV CNS CSF indices do not have significant numbers of red blood cells unless the procedure was traumatic. Performance of whole blood PCR adds to the other diagnostic

tools (surface and CSF cultures and PCR) but should not be used as the sole test for ruling in or ruling out neonatal HSV infection. Furthermore, viremia can occur in any of the three neonatal HSV disease classifications, so a positive whole blood PCR simply rules in neonatal HSV infection but does not assist in disease classification. HSV isolates grown in culture or HSV DNA detected by PCR can be typed to determine whether it is HSV-1 or HSV-2. Chest radiographs and liver function tests can aid in the diagnosis of disseminated infection. Of note, all infants with HSV disease, regardless of classification, need to have an ophthalmologic exam to look for ocular involvement. Infected neonates also should have neuroimaging studies (MRI preferably, but CT head or ultrasound are acceptable) performed [25].

Treatment

Before antiviral therapies were utilized, disseminated HSV disease caused death by 1 year of age in 85% of patients. In babies with CNS disease, mortality was 50% (Table 1) [20]. In a series of research studies conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) between 1974 and 1997, parenteral vidarabine, lower dose acyclovir (30 mg/kg/day), and higher dose acyclovir (60 mg/kg/day) were evaluated sequentially [18, 20, 24]. These series of studies determined that babies with neonatal HSV disease should be treated with parenteral acyclovir at a dose of 60 mg/kg/day divided in three daily doses (Figs. 2 and 3) [16]; the dosing interval may need to be increased in premature babies, based on their creatinine clearance [26]. The treatment duration is 21 days for babies with disseminated disease or CNS disease, while babies with SEM disease should be treated for 14 days [25]. All patients with CNS HSV disease should have a repeat lumbar puncture near the end of the 21-day course of acyclovir to document that the CSF PCR is negative; if the PCR remains positive, another week of parenteral acyclovir should be administered, and CSF

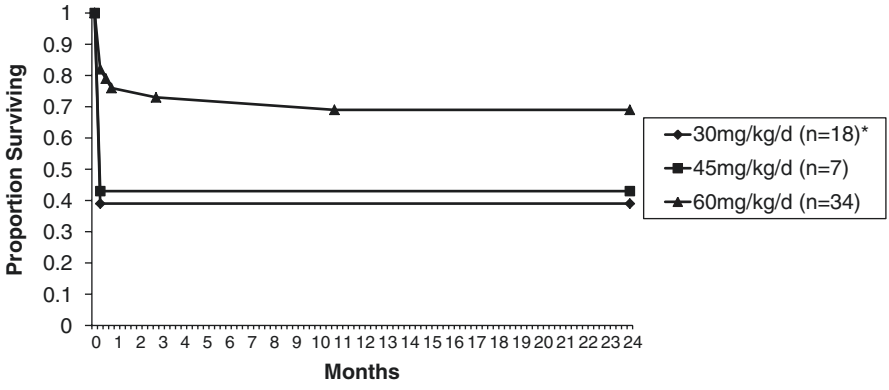

Fig. 2 Mortality in patients with disseminated neonatal herpes simplex virus disease. Adapted from [16]

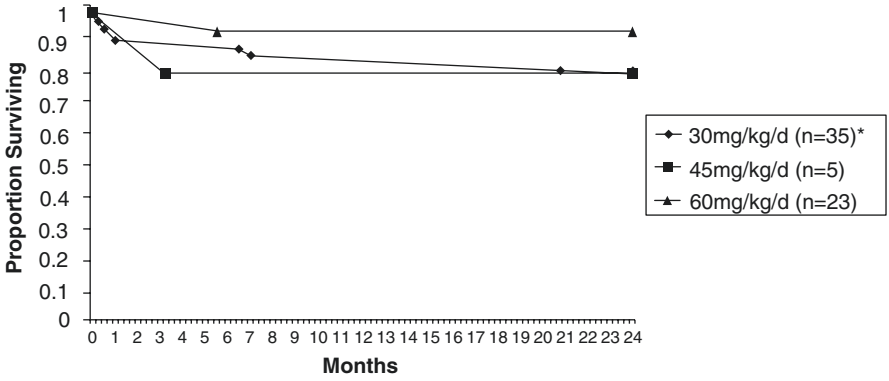

Fig. 3 Mortality in neonates with central nervous system HSV disease. Adapted from [16]

repeated in that manner until a negative CSF PCR is achieved [17, 27]. In contrast, the value of serial whole blood PCR determinations to gauge duration of therapy has not been established, and so blood PCR should not be performed following the initial testing to establish whether neonatal HSV infection exists.

The primary toxicity of higher dose parenteral acyclovir is neutropenia [16]. Absolute neutrophil counts (ANCs) should be monitored twice weekly throughout the course of parenteral therapy.

Oral acyclovir suppressive therapy for 6 months following acute parenteral treatment improves neurodevelopmental outcomes in babies with CNS disease [25]. HSV establishes latency in the sensory ganglia and occasionally reactivates and causes clinically apparent or occult recurrence of disease. A recent double-blind, placebo-controlled study conducted by the CASG involving infants with neonatal HSV with CNS involvement compared Bayley mental developmental scores at 1 year of babies receiving suppressive therapy with acyclovir for 6 months versus babies receiving placebo. The study found that the acyclovir group had a significantly higher mean Bayley score than the placebo group (88.2 vs. 68.1), indicating superior developmental outcomes at 1 year of age (Fig. 4) [29]. Suppressive acyclovir therapy has also been proven to prevent skin recurrences in any classification of HSV disease [28, 29]. Thus, infants should receive oral acyclovir at 300 mg/m^2/dose three times daily as suppressive therapy for 6 months following the initial parenteral treatment course. This dose should be adjusted for growth monthly, and ANCs should be monitored at 2 and 4 weeks after starting therapy and then monthly thereafter while oral acyclovir is administered [25].

Prevention

During pregnancy, all women should be asked about previous or current signs of genital infection. However, if they have not had signs, this does not rule out infection since most adults with genital HSV infection have never had clinically

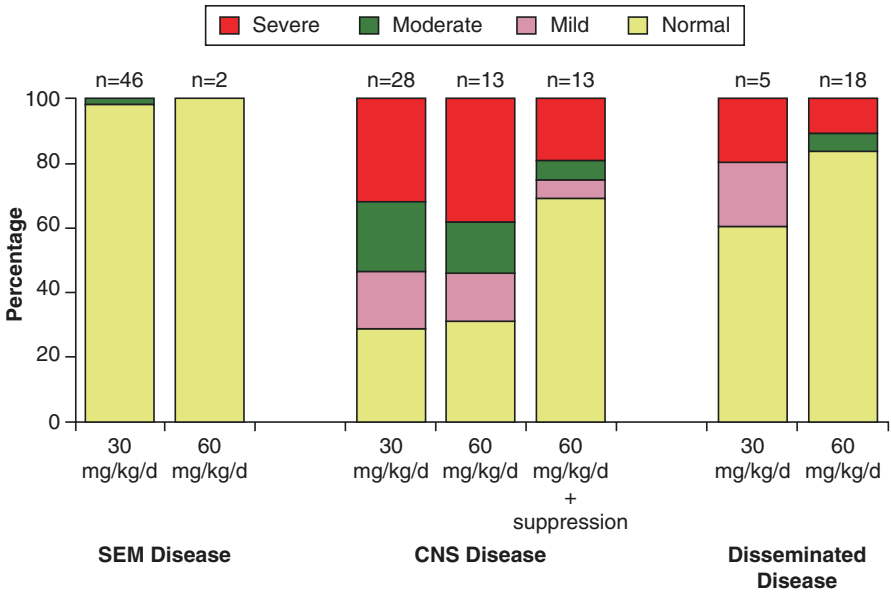

Fig. 4 Morbidity among patients with either skin, eye, and mouth (SEM), central nervous system (CNS), or disseminated neonatal herpes simplex virus disease with known outcomes after 12 months of life as a function of initial acyclovir treatment and suppressive therapy. Adapted from [16, 29]

identifiable symptomatic disease. Any pregnant woman with active genital infection should be given suppressive antiviral therapy at or beyond 36 weeks gestation, per the American College of Obstetricians and Gynecologists [25]. Any person coming in contact with a neonate should always have proper hand hygiene with good handwashing. Finally, any family members with known herpetic lesions on their mouths (cold sores or fever blisters) or hands (herpetic whitlow) should avoid contact with neonate, including nuzzling or kissing the neonate [25].

References

1. Whitley RJ, Roizman B. Herpes simplex virus infections. Lancet. 2001;357:1513–8.
2. Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. N Engl J Med. 1991;324:1247–52.
3. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med. 1987;317:1246–51.
4. Corey L, Wald A. Genital herpes. In: Holmes KK, Sparling PF, Mardh PA, Lemon SM, Stamm WE, Piot P, Wasserheit JN, editors. Sexually transmitted diseases. 3rd ed. New York: McGraw-Hill; 1999. p. 285–312.
5. Nahmias AJ, Josey WE, Naib ZM, et al. Perinatal risk associated with maternal genital herpes simplex virus infection. Am J Obstet Gynecol. 1971;110:825–37.
6. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA. 2003;289:203–9.

7. Yeager AS, Arvin AM. Reasons for the absence of a history of recurrent genital infections in mothers of neonates infected with herpes simplex virus. Pediatrics. 1984;73:188–93.
8. Prober CG, Sullender WM, Yasukawa LL, et al. Low risk of herpes simplex virus infections in neonates exposed to the virus at the time of vaginal delivery to mothers with recurrent genital herpes simplex virus infections. N Engl J Med. 1987;316:240–4.
9. Yeager AS, Arvin AM, Urbani LJ, et al. Relationship of antibody to outcome in neonatal herpes simplex virus infections. Infect Immun. 1980;29:532–8.
10. Parvey LS, Ch'ien LT. Neonatal herpes simplex virus infection introduced by fetal-monitor scalp electrodes. Pediatrics. 1980;65:1150–3.
11. Kaye EM, Dooling EC. Neonatal herpes simplex meningoencephalitis associated with fetal monitor scalp electrodes. Neurology. 1981;31:1045–7.
12. Whitley RJ. Herpes simplex viruses. In: Fields BN, Knipe DM, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman B, Straus SE, editors. Fields virology. 3rd ed. Philadelphia: Lippincott-Raven; 1996. p. 2297–342.
13. Anonymous. ACOG practice bulletin. Management of herpes in pregnancy. Number 8 October 1999. Clinical management guidelines for obstetrician-gynecologists. Int J Gynaecol Obstet. 2000;68:165–73.
14. Whitley RJ, Corey L, Arvin A, et al. Changing presentation of herpes simplex virus infection in neonates. J Infect Dis. 1988;158:109–16.
15. Peng J, Krause PJ, Kresch M. Neonatal herpes simplex virus infection after cesarean section with intact amniotic membranes. J Perinatol. 1996;16:397–9.
16. Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics. 2001;108:230–8.
17. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics. 2001;108:223–9.
18. Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. N Engl J Med. 1991;324:444–9.
19. Whitley R, Arvin A, Prober C, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. N Engl J Med. 1991;324:450–4.
20. Whitley RJ, Nahmias AJ, Soong SJ, et al. Vidarabine therapy of neonatal herpes simplex virus infection. Pediatrics. 1980;66:495–501.
21. Whitley RJ. Herpes simplex virus infections. In: Remington JS, Klein JO, editors. Infectious diseases of the fetus and newborn infants. 3rd ed. Philadelphia: W.B. Saunders Company; 1990. p. 282–305.
22. Sullivan-Bolyai JZ, Hull HF, Wilson C, et al. Presentation of neonatal herpes simplex virus infections: implications for a change in therapeutic strategy. Pediatr Infect Dis. 1986;5:309–14.
23. Arvin AM, Yeager AS, Bruhn FW, et al. Neonatal herpes simplex infection in the absence of mucocutaneous lesions. J Pediatr. 1982;100:715–21.
24. Whitley RJ, Yeager A, Kartus P, et al. Neonatal herpes simplex virus infection: follow-up evaluation of vidarabine therapy. Pediatrics. 1983;72:778–85.
25. American Academy of Pediatrics. Herpes simplex. In: Brady TD, Jackson MA, Long SS, Kimberlin DW, editors. Red book: 2015 report of the committee on infectious diseases. 30th ed. American Academy of Pediatrics: Elk Grove Village, IL; 2015. p. 432–43.
26. Englund JA, Fletcher CV, Balfour HH Jr. Acyclovir therapy in neonates. J Pediatr. 1991;119:129–35.
27. Kimberlin DW, Lakeman FD, Arvin AM, et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. J Infect Dis. 1996;174:1162–7.
28. Kimberlin DW. Advances in the treatment of neonatal herpes simplex infections. Rev Med Virol. 2001;11:157–63.
29. Kimberlin DW, Whitley RJ, Wan W, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med. 2011;365:1284–92.

Management of HIV-Exposed Infants

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Epidemiology

At the beginning of 2017, approximately 36 million people were living with HIV infection, including approximately 1% of women of childbearing age [1]. Pregnant women with HIV infection can transmit infection to their infant (maternal-to-child transmission [MTCT]). The rate of perinatal transmission of HIV in the absence of any intervention during the prenatal, intrapartum, and postnatal period is approximately 18–32%, where early intervention is crucial in the prevention of perinatal HIV infection [2]. The rate of MTCT has dramatically diminished to less than 2% in the United States and other resource-rich countries, due to the implementation of universal prenatal HIV counseling and testing, maintenance of virologic control in pregnant women with the use of ART, antiretroviral prophylaxis, scheduled cesarean delivery for high-risk pregnancies, and avoidance of breastfeeding [3, 4]. In the United States, where infant formula is widely available and safe, women with HIV are strongly advised to avoid breastfeeding. If an infant is not infected perinatally, the risk of infection from breastfeeding up to 24 months of age by a mother with HIV who is not virologically suppressed approaches 15% [5]. Ultimately, the goal is to minimize perinatal HIV transmission by effectively treating pregnant women with HIV and maintaining their viral load below the limit of detection throughout pregnancy, providing postnatal prophylaxis to all HIV-exposed infants, and avoiding breastfeeding in resource-rich conditions.

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Pathogenesis

Most MTCT of HIV occurs during the perinatal period, due to exposure to infected genital secretions. Perinatally infected infants have viral replication in their lymphoid tissue, including gut and respiratory lymphocytes, before developing viremia [6]. The median time to viremia in perinatally affected infants is approximately 10 days (interquartile range, 6–14 days) [7]. Less commonly, transmission can be congenital if HIV crosses the placenta. Congenital infection has been identified in fetal tissues as early as the first trimester [8]. Congenitally infected infants have positive blood PCR testing in the first 48 h of life [9]. However, there is no difference in the clinical courses of infants infected perinatally versus congenitally.

Several factors contribute to a high risk of MTCT, including:

- High viral load during pregnancy
- Plasma viral load >1000 copies/mL near the time of delivery
- Acute HIV infection
- No antepartum or only intrapartum ARV
- Known ARV drug-resistant virus
- Presence of ulcerative sexually transmitted diseases such as herpes
- Prolonged rupture of membranes and prolonged second stage of labor
- Use of fetal scalp electrodes, forceps, or other intrapartum devices

All of these risk factors increase either the amount of virus present in blood and genital fluid or the amount of time the infant is exposed to virus [10–16].

Clinical Findings

The majority of HIV-exposed infants are ultimately found to be uninfected. However, infants who are HIV-infected perinatally are initially asymptomatic, and therefore all HIV-exposed infants must receive prophylaxis and virologic follow-up to ensure that infected children are not missed (see Prevention, below) [17]. Infants who are infected with HIV can present in a variety of ways (Table 1) [18]. Most commonly, the infants do not yet have clinical signs when virologic testing becomes positive. Other infants may present with failure to thrive or growth delays. Diffuse lymphadenopathy, including hepatosplenomegaly as well as cervical and inguinal adenopathy, is a common but nonspecific presentation of perinatal HIV. Severe or persistent candida rash, chronic seborrhea, chronic diarrhea, and recurrent sinopulmonary infections (e.g., otitis media, sinusitis, pneumonia) are also common presenting signs but may be difficult to differentiate from normal childhood infections initially. As infections get more severe, clinical suspicion for HIV infection should increase. Invasive bacterial infections, recurrent viral infections, persistent or unexplained anemia, leukopenia, or thrombocytopenia, and the like should raise concerns, particularly if growth failure or adenopathy is present. Any AIDS-defining lesion—most commonly *Pneumocystis* pneumonia—should prompt immediate testing and treatment [19].

Table 1 Clinical presentations of infants and children with HIV infection (Adapted from [19])

Clinical category	
N	Asymptomatic
A	Mildly symptomatic • Generalized lymphadenopathy • Hepatosplenomegaly • Recurrent sinopulmonary infection • Dermatitis • Parotitis
B	Moderately symptomatic[a] • Lymphoid interstitial pneumonia • Leukopenia, anemia, thrombocytopenia • Invasive bacterial infection, single • Chronic diarrhea • Recurrent or unusual viral infection
C	Severely symptomatic • AIDS-defining illness (e.g., *Pneumocystis* pneumonia, disseminated tuberculosis, etc.) • Multiple or recurrent invasive bacterial infection
Immune category[b]	
1	No suppression, CD4+ T cells >25% of total lymphocytes
2	Moderate suppression, CD4+ T cells 15–24% of total lymphocytes
3	Severe suppression, CD4+ T cells <15% of total lymphocytes

[a]Partial list

[b]Percentages used rather than absolute CD4+ T cell count due to relatively higher total lymphocyte count in infants and young children (e.g., a child with 14% CD4+ T cells may have a CD4+ count of 1100 but still be considered severely immunosuppressed)

Diagnosis

Diagnosis of perinatal HIV infection is largely accomplished by HIV DNA PCR or antibody testing. Other testings, including viral genotyping and phenotyping, resistance testing, and CD4+ T cell testing, are best accomplished by—or in consultation with—an infectious diseases specialist.

HIV DNA PCR. PCR is >95% sensitive and specific for perinatal HIV infection after 1 week of age [20]. As mentioned above, infants who are perinatally infected (rather than congenitally) may have a falsely negative 48 h DNA PCR because the virus is still limited to their mucosal lymphocytes at that point and has not yet reached the blood. Therefore, DNA PCR testing is ordered several times during early infancy (Table 2). HIV RNA PCR is not routinely used, as RNA PCR can be falsely positive if it detects maternal virus that is coating the infant's skin but not replicating. In contrast, DNA PCR identifies active, replicating virus that has already undergone reverse transcription and therefore is a more specific test. However, any positive PCR should be promptly repeated, since false positives occur with any assay [21].

Antibody testing. The detection of HIV-1 antibody is extremely useful in adults; it appears 2–4 weeks after primary HIV infection and stays positive indefinitely.

Table 2 Diagnosis and management of HIV-exposed infants

	Birth	1-2 weeks	4 weeks	6 weeks	2 months	4 months	6 months	9 months	12 months	15 months	18 months
Zidovudine[a]	■	■	■	■							
Nevirapine[b]	▒										
TMP-SMX[c]	▒			■	■	■	■	■	■		
HIV DNA PCR	▒	X	X			X					
Complete blood cell count[d]	X		X		X						
Anti-HIV antibody test[e]									▒	▒	X
Immunizations[f]	X				X	X	X		X	X	X

Black bars or Xs indicate recommended management. Gray bars indicate optional situations
TMP-SMX, trimethoprim-sulfamethoxazole
[a]Zidovudine should be given for 4 or 6 weeks as per Table 3
[b]Nevirapine should be given in high-risk situations as per Table 3
[c]TMP-SMX should be given once zidovudine prophylaxis ends if HIV not already presumably excluded (two negative DNA PCR tests, at least one of which was obtained at age ≥ 4 weeks
[d]Complete blood counts before beginning zidovudine and then monthly; can be continued if antiretroviral therapy continues beyond 6 weeks
[e]Antibody test may be obtained as early as age 12 months; a negative test after age 12 months definitely excludes infection, but a positive test between 12–18 months should be repeated after age 18 months. A positive antibody test after age 18 months is consistent with infection
[f]Immunizations should be given as per usual childhood schedule for HIV-exposed and HIV-positive infants, including rotavirus. The only exceptions are that measles-mumps-rubella and varicella-zoster vaccine should not be given to HIV-positive children whose CD4+ T cell percentage is <15% and that live attenuated influenza vaccine is contraindicated for HIV-positive children

However, anti-HIV antibody is transmitted transplacentally and therefore is not useful for infants age <12 months. A negative antibody test after age 12 months excludes perinatal HIV infection, although maternal antibody may take up to 18 months to disappear. Therefore, positive antibody tests between age 12 and 18 months in an asymptomatic infant should be repeated after 18 months. A positive HIV antibody test beyond age 18 months is consistent with HIV infection [17, 21].

Treatment

Infants with proven or highly suspected HIV infection should be treated with combination ARV therapy. Therapy should be started immediately rather than waiting for signs of disease or a certain CD4+ T cell level, as prompt therapy is associated with markedly reduced morbidity and mortality [22]. Therapy should include at least three drugs from at least two different antiretroviral drug classes [23]. Many ARV agents, including the commonly used zidovudine and nevirapine, are available as liquid suspensions. Initiation, continuation, and monitoring of ARV therapy should be accomplished with the help of a pediatric infectious diseases specialist or a dedicated HIV treatment clinic.

Prevention

The fact that the vast majority of HIV-exposed infants are ultimately uninfected is a testament to advances in preventative care over the past 30 years. Prevention recommendations are described below.

Prenatal care. Combination ARV is recommended for all pregnant women, regardless of their CD4+ T cell counts or viral load [17]. ARV reduces maternal viral load in the blood and genital secretions, thus reducing the risk of perinatal transmission [24, 25]. Mothers who are already on an effective regimen should continue that regimen. Women who are not actively being treated with ARV should begin combination therapy guided by virologic resistance testing as soon as possible. Frequent monitoring of viral load is recommended throughout pregnancy and should be assessed again at approximately 34–36 weeks gestation to inform decisions about mode of delivery and infant prophylaxis [17].

Intrapartum care. The delivery of HIV-infected women is guided by their peripartum viral load. For women whose viral load is undetectable (<50 copies/mL, low risk), no antiviral prophylaxis is needed, and vaginal delivery is appropriate in the absence of other obstetrical indications for cesarean delivery [17]. For women whose viral load is >1000 copies/mL or unknown (high risk), intravenous zidovudine should be given during labor, and a cesarean delivery should be performed [2, 17]. Evidence supports scheduled cesarean delivery at 38 weeks for women with viral load >1000 copies/mL [26]. The optimal management of intermediate-risk women (50–1000 copies/mL) is unclear, but most obstetricians manage these women as though they were high risk [27]. Obstetric procedures that should generally be avoided for high-risk women include artificial rupture of membranes, episiotomy, use of fetal scalp electrodes, and delivery with forceps or a vacuum extractor [17].

Infant care. After delivery, all HIV-exposed infants should receive postpartum antiretroviral drugs as soon as possible (no later than age 6–12 h) to minimize the risk of perinatal HIV transmission (Table 3) [17]. Zidovudine is the primary agent and should be used for a minimum of 4–6 weeks pending results of the infant's virologic testing. Six weeks was the traditional duration, but recent evidence supports limiting zidovudine to 4 weeks if the mother's viral load was undetectable at the time of delivery.

For certain high-risk scenarios, a three-dose regimen of nevirapine can also be considered. Combination antiretroviral therapy as prophylaxis has received increasing attention due to the "Mississippi baby" experience [28]. In 2010, an extremely high-risk infant (premature, mother with no prenatal care) received prophylaxis with zidovudine, lamivudine, and nevirapine at birth and then transitioned to a treatment regimen of zidovudine, lamivudine, and boosted lopinavir. The child was confirmed to be infected and was treated for approximately 18 months, at which time they were lost to follow up for almost 1 year. When the child reestablished care, the viral load was still undetectable despite the prolonged treatment interruption, raising hope for a "functional cure." Unfortunately, the child's viral load became detectable again after

Table 3 Neonatal dosing of common antiretroviral drugs for prevention or treatment of perinatal HIV infection

Drug prophylaxis	Dosing	Duration
Zidovudine (ZDV) prophylaxis	≥35 weeks gestation: 4 mg/kg PO twice daily	4–6 weeks[a]
	>30 to <35 weeks gestation at birth: 2 mg/kg PO twice daily for 2 weeks, then 3 mg/kg PO twice daily for 4 weeks	
	<30 weeks gestation at birth: 2 mg/kg PO twice daily for 4 weeks, then 3 mg/kg PO twice daily for 2 weeks	
Nevirapine (NVP) prophylaxis[b]	Birth weight 1.5–2 kg: 8 mg dose PO flat dose Birth weight > 2 kg: 12 mg dose PO flat dose	Three doses in the first week of life: 1. Within 48 h of birth 2. 48 h after first dose 3. 96 h after second dose
Trimethoprim-sulfamethoxazole	5 mg/kg/day (of trimethoprim component) PO either once or divided BID on 3 consecutive days (e.g., Mon/Tue/Wed)	From when zidovudine prophylaxis is complete until HIV infection is excluded[c] *OR* 1 year of age, if HIV infected

[a]For infants whose mothers had antenatal therapy and undetectable viral load at the time of delivery, only 4 weeks of zidovudine are indicated

[b]Nevirapine should be added to zidovudine for infants born to mothers who (1) have not received any antepartum therapy, (2) had primary (acute) HIV infection during pregnancy, or (3) were treated but did not achieve undetectable viral load before delivery, particularly if delivery was vaginal

[c]If HIV infection is presumptively excluded before end of zidovudine therapy (e.g., 1-week and 4-week HIV DNA PCRs are negative and 6-week course of zidovudine is completed), then trimethoprim-sulfamethoxazole prophylaxis is not necessary

approximately 2 years, at which time the child was started on treatment. The prolonged viremia-free period was possibly due to decreased viral reservoirs at the time of infection; studies are investigating this hypothesis in clinical trials [29]. In the meantime, three-drug combination therapy is an option for prophylaxis in high-risk situations [17].

For infants born to women with known ARV resistance to AZT (or NVP), the optimal prophylactic regimen is unknown and should be determined in consultation with a pediatric HIV specialist or through consultation with the National Perinatal HIV Hotline (888-448-8765) [17]. In addition to ARV prophylaxis, exposed infants should also receive prophylaxis against *Pneumocystis jirovecii* pneumonia [30]. This is generally accomplished with trimethoprim-sulfamethoxazole prophylaxis beginning at age 4–6 weeks, unless HIV infection has been presumptively excluded by that time. Breastfeeding should be avoided regardless of virologic suppression, unless resources are unavailable for infant formula. In addition, pre-mastication of food should be avoided to prevent postnatal HIV transmission [31].

References

1. World Health Organization. Global health observatory data. Available at http://www.who.int/gho/hiv/en/. Accessed 13 Feb 2018.
2. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331:1173–80.
3. Centers for Disease Control and Prevention. Enhanced perinatal surveillance—15 areas, 2005–2008. HIV Surveillance Supplemental Report.
4. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. AIDS. 2014;28:1049–57.
5. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. BMJ. 2010;341:c6580.
6. Bunders MJ, van der Loos CM, Klarenbeek PL, et al. Memory CD4(+)CCR5(+) T cells are abundantly present in the gut of newborn infants to facilitate mother-to-child transmission of HIV-1. Blood. 2012;120:4383–90.
7. Rouzioux C, Costagliola D, Burgard M, et al. Estimated timing of mother-to-child human immunodeficiency virus type 1 (HIV-1) transmission by use of a Markov model. Am J Epidemiol. 1995;142:1330–7.
8. Lewis SH, Reynolds-Kohler C, Fox HE, et al. HIV-1 in trophoblastic and villous Hofbauer cells, and haematological precursors in eight-week fetuses. Lancet. 1990;335:565–8.
9. Nielsen K, Bryson YJ. Diagnosis of HIV infection in children. Pediatr Clin N Am. 2000;47:39–63.
10. International Perinatal HIVG, Andiman W, Bryson Y, de Martino M, et al. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1—a meta-analysis of 15 prospective cohort studies. N Engl J Med. 1999;340:977–87.
11. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. N Engl J Med. 1999;341:385–93.
12. Marinda ET, Moulton LH, Humphrey JH, et al. In utero and intra-partum HIV-1 transmission and acute HIV-1 infection during pregnancy: using the BED capture enzyme-immunoassay as a surrogate marker for acute infection. Int J Epidemiol. 2011;40:945–54.
13. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med. 2012;366:2368–79.
14. Welles SL, Pitt J, Colgrove R, et al. HIV-1 genotypic zidovudine drug resistance and the risk of maternal—infant transmission in the women and infants transmission study. The Women and Infants Transmission Study Group. AIDS. 2000;14:263–71.
15. Bollen LJ, Whitehead SJ, Mock PA, et al. Maternal herpes simplex virus type 2 coinfection increases the risk of perinatal HIV transmission: possibility to further decrease transmission? AIDS. 2008;22:1169–76.
16. Garcia-Tejedor A, Perales A, Maiques V. Duration of ruptured membranes and extended labor are risk factors for HIV transmission. Int J Gynaecol Obstet. 2003;82:17–23.
17. U.S. Department of Health and Human Services. AIDSinfo—Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0. Accessed 13 Feb 2018.
18. Lepage P, Hitimana DG. Natural history and clinical presentation of HIV-1 infection in children. AIDS. 1991;5:S117–25.
19. Caldwell MB, Oxtoby MJ, Simonds RJ, Rogers MF. Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Reccomm Rep. 1994;43:1–10.
20. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. AIDS. 1995;9:F7–11.

21. Read JS, Committee on Pediatric AIDS. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. Pediatrics. 2007;120:e1547–62.
22. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008;359:2233–44.
23. U.S. Department of Health and Human Services. AIDSinfo—Guidelines for the use of antiretroviral agents in pediatric HIV infection. https://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0. Accessed 14 Feb 2018.
24. Donnelly M, Davies JK. Contemporary management of human immunodeficiency virus in pregnancy. Obstet Gynecol Clin N Am. 2014;41:547–71.
25. Cu-Uvin S, Caliendo AM, Reinert S, et al. Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA. AIDS. 2000;14:415–21.
26. Kennedy CE, Yeh PT, Pandey S, Betran AP, Narasimhan M. Elective cesarean section for women living with HIV: a systematic review of risks and benefits. AIDS. 2017;31:1579–91.
27. Rowland BL, Vermillion ST, Soper DE. Scheduled cesarean delivery and the prevention of human immunodeficiency virus transmission: a survey of practicing obstetricians. Am J Obstet Gynecol. 2001;185:327–31.
28. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med. 2013;369:1828–35.
29. Rainwater-Lovett K, Luzuriaga K, Persaud D. Very early combination antiretroviral therapy in infants: prospects for cure. Curr Opin HIV AIDS. 2015;10:4–11.
30. U.S. Department of Health and Human Services. AIDSinfo—Guidelines for the prevention and treatment of opportunistic infections in hIV-exposed and HIV-infected children. https://aidsinfo.nih.gov/guidelines/html/5/pediatric-oi-prevention-and-treatment-guidelines/0. Accessed 14 Feb 2018.
31. Gaur AH, Dominguez KL, Kalish ML, Rivera-Hernandez D, Donohoe M, Brooks JT, et al. Practice of feeding premasticated food to infants: a potential risk factor for HIV transmission. Pediatrics. 2009;124(2):658–66.

Lymphocytic Choriomeningitis Virus

Joseph B. Cantey

Epidemiology

Lymphocytic choriomeningitis virus (LCMV) is found in rodents. Wild mice are the natural reservoir of LCMV and can transmit the virus both horizontally and vertically [1]. However, other rodents can be infected including pets such as mice, rats, guinea pigs, and hamsters. The virus is shed in the saliva, urine, and feces of rodents [2]. Humans acquire infection by direct contact with rodents or by aerosolizing infected particles (e.g., while cleaning a long-vacant cabin) [3]. Primary infections in adults may be asymptomatic or can present with either a nonspecific viral syndrome (a "flu-like illness"), aseptic meningitis, or—rarely—encephalitis. The prevalence of LCMV infection in humans has not been well described but is estimated to be between 2 and 5% [4, 5]. However, prevalence may be higher in patients who are homeless or live in extreme poverty, presumably due to increased contact with rodents [6].

Pathogenesis

LCMV displays a marked tropism for developing neurons and the retina [2]. In contrast to other congenital pathogens, LCMV causes minimal disruption outside the central nervous system—an important consideration when trying to differentiate LCMV from its much more common mimic, cytomegalovirus.

Neuronal injury: After reaching the fetus, LCMV preferentially infects neuroblasts—progenitors of neurons that arise in the periventricular space and migrate toward the periphery of the cortex to their final locations. LCMV infects

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and destroys neuroblasts before they can mature, leading to periventricular calcifications and neuronal migration defects [7].

Chorioretinitis: As noted below, all reported cases of congenital LCMV infection have included chorioretinitis. Scarring in the periphery of the retina is common and generally leads to visual impairment [8].

Clinical Findings

Congenital LCMV infection should be suspected when some combination of chorioretinitis, microcephaly, ventriculomegaly, periventricular calcifications, or neuronal migration defects are seen. Chorioretinitis (100% of cases) and microcephaly (~70% of cases) are the two most common findings [9].

Notably, the clinical features of LCMV are indistinguishable from congenital cytomegalovirus infection, but the latter is much more common. Congenital toxoplasmosis also has a similar presentation. Therefore, testing for LCMV should be deferred until congenital cytomegalovirus and toxoplasmosis are excluded [10]. Notably, non-central nervous system findings that are common in congenital cytomegalovirus or toxoplasmosis (e.g., growth restriction, hepatosplenomegaly, rash) are rare in LCMV.

Whether LCMV can cause asymptomatic congenital infection is not known. Both animal studies of LCMV and experience with other congenital pathogens (see chapter "Pathogenesis of Congenital Infections") suggest that infection later in pregnancy could result in asymptomatic infection, but data in human infants is limited to those with clinically apparent disease.

Diagnosis

The diagnosis of LCMV is based on serology. IgM and IgG testing is commercially available and relatively accurate [11]. A positive IgM or an elevated IgG level in the setting of clinical signs is generally acceptable diagnostic criteria. In some cases, the infant's initial IgG may be low (<1:256), and the IgM may be negative; in these cases, a stable or rising titer in 4–6 months is consistent with infection.

PCR testing is available in certain laboratories but is not widely available for clinical use; the timing of LCMV disappearance from blood and cerebrospinal fluid after congenital infection is also unclear.

Treatment

There is no effective antiviral therapy for LCMV; treatment is supportive. Multidisciplinary follow-up care—including ophthalmology as well as speech, occupational, and physical therapy—should be offered to infants with congenital LCMV in order to maximize their functional outcome [3].

Prevention

Women who are pregnant or trying to conceive should avoid contact with rodents or their excreta. Homes with known or suspected rodent infections should undergo rodent control, including sealing rodent access points from the outside. Removal of pet rodents from the home is unnecessary, but pregnant women should avoid direct handling or cleaning of cages for the duration of pregnancy.

References

1. Bonthius DJ. Lymphocytic choriomeningitis virus: a prenatal and postnatal threat. Adv Pediatr Infect Dis. 2009;56:75–86.
2. Cole GA, Nathanson N. Lymphocytic choriomeningitis virus: pathogenesis. Prog Med Virol. 1974;18:94–110.
3. Bonthius DJ. Lymphocytic choriomeningitis virus: an under-recognized cause of neurologic disease in the fetus, child, and adult. Semin Pediatr Neurol. 2012;19:89–95.
4. Park JY, Peters CJ, Rollin PE, et al. Age distribution of lymphocytic choriomeningitis virus serum antibody in Birmingham, Alabama: evidence of a decreased risk of infection. Am J Trop Med Hyg. 1997;57:37–41.
5. Childs JE, Glass GE, Ksiazek TG, et al. Human-rodent contact and infection with lymphocytic choriomeningitis and Seoul viruses in an inner-city population. Am J Trop Med Hyg. 1991;44:117–21.
6. Leibler JH, Zakhour CM, Gadhoke P, Gaeta JM. Zoonotic and vector-borne infections among urban homeless and marginalized people in the United States and Europe, 1990-2014. Vector Borne Zoonotic Dis. 2016;16:435–44.
7. Sun T, Vasek MJ, Klein RS. Congenitally acquired persistent lymphocytic choriomeningitis viral infection reduces neuronal progenitor pools in the adult hippocampus and subventricular zone. PLoS One. 2014;9:e96442.
8. Zinkernagel MS, Bolinger B, Krebs P, et al. Immunopathological basis of lymphocytic choriomeningitis virus-induced chorioretinitis and keratitis. J Virol. 2009;83:159–66.
9. Bonthius DJ, Wright R, Tseng B, et al. Congenital lymphocytic choriomeningitis virus infection: spectrum of disease. Ann Neurol. 2007;62:347–55.
10. Anderson JL, Levy PT, Leonard KB, et al. Congenital lymphocytic choriomeningitis virus: when to consider the diagnosis. J Child Neurol. 2014;29:837–42.
11. Barton LL, Mets MB. Congenital lymphocytic choriomeningitis virus infection: decade of rediscovery. Clin Infect Dis. 2001;33(3):370–4.

Malaria

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Epidemiology

More than 100 million pregnant women acquire malaria annually [1]. Pregnant women—particularly primigravidas—are at higher risk of both infection and poor pregnancy outcomes. These include spontaneous abortion, stillbirths, and growth restriction [2]. Malaria in pregnancy contributes to approximately 200,000 infant deaths annually in addition to an unknown number of early pregnancy losses. The majority of pregnant women who acquire malaria reside and deliver in endemic areas, but an increasing number of pregnant women who reside in areas without malaria are acquiring travel-related malaria during their pregnancy and returning home to deliver (Fig. 1) [3–11].

Pathogenesis

Protection against malaria is conferred largely by antibody [12]. Pregnant women who have never been exposed to malaria (i.e., travelers from non-endemic regions) are at the highest risk. For women living in endemic regions, increasing age and increasing parity are associated with protective antibody levels and decreased risk for clinically apparent malaria [13, 14]. Therefore, young women and primigravidas are at higher risk for malaria in pregnancy [15].

The transmission of malaria to the fetus is shown in Fig. 2. Within 30 min of a mosquito bite, sporozoite forms of *Plasmodium sp.* are injected into the blood and spread to the liver, where they mature into schizonts. Each schizont contains

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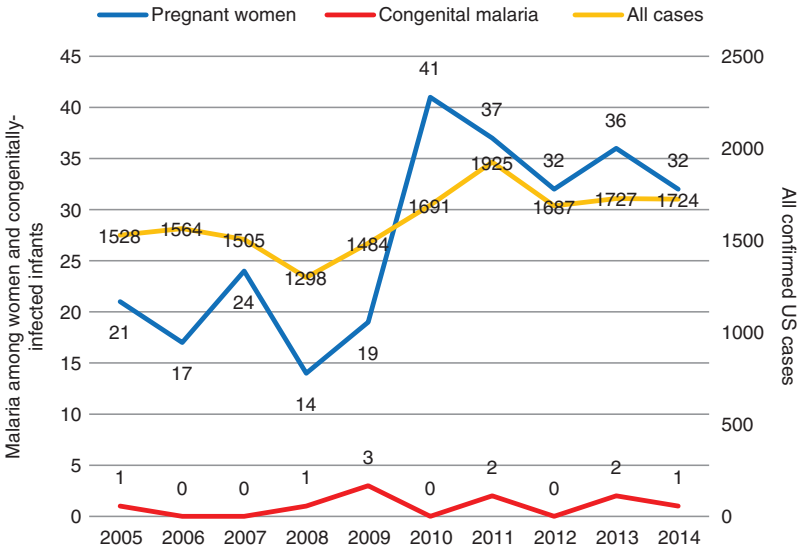

Fig. 1 US surveillance data from the CDC during the 10-year period from 2005 to 2014 [3–11]. Despite increasing incidence of malaria overall (yellow line) and among pregnant women (blue line), congenital malaria remains rare (red line). However, the outcome of the pregnancy was not known in many cases, and therefore congenital malaria rates may be underrecognized

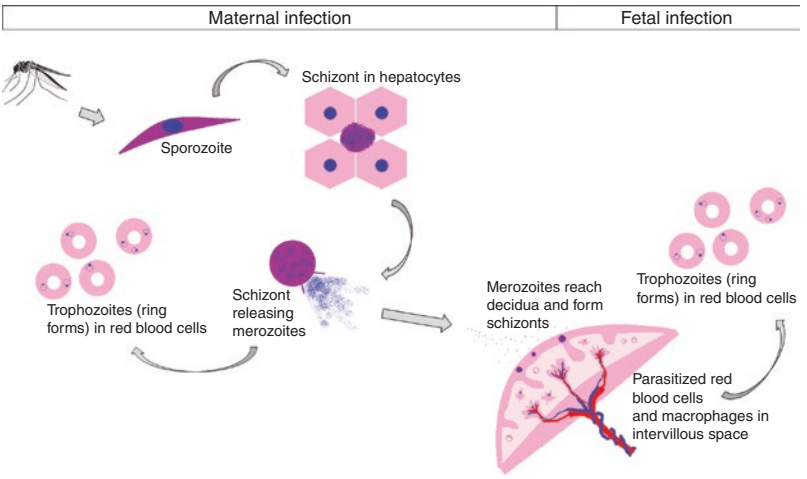

Fig. 2 The stages of maternal-fetal malaria infection are shown here. Mosquitos inject sporozoites into maternal circulation during a blood meal. Sporozoites infect hepatocytes and mature into schizonts, which release merozoites into maternal circulation. Merozoites that infect maternal red blood cells become trophozoites (the characteristic "ring forms" of malaria) or gametocytes (not shown, allow reproduction inside the mosquito when gametocytes are ingested during a subsequent blood meal). Merozoites that reach the maternal side of the placenta (decidua) will infect endometrial cells and mature into schizonts. Malaria reaches the intervillous space either by translocation of the parasite directly via antigen/antibody complexes, infected red blood cells, or within macrophages. In 95% of the cases, the placenta is able to prevent transmission to the fetus. In the remaining 5%, parasites reach the fetus and can lead to true congenital malaria

thousands of merozoites, which are released into the blood. Merozoites then infect red blood cells and become trophozoites (ring forms). The trophozoite within each cell then matures into a schizont and ruptures, causing marked hemolysis and inflammation. The newly released merozoites are capable of infecting new red blood cells in turn, leading to cycles of hemolysis and fever [16].

When merozoites reach the maternal side of the placenta (the decidua), they can infect both endometrial cells as well as the decidual macrophages. The intervillous space becomes crowded with parasite-infected macrophages, decreasing nutrition and oxygen exchange and contributing to fetal growth restriction [17].

In rare cases, *Plasmodium sp*. can reach fetal circulation either by maternal-fetal hemorrhage or active transport of antibody-*Plasmodium* complexes. However, the placenta is an effective barrier to fetal transmission; only approximately 5% of infants with infected placentas will have parasitemia [15].

To complicate matters, sporozoite forms of *P. vivax* and *P. ovale* are capable of forming hypnozoites ("sleeping animals" in Greek) that can remain latent within hepatocytes for prolonged periods before reactivating. Since hypnozoites are not susceptible to all anti-parasitic therapies, maternal treatment of *P. vivax* and *P. ovale* requires the addition of primaquine. However, sporozoites are not transmitted to the fetus in congenital malaria, so treatment of newborns with primaquine is not necessary (see Treatment, below).

Clinical Findings

Growth Restriction and Prematurity

The most common findings (Box 1) among infants born to mothers with malaria during pregnancy include lower birth weight than matched controls at similar gestational ages, with an average decrease of approximately 200–300 g [18]. Preterm

Box 1 Clinical Findings Among Infants Born to Mothers with Malaria During Pregnancy

- Intrauterine growth restriction (+++)
- Prematurity (++)
- Congenital malaria (+)
- Fever (+)
- Anemia (+)
- Splenomegaly (+)
- Jaundice *
- Hepatomegaly *

+++Most common, ++common, +least common, *rare

delivery is also more common but more difficult to quantify in low-resource settings where pregnancy dates may be uncertain [19]. As a correlate, regional malaria control efforts have been associated with decreased rates of preterm delivery and low birth weight [20, 21].

Congenital Malaria

A small fraction of infants will develop congenital malaria (i.e., parasitemia). The average age at presentation for infants with congenital malaria is approximately 2–4 weeks (95% confidence interval, 1–8 weeks) [22, 23]. However, symptomatic infants have been identified within the first 24 h after delivery when parasite burden is very high [24]. The most common presentation for infants with congenital malaria includes fever, anemia, and splenomegaly. The fever usually does not achieve the cyclical pattern seen in older patients with malaria. The anemia may be striking and can be associated with hyperbilirubinemia and reticulocytosis. Hepatomegaly may also be present but is less common and less severe than splenomegaly [23].

Postnatal Malaria

Mosquito-acquired malaria presents similarly to congenital malaria. Because many infants at risk for congenital malaria are delivered and raised in malaria-endemic areas, it may be difficult to differentiate postnatal malaria from congenital infection. In the United States and other malaria-free areas, infants are assumed to be congenitally infected unless they have traveled to a malaria-endemic region postnatally [25]. Notably, fetal exposure to malaria has been clearly linked to earlier and more frequent episodes of mosquito-acquired malaria in the first few years of life. It is hypothesized that the fetus is forced to develop a decreased immune response (tolerance) in order to survive, which predisposes the infant to postnatal infections [26, 27].

Diagnosis

The diagnosis of congenital malaria can be made via several modalities (Table 1), but thick and thin smears of peripheral blood are the gold standard [28].

Thick and Thin Smears

When performed by an experienced provider, microscopic examination of serial thick and thin smears of the peripheral blood obtained via heel stick has excellent sensitivity and specificity and is the gold standard for diagnosis. When congenital malaria is suspected, a minimum of three sets of thick and thin smears should be obtained every 12–24 h until malaria has been confirmed or excluded.

Table 1 Diagnostic tests for congenital malaria

Test	Advantages	Disadvantages
Thick smear	• Excellent sensitivity for parasite detection	• Does not allow speciation
Thin smear	• Allows speciation by parasite morphology	• Less sensitive than thick smears
Rapid antigen test	• Portable and inexpensive	• Less sensitive • Not all kits provide species information • Not recommended in the United States
Nucleic acid detection	• Extremely sensitive	• Expensive • Relatively slow compared to smears • Not widely available
Serology	• Used for screening blood donors	• Neither sensitive nor specific for congenital malaria • Does not preclude need for thick and thin smears when malaria suspected

Thick smears have good sensitivity and allow quantification of parasitemia, usually expressed as percentage of red blood cells infected. Thin smears allow speciation of the *Plasmodium* species based on the morphology, which in turn will inform treatment. Before peripheral smears are obtained, nursery providers should coordinate with the microbiology lab and infectious diseases service in order to ensure that the smears can be properly fixed, stained, and read. The Centers for Disease Control and Prevention (CDC) have a telemedicine service that allows fast and accurate identification if parasitology is not locally available (http://www.cdc.gov/dpdx/contact.html) [29].

Microscopic examination of the placenta is very sensitive for congenital malaria, as placental malaria is a prerequisite for fetal infection. However, the placenta is an effective barrier to malaria transmission, and the majority of infants born to mothers with placental malaria do not have congenital malaria (see Pathophysiology, above) [15, 30].

Rapid Antigen Detection

A variety of antigen detection tests are available for malaria and are widely used in low-resource settings. Although inexpensive and easily portable, these tests have lower sensitivity than peripheral blood smears and are not recommended for use in high-resource settings [31].

Nucleic Acid Detection

Polymerase chain reaction (PCR) testing and other nucleic acid-based detection methods are increasingly used for research purposes but have not become widely available for clinical use. Unsurprisingly, nucleic acid-based tests have excellent sensitivity but are expensive and comparatively slow relative to peripheral blood smears and do not currently quantify parasitemia [32].

Serology

Serology is not indicated for the evaluation of congenital malaria. Since the majority of women of childbearing age living in a malaria-endemic region possess antibody, detection of antibody is not specific for congenital malaria. Since preexisting immunity is not sufficient for protection during pregnancy (see Epidemiology), infants with detectable levels of antimalarial immunoglobulin are still at risk for congenital malaria. However, maternal-fetal risk is greatest with primigravid, nonimmune mothers, whose infants may lack transplacental antibody. Therefore, serologic testing is of little clinical value when congenital malaria is suspected.

Treatment

Treatment of congenital malaria should be provided in coordination with pediatric infectious diseases and with the local health department. Up-to-date treatment guidelines are available on the CDC website (https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html) [33].

For sensitive strains of *P. falciparum* and all *P. vivax*, *P. ovale*, and *P. malariae*, chloroquine is the recommended treatment (Table 2). Chloroquine can be given orally and is well tolerated. For infants who cannot receive oral therapy, intravenous quinidine can be substituted. Resistant strains of *P. falciparum* require combination therapy, usually with quinidine and clindamycin.

Severe malaria (e.g., >5% parasitemia or end-organ dysfunction) should be treated with intravenous quinidine and clindamycin. Exchange transfusion should also be considered for very high levels of parasitemia, usually >10%.

Prevention

Nonimmune pregnant women traveling to malaria-endemic regions represent an extremely high-risk population. Eliminating exposure to mosquitos that may transmit malaria is the most effective strategy for prevention. Avoiding travel to

Table 2 Treatment of congenital malaria

Diagnosis	Treatment
P. falciparum, chloroquine-resistant	Quinine PO and clindamycin PO
P. falciparum, chloroquine-sensitive	Chloroquine PO
P. malariae, *vivax*, and *ovale*	Chloroquine PO
Severe malaria, any species (>5% parasitemia or signs of organ failure)	Quinidine IV and clindamycin IV Consider exchange transfusion if >10% load

Note: Up-to-date recommendations, including information regarding worldwide chloroquine resistance, can be found on the CDC website [33]. Treatment of congenital malaria should always be administered via coordination with the health department and pediatric infectious diseases

malaria-endemic areas during pregnancy is the most certain means of prevention. Use of long sleeves and pants to minimize skin exposure, mosquito repellants containing DEET, and mosquito netting around sleeping areas are critical.

In addition, chemoprophylaxis for pregnant women traveling to malaria-endemic areas is recommended. For chloroquine-sensitive areas, chloroquine or hydroxychloroquine can be taken safely during all trimesters. In chloroquine-resistant areas, mefloquine is recommended. Atovaquone has not been well studied but is sometimes used as a second agent in chloroquine-resistant areas for women who have hallucinations or other severe side effects from mefloquine. Doxycycline and primaquine are not recommended in pregnancy.

Finally, pregnant women who live in an endemic area should take intermittent preventive treatment (IPT). Historically, this was accomplished with sulfadoxine-pyrimethamine monthly beginning in the second trimester [34]. However, recent studies suggest that the combination of dihydroartemisinin-piperaquine has superior efficacy and a similar safety profile [35, 36]. IPT is associated with less maternal malaria, less placental malaria, longer pregnancies, and higher birth weights.

References

1. Conroy AL, McDonald CR, Kain KC. Malaria in pregnancy: diagnosing infection and identifying fetal risk. Expert Rev Anti-Infect Ther. 2012;10:1331–42.
2. Moore KA, Simpson JA, Scoullar MJL, et al. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:e1101–12.
3. Mace KE, Arguin PM. Malaria surveillance—United States, 2014. MMWR Surveill Summ. 2017;66:1–24.
4. Cullen KA, Mace KE, Arguin PM. Malaria surveillance—United States, 2013. MMWR Surveill Summ. 2016;65:1–22.
5. Cullen KA, Arguin PM. Malaria surveillance—United States, 2012. MMWR Surveill Summ. 2014;63:1–22.
6. Cullen KA, Arguin PM. Malaria surveillance—United States, 2011. MMWR Surveill Summ. 2013;62:1–17.
7. Mali S, Kachur SP, Arguin PM. Malaria surveillance—United States, 2010. MMWR Surveill Summ. 2012;61:1–17.
8. Mali S, Tan KR, Arguin PM. Malaria surveillance—United States, 2009. MMWR Surveill Summ. 2011;60:1–15.
9. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance—United States, 2008. MMWR Surveill Summ. 2010;59:1–15.
10. Mali S, Steele S, Slutsker L, Arguin PM. Malaria surveillance—United States, 2006. MMWR Surveill Summ. 2008;57:24–39.
11. Thwing J, Skarbinski J, Newman RD, et al. Malaria surveillance—United States, 2005. MMWR Surveill Summ. 2007;56:23–40.
12. Teo A, Feng G, Brown GV, et al. Functional antibodies and protection against blood-stage malaria. Trends Parasitol. 2016;32:887–98.
13. Agomo CO, Oyibo WA. Factors associated with risk of malaria infection among pregnant women in Lagos, Nigeria. Infect Dis Poverty. 2013;2:19.
14. Beeson JG, Rogerson SJ, Elliott SR, Duffy MF. Targets of protective antibodies to malaria during pregnancy. J Infect Dis. 2005;192:1647–50.

15. Okafor UH, Oguonu T, Onah HE. Risk factors associated with congenital malaria in Enugu, South Eastern Nigeria. J Obstet Gynaecol. 2006;26:612–6.
16. Cowman AF, Healer J, Marapana D, Marsh K. Malaria: biology and disease. Cell. 2016;167:610–24.
17. Brabin BJ, Romagosa C, Abdelgalil S, et al. The sick placenta—the role of malaria. Placenta. 2004;25:359–78.
18. Eisele TP, Larsen DA, Anglewicz PA, et al. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. Lancet Infect Dis. 2012;12:942–9.
19. Menendez C, Ordi J, Ismail MR, et al. The impact of placental malaria on gestational age and birth weight. J Infect Dis. 2000;181(5):1740.
20. Hershey CL, Florey LS, Ali D, et al. Malaria control interventions contributed to declines in malaria parasitemia, severe anemia, and all-cause mortality in children less than 5 years of age in Malawi, 2000-2010. Am J Trop Med Hyg. 2017;97:76–88.
21. Ramharter M, Schuster K, Bouyou-Akotet MK, et al. Malaria in pregnancy before and after the implantation of a national IPTp program in Gabon. Am J Trop Med Hyg. 2007;77:418–22.
22. Vottier G, Arsac M, Farnoux C, et al. Congenital malaria in neonates: two case reports and review of the literature. Acta Paediatr. 2008;97:505–8.
23. Lesko CR, Arguin PM, Newman RD. Congenital malaria in the United States: a review of cases from 1966 to 2005. Arch Pediatr Adolesc Med. 2007;161:1062–7.
24. Opare DA. Congenital malaria in newborn twins. Ghana Med J. 2010;44:76–8.
25. Hagmann S, Khanna K, Niazi M, Purswani M, Robins EB. Congenital malaria, an important differential diagnosis to consider when evaluating febrile infants of immigrant mothers. Pediatr Emerg Care. 2007;23:326–9.
26. Boudova S, Divala T, Mungwira R, et al. Placental but not peripheral Plasmodium falciparum infection during pregnancy is associated with increased risk of malaria in infancy. J Infect Dis. 2017;216:732–5.
27. Bardaji A, Sigauque B, Sanz S, et al. Impact of malaria at the end of pregnancy on infant mortality and morbidity. J Infect Dis. 2011;203:691–9.
28. Mathison BA, Pritt BS. Update on malaria diagnostics and test utilization. J Clin Microbiol. 2017;55:2009–17.
29. Centers for Disease Control and Prevention. DPDx—laboratory identification of parasitic diseases of public health concern. http://www.cdc.gov/dpdx/contact.html. Accessed 9 Jan 2018.
30. Fried M, Muehlenbachs A, Duffy PE. Diagnosing malaria in pregnancy: an update. Expert Rev Anti-Infect Ther. 2012;10:1177–87.
31. Boyce MR, O'Meara WP. Use of malaria RDTs in various health contexts across sub-Saharan Africa: a systematic review. BMC Public Health. 2017;17:470.
32. Zheng Z, Cheng Z. Advances in molecular diagnosis of malaria. Adv Clin Chem. 2017;80:155–92.
33. Centers for Disease Control and Prevention. Malaria: Malaria treatment (United States). https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Accessed 9 Jan 2018.
34. World Health Organization. Malaria: intermittent preventive treatment in pregnancy (IPTp). Available at http://www.who.int/malaria/areas/preventive_therapies/pregnancy/en/. Accessed 9 Jan 2018.
35. Desai M, Gutman J, L'lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomized controlled superiority trial. Lancet. 2015;386:2507–19.
36. Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. N Engl J Med. 2016;374:928–39.

Parvovirus

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Epidemiology

Humans are the only hosts of parvovirus B19. Parvovirus is extremely contagious and is transmitted via respiratory tract secretions [1]. The incubation period from acquiring parvovirus B19 infection to the development of symptoms is approximately 1 week (range, 4–21 days). In older children and adults, parvovirus B19 may cause a nonspecific viral syndrome with fever, malaise, and myalgias. However, in younger children, the classic presentation is erythema infectiosum (fifth disease), an erythematous rash on the face with a characteristic "slapped-cheek" appearance [2]. Rash can also occur on the trunk, arms, buttocks, and thighs.

The presence of anti-parvovirus IgG in serum is considered protective; approximately 60% of adults are seropositive for parvovirus B19. Transmission is highest during cold weather months but can occur year-round. Pregnant women who have young children of their own or who work in schools or daycare are at higher risk of being infected [3]. The risk of infection during pregnancy for seronegative women is estimated around 2% per pregnancy [4].

Parvovirus serotypes other than B19 are gastrointestinal pathogens in dogs and cats. These serotypes do not infect humans.

Pathogenesis

Parvovirus B19 affects human erythroid progenitor cells in the bone marrow. Once it enters erythroblastic cells, parvovirus establishes a lytic infection cycle that results in suppression of erythrogenesis [5]. Bone marrow histopathology reveals

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diminished erythroid precursors and intranuclear viral inclusions in immature erythroid progenitor cells [6]. Platelet progenitors (megakaryocytes) can also be affected, leading to thrombocytopenia, but this is usually milder than the red cell aplasia. White blood cells are generally minimally affected. At the peak of viremia, infected patients have anemia with low or absent reticulocyte count. The degree of anemia is most severe in preterm infants or fetuses (see Clinical Findings, below).

Parvovirus is also capable of infecting cells other than erythroblasts, although it cannot reproduce in them. This includes neurons and cardiac myocytes, and parvovirus is capable of causing encephalitis [7] and myocarditis [8] in the fetus and young infant.

Clinical Findings

Pregnant Women

Pregnant women infected with parvovirus may experience a mild febrile exanthem, generally with a nonspecific maculopapular rash. Rarely, women may experience overt anemia or arthralgias. However, most pregnant women with parvovirus infection will be asymptomatic, highlighting the importance of testing exposed women even in the absence of symptoms [9].

Congenital Infection

As with other pathogens, congenital infection with parvovirus B19 is capable of causing a variety of clinical presentations depending on timing and severity of infection, ranging from subclinical infection to fetal hydrops or death [10].

Asymptomatic fetal infection. The majority of congenital infections are asymptomatic. Prospective cohort studies have shown that following primary maternal infection during pregnancy, approximately 30–50% of fetuses will be infected, but most will not have any clinical signs of infection [11].

Fetal anemia. For the minority of infants with clinically apparent congenital parvovirus infection, anemia is the most common presentation. As described above, parvovirus can cross the placenta and destroy fetal erythroblastic cells, leading to fetal anemia. This can be detected during fetal ultrasound if there is increased velocity of blood flow in the fetal middle cerebral arteries [12]. For some infants, fetal anemia is isolated and mild to moderate. However, severe cases of fetal anemia are associated with the development of nonimmune fetal hydrops.

Fetal hydrops. Hydrops is an uncommon (but perhaps the best known) sequela of congenital parvovirus infection. When fetal anemia is severe, the destruction of the fetal red blood cells leads to low intravascular oncotic pressure and loss of fluid into tissue. Simultaneously, the infected fetal myocardium will compensate for severe anemia by attempting to increase cardiac output, leading to high-output cardiac failure. The combination of cardiac failure and decreased oncotic pressure leads to

nonimmune hydrops. The accumulation of fluid in the skin or pleural, pericardial, and peritoneal spaces is readily evident on ultrasound [13].

Fetal death. Approximately 5–10% of pregnancies with clinically evident congenital parvovirus infection are lost. This is often due to fetal hydrops leading to in utero demise or stillbirth; approximately 30% of fetuses with hydrops will not survive. However, the majority of fetal deaths associated with parvovirus are not attributable to hydrops but instead may be due to inflammation, anemia alone, cardiac arrhythmias, or other causes [14].

Diagnosis

Diagnosis of parvovirus B19 infection can be accomplished with serologic testing, PCR testing, or both. Routine screening for parvovirus is not recommended [15, 16]. However, if a pregnant woman is exposed to or suspected to be infected with parvovirus, maternal serum should be tested for parvovirus IgG, IgM, and PCR approximately 2 weeks after exposure. In a small fraction of cases (~5%), IgM may be falsely negative. Adding PCR to serologic testing, particularly in high-probability cases, improves sensitivity and may be cost effective [17]. A positive IgM or PCR test, regardless of IgG result, should prompt additional evaluation of the fetus (Fig. 1). If IgM and PCR are both negative ≥2 weeks after exposure or illness, acute infection is unlikely.

A pregnant woman with clinical or serologic evidence of acute parvovirus infection should have prompt fetal sonography. Fetal manifestations usually appear within 2–12 weeks after maternal infection (median, 6 weeks), and so serial sonography is critical even if the initial ultrasound is unremarkable.

If severe fetal anemia or hydrops develops, and the infant is large enough for cordocentesis (generally approximately 18 weeks' gestation), the umbilical cord blood can be sampled percutaneously for complete blood count, reticulocyte count, and parvovirus testing with IgM and PCR [18]. Of note, parvovirus DNA can persist for a long period after initial infection, and viral loads do not seem to correlate with clinical outcome, so repeated testing or monitoring of viral load is unnecessary.

Treatment

There is no vaccine or medication to prevent parvovirus B19 infection; treatment is supportive. Intravenous immunoglobulin administered to the neonate or the fetus has been used in severe cases with some success, although this approach has not been evaluated in controlled trials [19–22]. For severe fetal anemia or hydrops, the same percutaneous umbilical sampling procedure used for diagnostic testing can also be used for packed red blood cell or platelet transfusions if needed [18]. Transfusions can be repeated as necessary. When the infant is approximately 32 weeks' gestation, or if cord blood transfusion is not effective, delivery should be considered [15, 16].

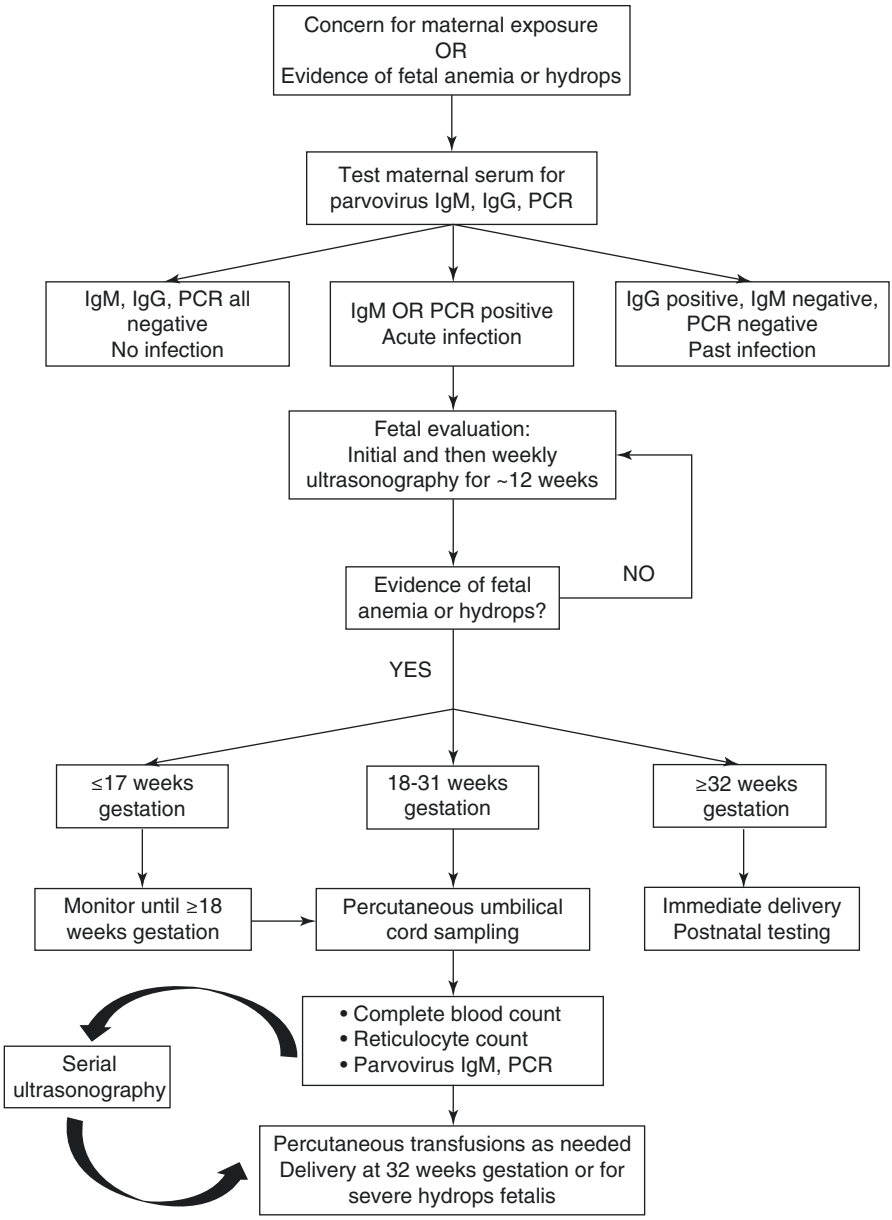

Fig. 1 Flow diagram for the diagnosis and treatment of congenital parvovirus infection

Prevention

Similar to cytomegalovirus (see chapter "Cytomegalovirus Infection"), hand hygiene is critical to parvovirus prevention, especially for pregnant women exposed to young children—the most likely source of parvovirus. Women with young children in the home or who work in education or childcare are at higher risk of acquiring parvovirus infection. Washing hands frequently with soap and water or ethanol-based hand sanitizers; avoiding touching the eyes, nose, or mouth; and avoiding close contact with people who are sick are some ways to reduce the chance of being infected with parvovirus B19. Notably, infectivity is highest before the rash appears; once the exanthem is evident, the infected individual is no longer considered contagious [23]. Therefore, avoidance of children with fifth disease does not prevent exposure to parvovirus.

References

1. Rogo LD, Mokhtari-Azad T, Kabir MH, Rezaei F. Human parvovirus B19: a review. Acta Virol. 2014;58:199–213.
2. Valentin MN, Cohen PJ. Pediatric parvovirus B19: spectrum of clinical manifestations. Cutis. 2013;92:179–84.
3. Mor O, Ofir I, Pavel R, et al. Parvovirus B19V infection in Israel: prevalence and occurrence of acute infection between 2008 and 2013. Epidemiol Infect. 2016;144:207–14.
4. Adler SP, Manganello AM, Koch WC, et al. Risk of human parvovirus B19 infections among school and hospital employees during endemic periods. J Infect Dis. 1993;168:361–8.
5. Morita E, Sugamura K. Human parvovirus B19-induced cell cycle arrest and apoptosis. Springer Semin Immunopathol. 2002;24:187–99.
6. Takahashi T, Ozawa K, Takahashi K, Asano S, Takaku F. Susceptibility of human erythropoietic cells to B19 parvovirus in vitro increases with differentiation. Blood. 1990;75:603–10.
7. Barah F, Whiteside S, Batista S, Morris J. Neurological aspects of human parvovirus B19 infection: a systematic review. Rev Med Virol. 2014;24:154–68.
8. Vigneswaran TV, Brown JR, Breuer J, Burch M. Parvovirus B19 myocarditis in children: an observational study. Arch Dis Child. 2016;101:177–80.
9. de Jong EP, Walther FJ, Kroes AC, Oepkes D. Parvovirus B19 infection in pregnancy: new insights and management. Prenat Diagn. 2011;31:419–25.
10. Dijkmans AC, de Jong EP, Dijkmans BA, et al. Parvovirus B19 in pregnancy: prenatal diagnosis and management of fetal complications. Curr Opin Obstet Gynecol. 2012;24:95–101.
11. Koch WC, Harger JH, Barnstein B, et al. Serologic and virologic evidence for frequent intrauterine transmission of human parvovirus B19 with a primary maternal infection during pregnancy. Pediatr Infect Dis J. 1998;17:489–94.
12. Moise KJ. The usefulness of middle cerebral artery doppler assessment in the treatment of the fetus at risk for anemia. Am J Obstet Gynecol. 2008;18:e1–4.
13. Brown T, Anand A, Ritchie LD, et al. Intrauterine parvovirus infection associated with hydrops fetalis. Lancet. 1984;2:1033–4.
14. Al-Buhtori M, Moore L, Benbow EW, Cooper RJ. Viral detection in hydrops fetalis, spontaneous abortion, and unexplained fetal death in utero. J Med Virol. 2011;83:679–84.
15. Crane J, Mundle W, Boucoiran I, et al. Parvovirus B19 infection in pregnancy. J Obstet Gynaecol Can. 2014;36:1107–16.

16. American College of Obstetricians and Gynecologists. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015;125:1510–25.
17. Dieck D, Schild RL, Hansmann M, Eis-Hubinger AM. Prenatal diagnosis of congenital parvovirus B19 infection: value of serological and PCR techniques in maternal and fetal serum. Prenat Diagn. 1999;19:1119–23.
18. Schild RL, Bald R, Plath H, et al. Intrauterine management of fetal parvovirus B19 infection. Ultrasound Obstet Gynecol. 1999;13:161–6.
19. Matsuda H, Sakaguchi K, Shibasaki T, et al. Intrauterine therapy for parvovirus B19 infected symptomatic fetus using B19 IgG-rich high titer gammaglobulin. J Perinat Med. 2005;33:561–3.
20. Lejeune A, Cremer M, von Bernuth H, et al. Persistent pure red cell aplasia in dicygotic twins with persistent congenital parvovirus B19 infection-remission following high dose intravenous immunoglobulin. Eur J Pediatr. 2014;173:1723–6.
21. Crabol Y, Terrier B, Rozenberg F, et al. Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus B19 infection: a retrospective study of 10 patients and review of the literature. Clin Infect Dis. 2013;56:968–77.
22. Heegarard ED, Hasle H, Skibsted L, Bock J, Brown KE. Congenital anemia caused by parvovirus B19 infection. Pediatr Infect Dis J. 2000;19:1216–8.
23. Centers for Disease Control and Prevention. Parvovirus B19 and fifth disease. https://www.cdc.gov/parvovirusb19/fifth-disease.html. Accessed 17 Jan 2018.

Rubella

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Epidemiology

Rubella virus is transmitted person-to-person via infected respiratory droplets or, less commonly, from other sites such as urine, stool, and skin. Rubella circulates year-round, with a peak in winter and early spring; however, outbreaks are possible in crowded conditions (e.g., dormitories, barracks, cruise ships) or in populations where vaccine coverage is low [1].

Rubella virus has a basic reproduction number (R_0, the number of subsequent infections that result from a single infection in a homogenous population) of 5–7. This means that rubella vaccination coverage needs to be at least 80–86% to maintain effective herd immunity [2]. Data from National Health and Nutrition Examination Surveys shows that the proportion of US women with rubella immunity, defined as rubella antibody ≥10 IU, has steadily increased over the past 30 years (Fig. 1), since the inclusion of rubella vaccine as part of routine childhood immunization practice [3–5]. Ninety-four percent of kindergartners and 90% of adolescents surveyed during the 2016–2017 school year had received ≥2 doses of measles-mumps-rubella (MMR) vaccine; these rates have been relatively stable over the past decade [6, 7].

In 2015, the World Health Organization declared rubella and CRS eradicated in the Americas, as the incidence of CRS had dropped to <2 per 100,000 live births [8]. However, CRS remains common in other parts of the world, with an estimated incidence of 90–120 per 100,000 live births in Asia and Africa [9].

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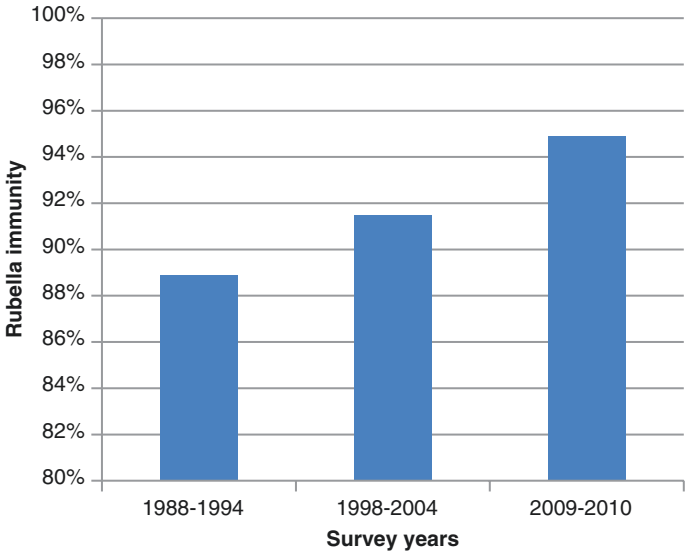

Fig. 1 Proportion of childbearing-age women who are rubella immune (≥10 IU) according to National Health and Nutrition Examination Survey data [3–5]. Women who are nonimmune should receive a single dose of rubella vaccine in the postpartum period or >28 days before becoming pregnant. Immunization during pregnancy is contraindicated

Pathogenesis

Congenital rubella syndrome has a similar pathogenesis to other congenital infections. Pregnant women with primary rubella infection have a period of viremia, during which time the virus can cross the placenta and reach the fetal circulation [10]. The probability of rubella virus crossing the placenta and the severity of fetal infection both decrease at later stages of pregnancy (Fig. 2) [11, 12]. For the purposes of this chapter, infants with signs of rubella infection are said to have CRS; infants with proven rubella infection but no clinical manifestations are said to be silently infected. These infants with clinically inapparent infections are more common—but less likely to be identified—than infants with CRS.

Clinical Findings

The classic triad of CRS includes congenital cataracts, cardiac defects, and sensorineural hearing loss (SNHL) [13]. However, most infants with in utero rubella infection are asymptomatic at birth but remain at risk for sequelae (e.g., hearing impairment) later in childhood.

Fig. 2 The risk of fetal loss and congenital rubella syndrome decreases markedly as gestation progresses. Fetuses of women infected in the first trimester are at highest risk due to ongoing organogenesis and eye development. Risk decreases after 10 weeks, and clinically apparent disease is unusual in infants infected after 20 weeks' gestation

Congenital Cataracts

Cataracts may be unilateral or bilateral and may be present at birth or develop over the first few weeks of life. Affected infants may also have microphthalmia. Fundoscopy may reveal focal areas of hyper- and hypopigmentation around the macula (the so-called "salt and pepper" retinopathy); this finding may be present even in the absence of cataract and is the most common ocular manifestation of CRS [14].

Congenital Heart Disease

Congenital heart disease occurs in the majority of infants with CRS. Patent ductus arteriosus is the most common lesion, followed by stenosis of the pulmonary valve or artery, aortic valve stenosis, coarctation, and tetralogy of Fallot. Atrial and ventricular septal defects seem to occur at the same rate in infants with and without CRS [15].

Sensorineural Hearing Loss

SNHL is the most common sequela of CRS and may be an isolated finding. Similar to congenital cytomegalovirus infection, CRS can cause unilateral or bilateral hearing loss, ranging from mild to profound, with onset in the newborn period or in later childhood [16].

Other Manifestations

CRS may present similarly to other congenital infections, with nonspecific signs of fetal infection such as intrauterine growth restriction, jaundice, hepatosplenomegaly, blueberry muffin spots, anemia, thrombocytopenia, and bony radiolucencies. However, these findings are nonspecific.

Diagnosis

Pregnant women: Pregnant women should undergo rubella antibody testing at their first prenatal visit. Generally, a titer of ≥10 IU is sufficient to provide immunity, although reinfection has been reported for women with low-level immunity (10–30 IU) [17, 18]. Pregnant women who are nonimmune or with low-level immunity who:

1. Have been exposed to an individual with a febrile exanthem
2. Develop a febrile exanthem

should be tested within 1–4 weeks for rubella and parvovirus (see chapter "Parvovirus") [19]. Identification of rubella IgM or IgG in a nonimmune woman, or ≥4-fold increase in IgG for a woman with low-level immunity (e.g., from 15 to 100 IU), is concerning for maternal infection (Fig. 3).

Fetus: For women with confirmed rubella infection during the first or early second trimester, amniocentesis, chorionic villus sampling, or fetal blood sampling allows direct testing of the fetus by PCR and can help inform decision-making discussions between the family and the perinatal care team [20].

Infants: Rubella virus is heavily excreted by infants with CRS and can be identified by culture or PCR from body fluids [21]. Rubella is most concentrated in the pharynx, but urine, conjunctivae, or cerebrospinal fluid can also be tested. Prompt, direct identification of the virus is the gold standard for diagnosis as it decreases the risk of confusing a postnatal infection with a congenital infection. Alternatively, serologic diagnosis is also possible either by identification of rubella IgM from the infant or by persistence of rubella IgG beyond 6–12 months of age, until such time as the child is immunized with measles-mumps-rubella vaccine [22].

Infants with probable or proven CRS should undergo thorough evaluation, including a complete physical examination and fundoscopy, echocardiogram, and baseline and follow-up audiologic evaluation.

Treatment

There is no effective antiviral therapy for CRS; treatment is supportive. Multidisciplinary follow-up care—including audiology, speech, occupational, and physical therapy—is required for infants with CRS in order to maximize their functional outcome [1].

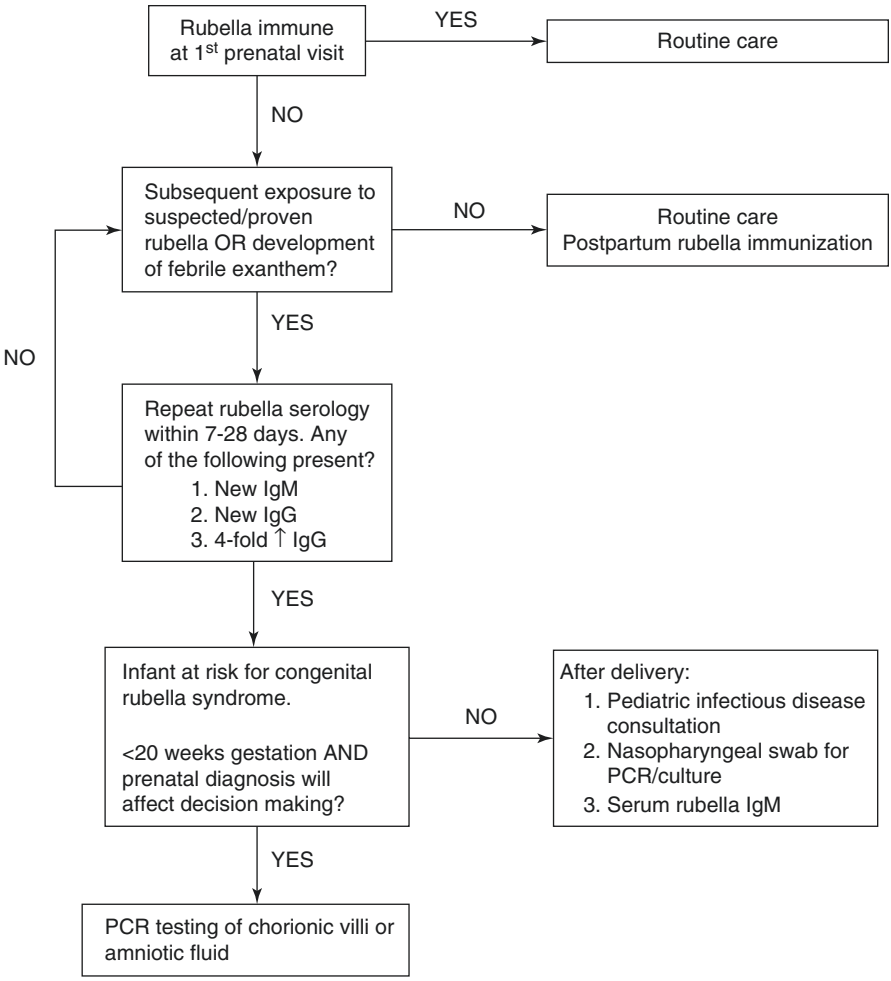

Fig. 3 Management approach to rubella nonimmune women and their infants during and after pregnancy

Prevention

Strategy: Active immunization with rubella-containing vaccines has virtually eliminated endemic rubella in the Western hemisphere. Immunization strategies in the United States include routine immunization with MMR at age 1 and 4 years as well as selective immunization for rubella nonimmune women of childbearing age.

Contraindications: MMR is composed of live-attenuated virus and is therefore contraindicated in pregnancy due to concerns for potential teratogenicity. It is also recommended that women avoid becoming pregnant for 28 days after receiving MMR [23]. However, there are no known cases of CRS following inadvertent

immunization of pregnant women with MMR vaccine. Therefore, women with undiagnosed pregnancy who receive MMR should receive routine antepartum care; pregnancy termination is not recommended [24]. Ideally, MMR should be given to nonimmune women during the immediate postpartum period [25, 26].

References

1. Lambert N, Strebel P, Orenstein W, Icenogle J, Poland GA. Rubella. Lancet. 2015;385:2297–307.
2. Kanaan MN, Farrington CP. Matrix models for childhood infections: a Bayesian approach with applications to rubella and mumps. Epidemiol Infect. 2005;133:1009–21.
3. Lebo EJ, Kruszon-Moran DM, Marin M, et al. Seroprevalence of measles, mumps, rubella, and varicella antibodies in the United States population, 2009-2010. Open Forum Infect Dis. 2015;20:ofv006.
4. Hyde TB, Kruszon-Moran D, McQuillan GM, et al. Rubella immunity levels in the United States population: has the threshold of viral elimination been reached? Clin Infect Dis. 2006;43(S3):S146–50.
5. Dykewicz CA, Kruszon-Moran D, McQuillan GM, et al. Rubella seropositivity in the United States, 1988-1994. Clin Infect Dis. 2001;33:1279–86.
6. Seither R, Calhoun K, Street EJ, et al. Vaccination coverage for selected vaccines, exemption rates, and provisional enrollment among children in kindergarten—United States, 2016-17 school year. MMWR. 2017;66:1073–80.
7. Walker TY, Elam-Evans LD, Singleton JA, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2016. MMWR. 2017;66:874–82.
8. Papania MJ, Wallace GS, Rota PA, et al. Elimination of endemic measles, rubella, and congenital rubella syndrome from the Western hemisphere: the US experience. JAMA Pediatr. 2014;168:148–55.
9. Vynnycky E, Adams EJ, Cutts FT, et al. Using seroprevalence and immunization coverage data to estimate the global burden of congenital rubella syndrome, 1996-2010: a systematic review. PLoS One. 2016;11:e0149160.
10. Cradock-Watson JE, Miller E, Ridehalgh MK. Detection of rubella virus in fetal and placental tissues and in the throats of neonates after serologically confirmed rubella in pregnancy. Prenat Diagn. 1989;9:91–6.
11. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet. 1982;2:781–4.
12. Collins IS. The incidence of congenital malformations following maternal rubella at various stages of pregnancy. Med J Aust. 1953;2:456–8.
13. Gregg NM. Congenital cataract following German measles in the mother. Trans Ophthal Soc Austr. 1941;3:35–44.
14. Givens KT, Lee DA, Jones T, Ilstrup DM. Congenital rubella syndrome: ophthalmic manifestations and associated systemic disorders. Br J Opthalmol. 1993;77:358–63.
15. Overall JC. Intrauterine virus infections and congenital heart disease. Am Heart J. 1972;84:823–33.
16. Wild NJ, Sheppard S, Smithells RW, Holzel H, Jones G. Onset and severity of hearing loss due to congenital rubella infection. Arch Dis Child. 1989;64:1280–3.
17. Munoz FM. Maternal immunization: an update for pediatricians. Pediatr Ann. 2013;42:153–8.
18. Bullens D, Smets K, Vanhaesebrouck P. Congenital rubella syndrome after maternal reinfection. Clin Pediatr. 2000;39:113–6.

19. Centers for Disease Control and Prevention. Control and prevention of rubella: evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome. MMWR Recomm Rep. 2001;50(RR-12):1–23.
20. Grose C, Itani O, Weiner CP. Prenatal diagnosis of fetal infection: advances from amniocentesis to cordocentesis—congenital toxoplasmosis, rubella, cytomegalovirus, varicella virus, parvovirus, and human immunodeficiency virus. Pediatr Infect Dis J. 1989;8:459–68.
21. Jin L, Thomas B. Application of molecular and serological assays to case based investigations of rubella and congenital rubella syndrome. J Med Virol. 2007;79:1017–24.
22. Hubschen JM, Bork SM, Brown KE, et al. Challenges of measles and rubella laboratory diagnostics in the era of elimination. Clin Microbiol Infect. 2017;23:511–5.
23. Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2013;62(RR-4):13.
24. Centers for Disease Control and Prevention. Rubella vaccination during pregnancy—United States, 1971-1988. MMWR. 1989;38:289–93.
25. Yamada T, Mochizuki J, Hanaoka M, et al. Effects of campaign for postpartum vaccination on seronegative rate against rubella among Japanese women. BMC Infect Dis. 2014;14:152.
26. Vilajeliu A, Garcia-Basteiro AL, Valencia S, et al. Rubella susceptibility in pregnant women and results of a postpartum immunization strategy in Catalonia, Spain. Vaccine. 2015;33:1767–72.

Congenital Syphilis

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Epidemiology

Congenital syphilis, a result of fetal infection with *Treponema pallidum*, remains a major public health problem worldwide [1, 2]. In 2016 in the United States, the number of cases reported to the Centers for Disease Control and Prevention (CDC) increased to 628 (15.7/1000,000 live births), of which 41 were syphilitic stillbirths. This increase in congenital syphilis paralleled increases in primary and secondary syphilis among women [3].

Pathogenesis

Transmission of syphilis to the fetus occurs transplacentally during maternal spirochetemia, although it can occur intrapartum by contact with maternal genital lesion(s) [4–6]. Vertical transmission increases as the stage of pregnancy advances (see chapter "Pathogenesis of Congenital Infections") but can occur at any time in gestation. Vertical transmission is related to the stage of maternal syphilis, with transmission rates of about 30%, 60%, 50%, and 13% in mothers with primary,

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secondary, early latent, and late latent infection, respectively [7]. Latent syphilis is the most common stage for syphilis diagnosed during pregnancy.

Syphilis during pregnancy is associated with such adverse outcomes as spontaneous abortion, stillbirth, nonimmune hydrops, premature delivery, perinatal death, and the clinical syndromes of early (<2 years of age) and late (≥2 years of age) congenital syphilis [8]. The placenta of newborns with syphilis may be large, thick, and pale. Histopathologic examination demonstrates necrotizing funisitis ("barber's pole" appearance), villous enlargement, and acute villitis, and spirochetes may be visualized by special staining techniques [9].

Clinical Findings

The majority of infants born to mothers with untreated syphilis appear normal and have no clinical or laboratory evidence of infection at birth but may develop manifestations of disease months to years later if left untreated [10, 11]. The clinical manifestations of early congenital syphilis are provided in Table 1. The most frequent abnormalities include hepatosplenomegaly with or without hepatitis, rash, and abnormal long bone radiographs (osteochondritis, periostitis). The bone lesions may be painful and result in subepiphyseal fracture and epiphyseal dislocation with pseudoparalysis of the affected limb (pseudoparalysis of Parrot). The rash can vary from maculopapular (copper-colored) with desquamation mostly on the palms and soles to fluid-filled vesiculobullous lesions that may progress to peeling and crusting with associated skin wrinkling. Condylomata lata, white, flat, moist, raised plaques on the lips, tongue, palate, perineum, or intertriginous areas, also may occur. Thrombocytopenia may be the only manifestation. Neurological signs related to central nervous system disease are rare in the neonatal period, even though 41% of neonates who have clinical, laboratory, or radiographic findings will have spirochetes detected in cerebrospinal fluid (CSF) by rabbit infectivity testing (inoculation of CSF into rabbit testes with resultant syphilitic infection of the rabbit) [12, 13].

The classic Hutchinson triad consisting of interstitial keratitis, eighth cranial nerve deafness, and Hutchinson teeth (small, widely spaced, barrel-shaped, and notched central incisors) is seen in infants with late congenital syphilis, as are frontal bossing and hearing loss [11].

Diagnosis

The diagnosis of congenital syphilis is often difficult to establish since many infected neonates will have a normal physical examination and their reactive serologic tests for syphilis may only reflect transplacental passage of maternal IgG antibodies. Therefore, it is important to obtain and document the maternal history of syphilis (including stage of infection) and treatment of the mother and her sexual partner as well as her serologic test results in order to guide neonatal management.

Table 1 Clinical, laboratory, and radiographic findings in early congenital syphilis (<2 years of age)

Physical examination	Stillborn Preterm Nonimmune hydrops fetalis Intrauterine growth restriction/small for gestational age **Hepatomegaly**[a] **Splenomegaly**[a] Jaundice **Skin rash**[a] Adenopathy Rhinitis (snuffles) Mucus patch Condylomata lata Pseudoparalysis of Parrot Eye: chorioretinitis, cataract, glaucoma, uveitis Central nervous system: cranial nerve palsies, seizure
Laboratory findings	Anemia **Thrombocytopenia**[a] Hypoglycemia Liver transaminitis and direct hyperbilirubinemia Cerebrospinal fluid pleocytosis[b] and elevated protein content[c]
Radiographic findings	**Periostitis**[a] **Osteochondritis**[a] Pneumonia alba
Other	Nephrotic syndrome Pancreatitis Myocarditis Fever Gastrointestinal malabsorption Hypopituitarism (diabetes insipidus)

Adapted from Syphilis. Velaphi S and Sánchez PJ. in *Infectious Disease: Congenital and Perinatal Infections: A Concise Guide to Diagnosis*. Edited by: C. Hutto © Humana Press Inc., Totowa, NJ, 2005

[a]Prominent features shown in **bold** type

[b]White blood cell count (WBC): normal <18–25 WBC/mm^3

[c]Protein: normal <150 mg/dL in full term neonates, <170 mg/dL in preterm infants

All individuals with syphilis and their sexual partner(s) should be tested for coinfection with the human immunodeficiency virus (HIV), although infants born to mothers coinfected with syphilis and HIV do not require different evaluation, therapy, or follow-up.

Serologic tests for syphilis are classified into nontreponemal and treponemal tests. Nontreponemal tests include the rapid plasma reagin (RPR) test and the venereal disease research laboratory (VDRL) test. Treponemal tests include the *T. pallidum* particle agglutination (TP-PA) test, fluorescent treponemal antibody-absorption (FTA-ABS) test, treponemal enzyme immunoassays (EIA), and chemiluminescence immunoassays (CIA). Treponemal assays become reactive before nontreponemal tests in individuals with syphilis, and they are used to confirm its diagnosis.

Clinical laboratories often use the treponemal EIA or CIA for syphilis screening ("reverse sequence" screening; Fig. 1) [14–18]. If the EIA or CIA is positive, then a quantitative nontreponemal test (e.g., RPR) is performed which, if also reactive, confirms the diagnosis of syphilis. However, if the RPR test is nonreactive, then a second treponemal test (e.g., TP-PA) is performed, preferably on the same serum specimen. If the second treponemal test is reactive, current or past syphilis infection is confirmed. For women with a history of adequately treated syphilis, no further evaluation or treatment is necessary. A nonreactive TP-PA test is suggestive of a false-positive EIA/CIA screen, and no further evaluation or treatment of the infant is recommended.

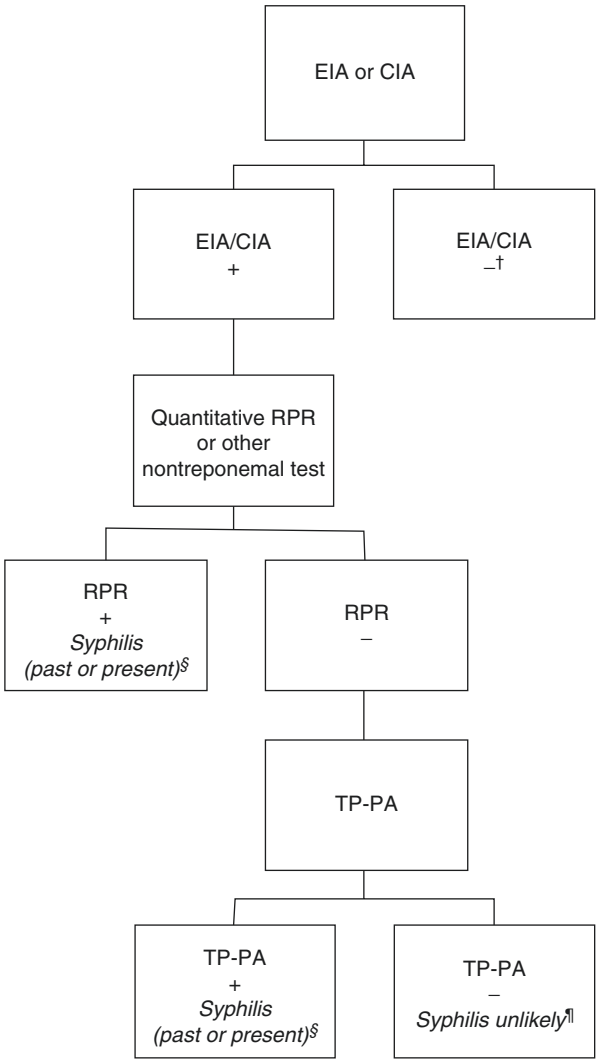


Fig. 1 Recommended algorithm for reverse sequence syphilis screening where enzyme or chemiluminescence immunoassay is used as initial test for testing pregnant women for syphilis. Adapted from [15]. *CDC* Center for Disease Control and Prevention, *EIA/CIA* enzyme immunoassay/chemiluminescence immunoassay, *RPR* rapid plasma reagin, *TP-PA* *Treponema pallidum* particle agglutination. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. §Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC's *2015 STD Treatment Guidelines* [18]. ¶If at risk for syphilis, repeat RPR in several weeks

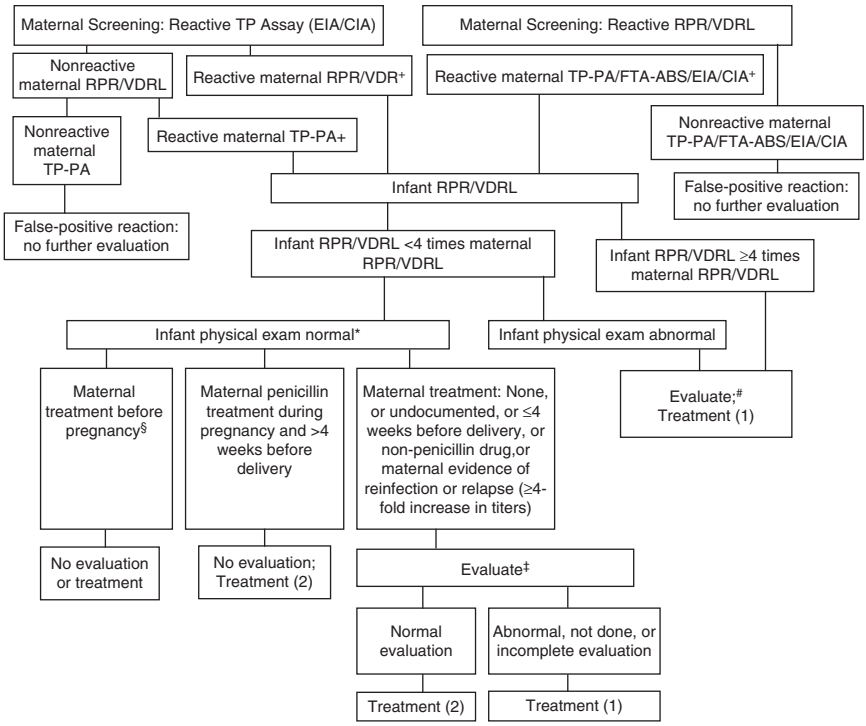
In addition to a thorough physical examination, all infants born to mothers with reactive serologic tests for syphilis should be tested with a serum RPR or VDRL test, preferably the same test that was performed on the mother so that quantitative titers can be compared. Infant serum from a vein, artery, or heel stick is preferred to umbilical cord blood as both false-positive and false-negative results may occur from either contamination with maternal blood or interference due to Wharton's jelly, respectively. If the mother has a reactive treponemal test, then a treponemal test is not indicated for the infant since it also will be reactive due to IgG transplacental transfer. In addition, there is no commercially available serum or CSF total or specific IgM test that is recommended due to both false-positive and false-negative results.

The diagnosis of congenital syphilis is established by the observation of spirochetes in body fluids or tissue such as cutaneous lesions, nasal discharge, amniotic fluid, placenta, umbilical cord, or autopsy specimens by dark-field microscopy, polymerase chain reaction (PCR) test, or fluorescent antibody or silver staining. In most neonates, however, the diagnosis can only be inferred by serologic testing due to persistence of transplacentally acquired maternal nontreponemal and treponemal IgG antibodies up to 18 months of age. Congenital infection can also be confirmed if the infant's serum nontreponemal serologic titer is at least fourfold higher than the mother's titer (e.g., 1:8 versus 1:32 or greater, 2 or more dilutions). However, fourfold increases are unusual, and the absence of such a finding does not exclude a diagnosis of congenital syphilis. Guidance on the management of infants born to mothers with reactive serologic tests for syphilis is provided in Fig. 2 and Table 2 [18].

Congenital neurosyphilis is difficult to diagnose as most neonates who have *T. pallidum* detected in CSF do not manifest any neurological abnormalities. Central nervous system infection is inferred from CSF abnormalities such as a reactive VDRL test, pleocytosis (>18–25 white blood cells per microliter), and elevated protein content (>150 mg/dL; >170 mg/dL if infant is premature). However, a reactive CSF VDRL test in neonates may be caused by passive transfer of nontreponemal IgG antibodies from serum into CSF. The sensitivity and specificity of a reactive CSF VDRL test, pleocytosis, and elevated protein content are only 53% and 90%, 38% and 88%, and 56% and 78%, respectively. Therefore, if clinical, laboratory, or radiographic evaluation supports a diagnosis of congenital syphilis, then therapy effective against central nervous system disease is warranted irrespective of the results of CSF analyses.

Treatment

Initial treatment. The treatment of syphilis and congenital syphilis is penicillin G [18, 19]. Pregnant women should receive the treatment regimen that corresponds with the stage of infection (Table 3), and those who have a penicillin allergy should undergo desensitization [18, 20]. Infants who require a 10-day treatment course include those who have (1) an abnormal physical examination consistent with



+ Test for HIV-antibody. Infants of HIV-infected mothers do not require different evaluation or treatment.

* If the infant's RPR/VDRL is nonreactive AND the mother has had no treatment, undocumented treatment, treatment during pregnancy, or evidence of reinfection or relapse (≥ 4-fold increase in titers), THEN treat infant with a single IM injection of benzathine penicillin (50,000 U/kg). No additional evaluation is needed.

§ Women who maintain a VDRL titer ≤1:2 (RPR ≤1:4) beyond 1 year following successful treatment are considered serofast.

Evaluation consists of CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL. Other tests as clinically indicated: long-bone x-rays, neuroimaging, auditory brainstem response, eye exam, chest x-ray, liver function tests.

‡ CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; long-bone x-rays

Fig. 2 Algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis. [+]Test for HIV antibody. Infants of HIV-infected mothers do not require different evaluation or treatment. [*]If the infant's RPR/VDRL is nonreactive AND the mother has had no treatment, undocumented treatment, treatment during pregnancy, or evidence of reinfection or relapse (≥4-fold increase in titers), THEN treat infant with a single IM injection of benzathine penicillin (50,000 U/kg). No additional evaluation is needed. [§]Women who maintain a VDRL titer ≤1:2 (RPR ≤1:4) beyond 1 year following successful treatment are considered serofast. [#]Evaluation consists of CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL. Other tests as clinically indicated: long bone X-rays, neuroimaging, auditory brainstem response, eye exam, chest X-ray, liver function tests. [‡]CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; long bone X-rays. **Treatment**: (1) Aqueous penicillin G 50,000 U/kg IV q 12 h (≤1 week of age), q 8 h (>1 week), or procaine penicillin G 50,000 U/kg IM single daily dose, × 10 days. (2) Benzathine penicillin G 50,000 U/kg IM × 1 dose

Table 2 Management of neonates (≤4 weeks of age) born to mothers with reactive serologic tests for syphilis

Clinical status		Evaluation	Treatment
Scenario 1 Proven or highly probable disease	1. Abnormal physical examination 2. Serum quantitative nontreponemal serologic titer that is fourfold or higher than the mother's titer 3. Positive dark-field/ fluorescent antibody test or positive PCR test of lesion or body fluid(s)	CSF analysis for VDRL, cell count, and protein CBC and platelet count Other tests as clinically indicated (e.g., long bone radiographs, chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, hearing evaluation)	Aqueous crystalline penicillin G 50,000 U/kg/ dose IV every 12 h during the first 7 days of age and every 8 h thereafter for 10 days[a] *OR* Penicillin G procaine, 50,000 U/kg per day IM in a single dose for 10 days[a]
Scenario 2 Possible congenital syphilis	Normal physical examination and serum quantitative nontreponemal serologic titer <4-fold the maternal titer and mother: (a) Not treated, inadequately treated, or undocumented treatment (b) Treated with azithromycin or other nonpenicillin regimen (c) Treated <4 weeks before delivery	CSF analysis for VDRL, cell count, and protein CBC and platelet count Long bone radiographs	Aqueous crystalline penicillin G 50,000 U/kg/ dose IV every 12 h during the first 7 days of age and every 8 h thereafter for 10 days[a] *OR* Penicillin G procaine, 50,000 U/kg per day IM in a single dose for 10 days[a] *OR* Penicillin G benzathine, 50,000 U/kg, IM, in a single dose[b]
Scenario 3 Congenital syphilis less likely	Normal physical examination and serum quantitative nontreponemal serologic titer <4-fold the maternal titer and mother: (a) Treated during pregnancy, appropriate for stage of infection, and >4 weeks before delivery (b) No evidence of reinfection or relapse	None	Penicillin G benzathine 50,000 U/kg IM in a single dose

(continued)

Table 2 (continued)

Clinical status		Evaluation	Treatment
Scenario 4 Congenital syphilis unlikely	Normal physical examination and serum quantitative nontreponemal serologic titer <4-fold the maternal titer and: (a) Mother treated adequately before pregnancy (b) Nontreponemal serologic titer remained low and stable during pregnancy and at delivery	None	None

PCR polymerase chain reaction, *VDRL* venereal disease research laboratory, *CBC* complete blood cell count, *CSF* cerebrospinal fluid, *IV* intravenous, *IM* intramuscular, *CSF* cerebrospinal fluid, *CBC* complete blood cell

[a]If more than 1 day of therapy is missed, the entire course should be restarted

[b]A complete evaluation (CBC and platelet, CSF analysis, long bone radiographs) must be normal. If any part of the infant's evaluation is abnormal or not performed, the 10-day course of penicillin is required

Table 3 Recommended treatment of pregnant women for syphilis

Stage of infection	Treatment[a]
Primary	Benzathine penicillin G 2.4 million units IM in a single dose
Secondary syphilis	Benzathine penicillin G 2.4 million units IM in a single dose
Early latent syphilis[b]	Benzathine penicillin G 2.4 million units IM in a single dose
Late latent syphilis[c]	Benzathine penicillin G 2.4 million units IM at 1-week intervals (3 doses)
Latent syphilis of unknown duration	Benzathine penicillin G 2.4 million units IM at 1-week intervals (3 doses)
Tertiary syphilis	Benzathine penicillin G 2.4 million units IM at 1-week intervals (3 doses)
Neurosyphilis or Ocular syphilis	Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 h or continuous infusion, for 10–14 days

IM intramuscular

[a]Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin

[b]Latent syphilis less than a year's duration

[c]Latent syphilis of over a year's duration

congenital syphilis, (2) a nontreponemal titer that is fourfold or higher than the mother's titer, or (3) a positive dark-field test of body fluid(s).

Infants who have a normal physical examination, a serum quantitative nontreponemal serologic titer that is the same or less than fourfold the maternal titer, normal CBC and platelet counts, normal CSF studies, and normal long bone radiographs may receive a single intramuscular injection of benzathine penicillin G (50,000 U/kg) if the mother (a) was not treated, inadequately treated, or has no documentation of having received treatment or (b) was treated with a nonpenicillin G regimen or

(c) received recommended treatment initiated at <4 weeks before delivery [21, 22]. If the evaluation in these infants is abnormal or incomplete, then a 10-day course of penicillin is mandatory.

Normal neonates born to mothers who received appropriate treatment (Table 3) greater than 4 weeks before delivery should receive a single intramuscular injection of benzathine penicillin G (50,000 U/kg), although further evaluation is not required or recommended [7, 18, 23]. Similarly, normal infants who have a nonreactive serum nontreponemal test result but are born to mothers with untreated or inadequately treated syphilis can receive a single dose of intramuscular benzathine penicillin G (50,000 U/kg) without evaluation—an increasingly common scenario with the use of reverse sequence syphilis screening during pregnancy. Newborns who have normal physical exams and nonreactive nontreponemal testing are unlikely to have abnormal laboratory or radiographic testing [24, 25].

If more than 1 day of therapy is missed, the entire course of therapy should be restarted. Ampicillin for possible sepsis should not be included in the total duration of penicillin therapy for congenital syphilis. Infants who have a penicillin allergy or develop a possible allergic reaction during therapy should have penicillin desensitization performed. Rarely, within the first 24 hours of therapy, infants may experience an acute inflammatory "Jarisch-Herxheimer" reaction consisting of fever, hypotension, worsening of lesions, tachycardia, tachypnea, or cardiovascular collapse due to rapid killing of spirochetes. Only supportive care is indicated.

If aqueous or procaine penicillin G is not available, ceftriaxone for 10 days can be considered with careful clinical and serologic follow-up, including CSF evaluation (https://www.cdc.gov/std/tg2015/congenital.htm) [18]. In neonates, ceftriaxone should not be administered with calcium-containing products since lethal precipitates can form in the lungs and kidneys. It also should be used with caution in infants with jaundice as it could displace bilirubin from albumin-binding sites.

Infants with congenital syphilis should be cared for with standard precautions. If an infant has cutaneous or mucous membrane lesions, then contact precautions with gloves should be instituted until 24 h of treatment has been completed.

Follow-up. The vast majority of infants with congenital syphilis who are treated in early infancy do well without any long-term complications due to syphilis. Infants born to mothers with syphilis and have reactive serologic test results should have serial quantitative nontreponemal tests performed every 2–3 months until the test becomes nonreactive (preferably) or the titer has decreased fourfold. In infants with congenital syphilis, nontreponemal serologic tests should decline fourfold and become nonreactive within 6–12 months after adequate treatment. Uninfected infants usually become seronegative by 6 months of age. If serologic nontreponemal titers increase fourfold at any time or remain stable after 12–18 months, the child should be evaluated and (re)-treated with a 10-day course of parenteral penicillin G. A reactive treponemal test beyond 18–24 months of age when the child has lost all maternal IgG antibodies confirms the diagnosis of congenital syphilis. If the child was not previously treated, then treatment is indicated as for late congenital syphilis.

Neonates who have abnormal CSF findings should have a repeat lumbar puncture performed 6 months after therapy. A reactive CSF VDRL test, abnormal protein content, or abnormal cell count is an indication for re-treatment.

Prevention

All pregnant women should have a serologic test for syphilis performed at the first prenatal care visit in the first trimester and, in communities in which the prevalence of syphilis is high, repeated at 28–32 weeks and again at delivery [18]. The treatment status of all sexual partners should be determined for possibility of maternal reinfection. Serologic screening should be performed on mothers rather than newborns as neonates may have a nonreactive serologic test result if the maternal titer is reactive at a low dilution. Mothers and infants should not be discharged home without documentation of the mother's serologic status at least once during the pregnancy and preferably also at delivery if in a high prevalence area. All cases of syphilis should be reported to the local public health department to assist in the identification of core environments and populations.

References

1. Radolf JD, Deka RK, Anand A, Smajs D, Norgard MV, Yang XF. Treponema pallidum, the syphilis spirochete: making a living as a stealth pathogen. Nat Rev Microbiol. 2016;14:744–59.
2. Newman L, Kamb M, Hawkes S, et al. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. PLoS Med. 2013;10:e1001396.
3. Peterman TA, Su J, Bernstein KT, Weinstock H. Syphilis in the United States: on the rise? Expert Rev Anti-Infect Ther. 2015;13:161–8.
4. Wendel GD Jr, Sanchez PJ, Peters MT, Harstad TW, Potter LL, Norgard MV. Identification of Treponema pallidum in amniotic fluid and fetal blood from pregnancies complicated by congenital syphilis. Obstet Gynecol. 1991;78:890–5.
5. Nathan L, Twickler DM, Peters MT, Sanchez PJ, Wendel GD Jr. Fetal syphilis: correlation of sonographic findings and rabbit infectivity testing of amniotic fluid. J Ultrasound Med. 1993;12:97–101.
6. Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD Jr. Fetal syphilis: clinical and laboratory characteristics. Obstet Gynecol. 2001;97:947–53.
7. Sheffield JS, Sanchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. Am J Obstet Gynecol. 2002;186:569–73.
8. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. Bull World Health Organ. 2013;91:217–26.
9. Sheffield JS, Sanchez PJ, Wendel GD Jr, et al. Placental histopathology of congenital syphilis. Obstet Gynecol. 2002;100:126–33.
10. Dorfman DH, Glaser JH. Congenital syphilis presenting in infants after the newborn period. N Engl J Med. 1990;323:1299–302.
11. Fiumara NJ, Lessell S. The stigmata of late congenital syphilis: an analysis of 100 patients. Sex Transm Dis. 1983;10:126–9.
12. Michelow IC, Wendel GD Jr, Norgard MV, et al. Central nervous system infection in congenital syphilis. N Engl J Med. 2002;346:1792–8.

13. Sánchez PJ, Wendel GD, Grimprel E, et al. Evaluation of molecular methodologies and rabbit infectivity testing for the diagnosis of congenital syphilis and neonatal central nervous system invasion by Treponema pallidum. J Infect Dis. 1993;167:148–57.
14. Centers for Disease Control and Prevention. Syphilis testing algorithms using treponemal tests for initial screening—four laboratories, New York City, 2005-2006. MMWR. 2008;57:872–5.
15. Centers for Disease Control and Prevention. Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010. MMWR. 2011;60:133–7.
16. Mmeje O, Chow JM, Davidson L, Shieh J, Schapiro JM, Park IU. Discordant syphilis immunoassays in pregnancy: perinatal outcomes and implications for clinical management. Clin Infect Dis. 2015;61:1049–53.
17. Binnicker MJ, Jespersen DJ, Rollins LO. Direct comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012;50:148–50.
18. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1–137.
19. Alexander JM, Sheffield JS, Sanchez PJ, Mayfield J, Wendel GD Jr. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol. 1999;93:5–8.
20. Wendel GD Jr, Stark BJ, Jamison RB, Molina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med. 1985;312:1229–32.
21. Zhou P, Qian Y, Xu J, Gu Z, Liao K. Occurrence of congenital syphilis after maternal treatment with azithromycin during pregnancy. Sex Transm Dis. 2007;34:472–4.
22. Paryani SG, Vaughn AJ, Crosby M, Lawrence S. Treatment of asymptomatic congenital syphilis: benzathine versus procaine penicillin G therapy. J Pediatr. 1994;125:471–5.
23. Rac MW, Bryant SN, Cantey JB, McIntire DD, Wendel GD Jr, Sheffield JS. Maternal titers after adequate syphilotherapy during pregnancy. Clin Infect Dis. 2015;60:686–90.
24. Wozniak PS, Cantey JB, Zeray F, et al. Congenital syphilis in neonates with nonreactive nontreponemal test results. J Perinatol. 2017;37:1112–6.
25. Peterman TA, Newman DR, Davis D, Su JR. Do women with persistently negative nontreponemal test results transmit syphilis during pregnancy? Sex Transm Dis. 2013;40:311–5.

Tick-Borne Infections

Alaina K. Pyle

Babesiosis

Epidemiology

Babesiosis is caused by *Babesia microti*, an intraerythrocytic protozoan parasite that is transmitted to the incidental human host primarily through an *Ixodes* tick bite [1]. *Babesia* shares a vector with *Borrelia burgdorferi*, and the endemic range is similar—primarily the Northeast and upper Midwest [2]. There are sporadic cases from the Western United States, usually due to *B. duncani*. Less commonly, infection can occur via blood transfusion. The Red Cross reported in 2016 that *B. microti* was present in 0.4% of tested blood samples from Massachusetts and Connecticut [3]. *B. microti* is the most common transfusion-transmitted pathogen reported to the Food and Drug Administration [4]. As of January 2018, there is no licensed test for *Babesia* screening of donor blood, although a flourescent immunoassay-based approach is likely to be approved soon.

Pathogenesis

The life cycle of *B. microti* includes rodents and ticks; humans are an incidental host [1]. *Babesia* sporozoites are injected into the human during a tick blood meal, where they infect red blood cells and mature into trophozoites. Trophozoites then mature into merozoites of various morphologies, lyse the red blood cell, and spread to infect new red blood cells. Humans are a terminal host but can be transmitted to other humans via blood transfusion or via the placenta. *B. microti* is most commonly

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transmitted to infants via blood transfusion, but transplacental transmission of *Babesia* has also been well described [5].

Clinical Findings

Infants with babesiosis present with findings similar to congenital malaria. The incubation period ranges from 1 to 4 weeks after delivery for congenital cases and 1 to 9 weeks after transfusion for transfusion-related cases [6–8]. Fever, poor feeding, and hepatosplenomegaly are common. The most striking findings are anemia and jaundice due to severe hemolysis. Signs of hemolytic anemia on the peripheral smear, low haptoglobin, and elevated reticulocyte count are common. Elevated liver enzymes and thrombocytopenia are often seen.

Diagnosis

A high index of suspicion is necessary for babesiosis. Definitive diagnosis can be made with microscopic examination of a thin peripheral blood smear using Giemsa or Wright stain, which will highlight *B. microti* trophozoites as pleomorphic ring forms [9]. The rings have vacuoles and lack pigment, helping to distinguish them from *Plasmodium* ring forms. The "Maltese cross" tetrad ring form is not commonly seen but is highly specific for *Babesia* if present. If parasites are not visualized on thin smears, PCR testing is highly sensitive even with low-level parasitemia [10].

Treatment

Pregnant women with babesiosis should be treated as usual. The combination of atovaquone and azithromycin (for mild to moderate disease) or the combination of clindamycin and quinine (for severe disease) are recommended [11]. Infants with babesiosis are generally considered to have severe disease, and the literature supports treatment with clindamycin and quinine for 7–10 days (Table 1) [6–8]. However, atovaquone/azithromycin combination therapy has been used for mild disease in infants [12]. Exchange transfusion is recommended for patients with ≥10% parasitemia, severe anemia (hemoglobin <10 g/dL), or pulmonary, liver, or renal impairment [13].

Prevention

Avoidance of areas where ticks are prevalent and the use of protective clothing and DEET are mainstays of prevention [14]. Tick checks should be performed regularly when after any potential exposures, with prompt removal of the tick using tweezers

Table 1 Treatment of tick-borne infections in infants

Indication	Drug	Dose
Anaplasmosis	Doxycycline *OR* Rifampin[a]	4 mg/kg/day PO/IV divided q12 h 20 mg/kg/day PO divided 12 h
Babesia (mild)	Atovaquone *AND* Azithromycin	40 mg/kg/day IV divided q12 h 12 mg/kg/day PO/IV divided q24 h
Babesia (moderate, severe)[b,c]	Quinine *AND* Clindamycin	25 mg/kg/day PO divided q8 h 30 mg/kg/day PO/IV divided q8 h
Ehrlichiosis (human granulocytic ehrlichiosis)	Doxycycline *OR* Rifampin[c]	4 mg/kg/day PO/IV divided q12 h 20 mg/kg/day PO divided 12 h
Lyme disease, erythema migrans	Amoxicillin *OR* Cefuroxime	50 mg/kg/day PO divided q8 h ×14 days 50 mg/kg/day IV divided q24 h ×14 days
Lyme disease, central nervous system involvement	Ceftriaxone *OR* Penicillin G	50–75 mg/kg/day IV divided q24 h ×21–28 days 300,000 U/kg/day IV divided q4 h ×21–28 days
Rocky mountain spotted fever	Doxycycline	4 mg/kg/day PO/IV divided q12 h

[a]Rifampin can be considered if ehrlichiosis is confirmed and disease is mild; otherwise, doxycycline should be used
[b]Some experts consider all infant disease to be severe regardless of clinical findings
[c]Consider exchange transfusion if ≥10% parasitemia, hemoglobin <10 g/dL, or respiratory, liver, or renal failure

to grasp the mouth part. Screening of donor blood products has not been instituted nationally, but some states in endemic regions are using combined serology and PCR testing to prevent transfusion-associated infection [4].

Lyme Disease

Epidemiology

Lyme disease is caused by *Borrelia burgdorferi*, a spirochete that is transmitted to humans via the bite of an infected *Ixodes* tick [15]. It is endemic in much of the Northeast and upper Midwest United States, but travel-associated cases are reported throughout the United States annually. The incidence of Lyme disease has risen steadily over the past two decades; approximately 40,000 cases were reported in 2016 [16]. Primary risk factors for exposure include living in or traveling to a Lyme-endemic region, particularly during spring and summer, and engaging in activities that increase tick exposure (e.g., hiking, camping). Of note, increased Lyme disease activity has been noticed in states that border high-incidence states, suggesting that the range of *Ixodes* may be expanding [17].

Pathogenesis

There are case reports of congenital transmission of *Borrelia* across the placenta [18–21]. To date, these reports have been limited to visualization of spirochetes during autopsy of infants who expired due to seemingly unrelated causes (congenital heart disease, central nervous system trauma, and stillbirth, respectively). There is no evidence of a link between Lyme disease during pregnancy and adverse pregnancy outcomes or congenital malformations [22]. In addition, although *Borrelia* can be detected in breast milk, transmission via breast milk has not been documented [21].

Clinical Findings

Symptoms occur in an average of 10 days after a tick bite (range, 1–31). The classic findings of Lyme disease include rash and, less commonly, nonspecific symptoms such as fatigue, arthralgias, myalgias, and fever. Specific complications of progressive Lyme disease include CNS, cardiac, and joint involvement [15]. However, infants with Lyme disease are more likely to have erythema migrans (>85–90%) and less likely to have disseminated disease.

Erythema migrans. Erythema migrans, an erythematous, circular, or oval plaque, is the classic lesion of early Lyme disease. Notwithstanding the classic description of a "bull's-eye" appearance, most of these lesions are uniformly erythematous without central clearing. Hematogenous dissemination from the original bite site can result in multiple erythema migrans lesions.

Nervous system involvement. Disseminated disease can manifest as central nervous system disease. Common findings include facial palsy and aseptic meningitis. Neuroborreliosis should be considered in any patient living in or traveling to an endemic region who presents with facial nerve palsy.

Carditis. Lyme carditis is a rare manifestation of Lyme disease. Patients typically present with AV conduction or bundle branch block.

Arthritis. Lyme arthritis is a late manifestation of disseminated disease and can present weeks to months after the initial infection with joint swelling, arthralgias, or mild inflammation. The knee is the presenting joint in 90% of cases, and the arthritis is monoarticular in 2/3 of cases.

Diagnosis

Diagnostic testing can be challenging to interpret with Lyme disease due to poor sensitivity (especially in the acute phase), and prolonged antibody positivity after the infection has cleared. Diagnosis in young infants is further complicated by transplacental passage of anti-spirochetal antibody from mothers, particularly those living in endemic areas. The current recommendation (Fig. 1) is to base diagnosis on the presence of consistent history and physical including exposure

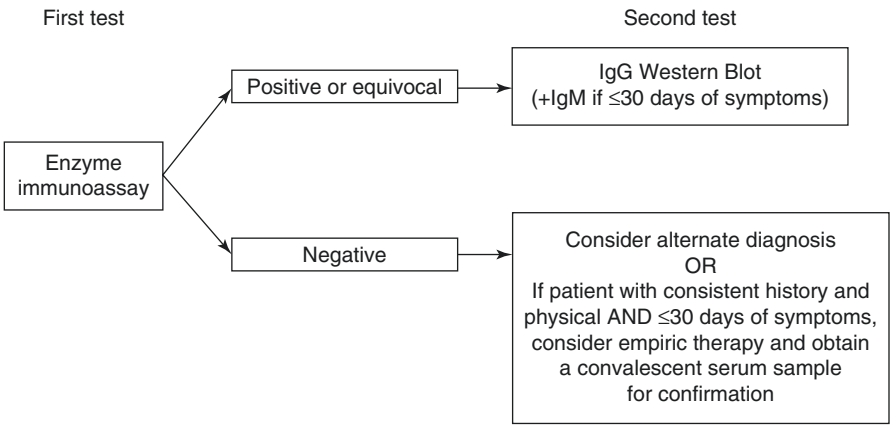

Fig. 1 Stepwise Lyme disease testing algorithm for adults and infants. A two-step process is recommended, beginning with an enzyme immunoassay. If positive or equivocal, the diagnosis should be confirmed with Western blot due to high false-positive rates with the EIA. If the EIA is negative, then in general an alternate diagnosis should be considered. However, EIAs can be falsely negative in the acute phase. Therefore, if the patient has consistent history and physical findings AND has had symptoms for less than a month, which includes all neonates with suspected Lyme disease by definition, empiric therapy can be considered

to endemic area [23]. However, for an infant with a known tick exposure and consistent clinical findings (e.g., erythema migrans), serologic confirmation is not necessary. In contrast, ordering antibody testing in the presence of vague constitutional symptoms or inconsistent rash is discouraged. If the symptoms and exposure are consistent with possible Lyme disease, a two-tier approach is recommended with initial quantitative testing for antibodies to *Borrelia burgdorferi* via enzyme immunoassay (EIA), followed by confirmatory Western blot if EIA results are equivocal or positive. However, false-negative results are possible in the first 2 weeks of infection, and negative EIA testing should not preclude treatment for patients with classic erythema migrans and probable *Ixodes* exposure. In cases of suspected neurologic involvement, cerebrospinal fluid should also be obtained. A lymphocytic pleocytosis is typically present in cerebrospinal fluid, and fluid can also be tested for the presence of IgM and IgG against *B. burgdorferi*.

Treatment

Pregnant women and infants with Lyme disease should receive appropriate treatment [14]. Since tetracyclines are pregnancy class D and contraindicated for children age <8 years, amoxicillin or cefuroxime should be used for erythema migrans, facial nerve palsy, carditis, or arthritis. Central nervous system disease requires parenteral therapy with ceftriaxone.

Prevention

Reducing exposure to tick vectors is paramount to prevention of Lyme disease. The use of protective clothing, diethyltoluamide (DEET), and daily tick checks with prompt removal are key methods of reducing risk for infection. Removing ticks promptly is important, because there is a 36- to 72-h delay between the start of feed and transmission of the spirochetes [24]. The evidence for either oral or topical antibiotic prophylaxis after a tick bite is unimpressive, with most of the efficacy limited to doxycycline [25, 26]. Therefore, routine use of antibiotic prophylaxis after a tick bite is not recommended for pregnant women.

Anaplasmosis, Ehrlichiosis, and Rocky Mountain Spotted Fever

Human granulocytic anaplasmosis (HGA) is caused by *Anaplasma phagocytophilum*, which is carried by the same tick vector as that for *B. microti* and *B. burgdorferi*—the *Ixodes* species [27]. Up to 10% of those with anaplasmosis have evidence of coinfection with Lyme disease or babesiosis [28]. Patients typically present with fever and malaise. Peripheral blood smear and PCR are the most sensitive diagnostic tests in the first 2 weeks of illness; serologic testing is recommended during the late portion of the disease.

Human monocytic ehrlichiosis is caused by *Ehrlichia chaffeensis* which is carried by the Lone Star tick (*Amblyomma americanum*) and the American dog tick (*Dermacentor variabilis*), which are present in the Southeastern, Midwest, and Northeast United States [27]. Incubation is typically 1–3 weeks after the tick bite. Presentation includes flu-like symptoms, occasional rash, thrombocytopenia, and elevated liver enzymes. Preferred diagnostic method is indirect fluorescent antibody, although PCR testing is also widely available.

Treatment for both ehrlichiosis and anaplasmosis is doxycycline. Perinatal transmission is rare but has been documented, so pregnant women with confirmed anaplasmosis or ehrlichiosis should be treated with rifampin, with the addition of cefuroxime or amoxicillin if coinfection with Lyme disease is present. Rifampin monotherapy can be considered for mild, confirmed ehrlichiosis in infants. However, if disease is severe or if Rocky Mountain spotted fever has not been excluded, doxycycline should be used.

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii* and is also transmitted by *D. variabilis* [29]. It is the most common fatal tick-borne illness in the United States but is exceedingly rare in the neonatal population. There is no evidence of placental transmission, but pregnant women should be treated with chloramphenicol (not doxycycline as recommended for all other populations) to prevent maternal disease [30]. Infants with suspected or confirmed Rocky Mountain spotted fever should be treated with doxycycline due to the lack of effective alternatives.

References

1. Vannier EG, Diuk-Wasser MA, Ben Mamoun C, Krause PJ. Babesiosis. Infect Dis Clin N Am. 2015;29:357–70.
2. Nelder MP, Russell CB, Sheehan NJ, et al. Human pathogens associated with the blacklegged tick Ixodes scapularis: a systematic review. Parasit Vectors. 2016;9:265.
3. Moritz ED, Winton CS, Tonnetti L, et al. Screening for Babesia microti in the U.S. blood supply. N Engl J Med. 2016;375:2236–45.
4. Levin AE, Krause PJ. Transfusion-transmitted babesiosis: is it time to screen the blood supply? Curr Opin Hematol. 2016;23:573–80.
5. Joseph JT, Purtill K, Wong SJ, et al. Vertical transmission of Babesia microti, United States. Emerg Infect Dis. 2012;18:1318–21.
6. Simonsen KA, Harwell JI, Lainwala S. Clinical presentation and treatment of transfusion-associated babesiosis in premature infants. Pediatrics. 2011;128:e1019–24.
7. Aderinboye O, Syed SS. Congenital babesiosis in a four-week-old female infant. Pediatr Infect Dis J. 2010;29:188.
8. Sethi S, Alcid D, Kesarwala H, Tolan RW. Probable congenital babesiosis in infant, New Jersey, USA. Emerg Infect Dis. 2009;15:788–91.
9. Krause PJ, Telford S, Spielman A, et al. Comparison of PCR with blood smear and inoculation of small animals for diagnosis of Babesia microti parasitemia. J Clin Microbiol. 1996;34:2791–4.
10. Wang G, Wormser GP, Zhuge J, et al. Utilization of a real-time PCR assay for diagnosis of Babesia microti infection in clinical practice. Ticks Tick Borne Dis. 2015;6:376–82.
11. Weiss LM. Babesiosis in humans: a treatment review. Expert Opin Pharmacother. 2002;3:1109–15.
12. Raju M, Salazar JC, Leopold H, Krause PJ. Atovaquone and azithromycin treatment for babesiosis in an infant. Pediatr Infect Dis J. 2007;26:181–3.
13. Powell VI, Grima K. Exchange transfusion for malaria and Babesia infection. Transfus Med Rev. 2002;16:239–50.
14. Feder HM, Lawlor M, Krause PJ. Babesiosis in pregnancy. N Engl J Med. 2003;349:195–6.
15. Steere AC. Lyme disease. N Engl J Med. 2001;345:115–25.
16. Centers for Disease Control and Prevention. Lyme disease graphs; cases by year. https://www.cdc.gov/lyme/stats/graphs.html. Accessed 25 Jan 2018.
17. Schwartz AM, Hinckley AF, Mead PS, Hook SA, Kugeler KJ. Surveillance for Lyme disease—United States, 2008-2015. MMWR Surveill Summ. 2017;66:1–12.
18. Schlesinger PA, Duray PH, Burke BA, Steere AC, Stillman MT. Maternal-fetal transmission of the Lyme disease spirochete, Borrelia burgdorferi. Ann Intern Med. 1985;103:67–8.
19. MacDonald AB, Benach JL, Burgdorfer W. Stillbirth following maternal Lyme disease. N Y State J Med. 1987;87:615–6.
20. Weber K, Bratzke HJ, Neubert U, Wilske B, Duray PH. Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatr Infect Dis J. 1988;7:286–9.
21. Mylonas I. Borreliosis during pregnancy: a risk for the unborn child? Vector Borne Zoonotic Dis. 2011;11:891–8.
22. Strobino BA, Williams CL, Abid S, Chalson R, Spierling P. Lyme disease and pregnancy outcome: a prospective study of two thousand prenatal patients. Am J Obstet Gynecol. 1993;169:367–74.
23. Schriefer ME. Lyme disease diagnosis: serology. Clin Lab Med. 2015;35:797–814.
24. Sood SK. Lyme disease in children. Infect Dis Clin N Am. 2015;29:281–94.
25. Schwameis M, Kundig T, Huber G, et al. Topical azithromycin for the prevention of Lyme borreliosis: a randomized, placebo-controlled, phase 3 efficacy trial. Lancet Infect Dis. 2017;17:322–9.

26. Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. N Engl J Med. 2001;345:79–84.
27. Ismail N, McBride JW. Tick-borne emerging infections: ehrlichiosis and anaplasmosis. Clin Lab Med. 2017;37:317–40.
28. Caulfield AJ, Pritt BS. Lyme disease coinfections in the United States. Clin Lab Med. 2015;35:827–46.
29. Woods CR. Rocky mountain spotted fever in children. Pediatr Clin N Am. 2013;60:455–70.
30. Dotters-Katz SK, Kuller J, Heine RP. Arthropod-borne bacterial diseases in pregnancy. Obstet Gynecol Surv. 2013;68:635–49.

Toxoplasmosis

A. Rebecca Ballard

Epidemiology

Toxoplasmosis is a parasitic infestation derived from the protozoan *Toxoplasma gondii*. This intracellular parasite infects humans as well as virtually all warm-blooded animals worldwide [1, 2]. Overall, 25–30% of the world's human population is infected by *T. gondii*, but prevalence between and within countries in the developing and developed world varies from 10 to 80% [3]. In the United States, seroprevalence of toxoplasmosis among women of childbearing age is less than 10% [4].

The exact incidence of congenital toxoplasmosis is unknown. Since toxoplasmosis is not a reportable disease—and the vast majority of infants with congenital infection are asymptomatic at birth—estimates vary widely. The best available evidence suggests that *at minimum*, the incidence in the United States is approximately 1 per 10,000 live births [5]. However, a comprehensive review and data modeling effort by Torgerson et al. [6]. estimated a worldwide incidence closer to 20 per 10,000 live births.

Pathogenesis

Maternal infection. The natural life cycle of *T. gondii* is shown in Fig. 1. Domestic cats and their close relatives (e.g., bobcats, lynx, cougars) are the definitive host for *T. gondii*. Approximately 30–50% of house cats in the United States are seropositive for *T. gondii* [7]. Cats shed oocysts in their stool, and rodents and birds acquire infection after ingesting soiled water, plants, or seeds. After ingestion, the cysts become tachyzoites which spread to brain and muscle tissue to become bradyzoites. When infected animals or birds are subsequently eaten by cats, the bradyzoites

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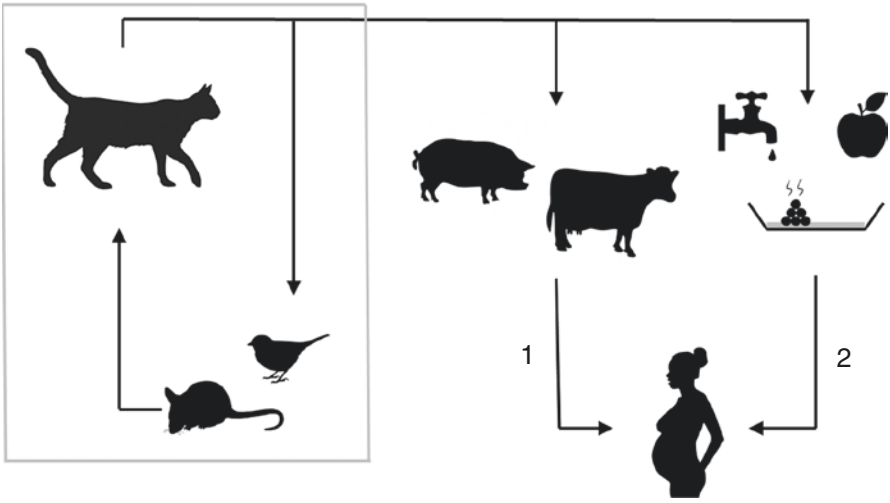

Fig. 1 The primary life cycle of *Toxoplasma gondii* is shown inside the gray box. Domestic cats and their close relatives are the definitive host. Cats shed oocysts in their stool, where they contaminate water, soil, and plant matter such as seeds. When rodents or birds ingest oocysts, the cysts transform into tachyzoites which establish infection in the animal's brain and muscle as bradyzoites. Cats ingest the infected animals and birds and become infected. Other animals, including livestock, can be incidental secondary hosts if they ingest contaminated plants or water. Humans may become infected if they (1) ingest bradyzoites in raw or undercooked meat from an infected animal or (2) ingest oocysts directly via contact with feline stool contaminating litter boxes, soil, unwashed fruits or vegetables, or water

activate and undergo sexual reproduction in the feline gut, leading to the production of oocysts [1, 2].

Non-feline mammals are accidental hosts. Animals such as pigs, cows, and sheep may ingest oocysts and develop infection; humans who ingest raw or undercooked meat from an infected animal can develop primary toxoplasmosis. Alternatively, humans can ingest oocysts directly either by contact with cat stool or indirectly through soil, untreated water, or unwashed fruits and vegetables. One or more risk factors (exposure to cats, ingestion of raw meat, or unwashed fruits and vegetables) can be identified in the majority of women whose infants have congenital toxoplasmosis. However, in approximately 25% of cases, no clear exposure history can be elicited [8].

Congenital infection. Congenital toxoplasmosis can occur in several ways. The most common situation is fetal infection following primary maternal infection during pregnancy. Infected women have a brief period of parasitemia with tachyzoites; it is during this period, presumably, that *T. gondii* crosses the placenta and infects the fetus [9]. Less commonly, fetal infection can follow reactivation of bradyzoites in a chronically infected pregnant woman, either due to underlying immunodeficiency (e.g., HIV) or rarely in immunocompetent women [10–12].

As with other congenital pathogens (see chapter "Pathogenesis of Congenital Infections"), vertical transmission of *T. gondii* is dependent on the timing of initial

infection. The placental barrier becomes more permeable to disease as pregnancy progresses, with parasitic passage to the fetus in 10% of cases in the first trimester, 30% in the second trimester, and 70% in third trimester. However, earlier infections are more damaging to the fetus [13, 14].

Clinical Findings

Adult infection. The majority of patients with acquired toxoplasmosis are asymptomatic. The small minority of patients who do come to clinical attention generally have non-specific "flu-like" symptoms such as low-grade fever, malaise, and generalized lymphadenopathy [15]. Unsurprisingly, primary toxoplasmosis is rarely recognized in the pregnant woman. Immunocompromised women may experience severe symptoms with a primary infection, including fever, confusion, poor coordination, and seizures [16].

Congenital infection. Approximately 90% of infants with congenital toxoplasmosis, particularly those infected during the third trimester, are asymptomatic in the newborn period. For the 10% of infants who are symptomatic, nonspecific signs of infection include hepatosplenomegaly, jaundice, anemia and thrombocytopenia, and intrauterine growth restriction. More specific findings for toxoplasmosis include the classic triad of diffuse intracerebral calcifications, hydrocephalus, and chorioretinitis (Table 1) [17–20].

Intracerebral calcifications. Infection of the fetal brain by the *T. gondii* parasite can lead to diffuse necrosis and inflammation, which results in calcified "scars" distributed throughout the cortex. This is in contrast to the calcifications of cytomegalovirus, which tend to be clustered in the periventricular space (see chapter "Cytomegalovirus Infection"). However, it can be difficult to differentiate the two types of calcification when severe hydrocephalus is present. In addition, the inflammation and necrosis of brain tissue can predispose to seizures.

Hydrocephalus. If *T. gondii* cysts develop within or adjacent to the ventricular system or if there is marked periventricular injury that results in necrotic tissue entering the ventricles, obstruction of cerebrospinal fluid drainage can lead to significant hydrocephalus. Ventricular dilatation may occur in one or both lateral

Table 1 Clinical findings in infants with symptomatic congenital toxoplasmosis (Adapted from [17–19])

Clinical finding	Frequency (%)
Chorioretinitis	90
Intracerebral calcifications	80
Hydrocephalus	60
Jaundice	50
Anemia or thrombocytopenia	50
Hepatosplenomegaly	40
Seizures	30
Microphthalmia	15
Microcephaly	15

ventricles and may include the third ventricle, depending on the location of the obstruction.

Chorioretinitis. *Toxoplasma* is particularly tropic for the eye, and severe chorioretinitis is a hallmark of congenital toxoplasmosis. The ocular inflammation can be severe enough to lead to microphthalmia in some infants. Infants with congenital toxoplasmosis, regardless of symptoms at birth, are at risk for recurrent retinal lesions later in childhood and into adulthood and require aggressive eye surveillance to prevent vision loss. Less common findings include cataract, glaucoma, and retinal detachment [21].

Infants with signs suggestive of congenital toxoplasmosis should undergo complete evaluation, including examination, fundoscopy, and head imaging with head ultrasound, MRI, or CT scan. Note that although congenital toxoplasmosis is classically associated with hydrocephalus, microcephaly can also be seen if there is significant brain destruction without obstruction of the ventricular system.

Diagnosis

Toxoplasmosis is primarily diagnosed with serologic testing. Anti-*T. gondii* IgG appears within a few weeks of primary infection and persists indefinitely. Initially, the IgG has low avidity (i.e., weak antibody-antigen binding) to *T. gondii*, but this improves over time until the IgG is highly avid. Therefore, if IgG is present, avidity testing can be used to get a sense of how recent the primary infection was. IgM and IgA are more acute markers of infection [22]. IgM appears within the first week of infection; IgA appears several weeks later.

PCR testing can also be used to detect *T. gondii* in tissue samples. It is most commonly used on amniotic fluid but is also appropriate for cerebrospinal fluid, blood, urine, or placental samples [23].

Pregnant women: Screening is not routinely conducted in the United States, but in high risk regions, particularly European countries, pregnant women may have monthly screenings. Testing includes maternal serum samples for IgG and IgM. In the United States, screening is usually limited to mothers whose infants have ultrasonographic findings concerning for congenital toxoplasmosis or when women who have influenza-like symptoms are screened by their obstetrician. The only routine screening in the United States occurs among HIV-infected women, for whom IgG screening is recommended at the time of HIV diagnosis [24].

Antenatal diagnosis of congenital toxoplasmosis. Detailed fetal ultrasonography should be performed if primary toxoplasmosis infection is diagnosed during pregnancy. Ultrasonographic findings concerning for toxoplasmosis include hydrocephalus, intracranial calcifications, hepatosplenomegaly, and growth restriction. In addition, amniocentesis should be performed as soon as possible after infection is diagnosed, but not earlier than 18 weeks' gestation. The sensitivity, specificity, and positive predictive value of amniotic fluid *Toxoplasma* PCR approach 100% [25].

Postnatal diagnosis of congenital toxoplasmosis. For infants with suspected congenital toxoplasmosis that was not evaluated antenatally, diagnosis can be made

using serology or direct antigen identification (Fig. 2). A reasonable screening step is to send maternal blood for *T. gondii* IgG; if the mother does not have IgG, the infant does not have congenital toxoplasmosis. If maternal *Toxoplasma* IgG

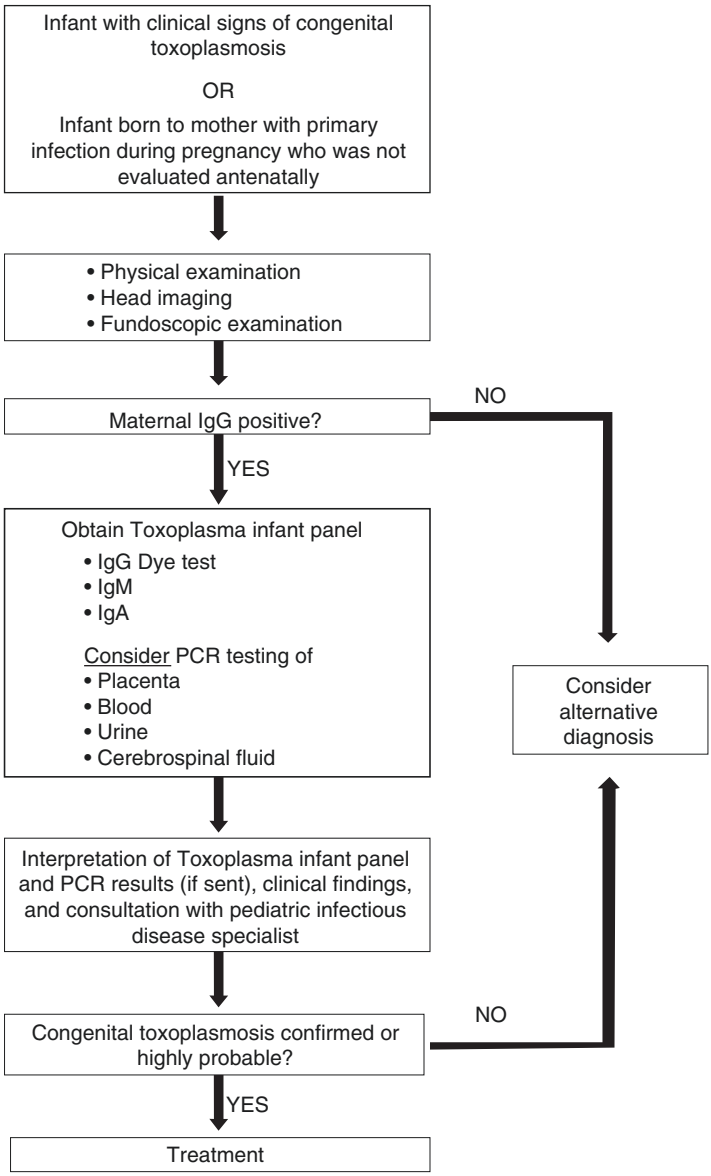

Fig. 2 Diagnostic algorithm for infants with suspected congenital toxoplasmosis. Determining whether the mother has anti-*T. gondii* IgG is an important step, as a negative IgG in the mother makes symptomatic congenital infection in the infant unlikely. Definitive serologic testing of the infant should be sent to the Palo Alto Medical Foundation *Toxoplasma* Serology Laboratory

(or infant IgG, which represents transplacental maternal antibody) is positive, then additional testing should include IgG Sabin-Feldman dye test, and IgA and IgM can be ordered from a reference lab [26]. The Palo Alto Medical Foundation *Toxoplasma* Serology Laboratory is widely used; specimen forms are available at http://www.pamf.org/serology. The sensitivity and specificity of serologic testing is not perfect, so decisions regarding treatment should be made in consultation with a pediatric infectious diseases specialist.

PCR testing can also be used on clinical samples. The specificity of a positive PCR test is quite good, but sensitivity varies from 20 to 50% for placenta, blood, urine, and cerebrospinal fluid, respectively [20]. There is evidence that the addition of PCR to serologic testing will increase the proportion of confirmed infection among infants with suspected congenital toxoplasmosis, but the overall yield is relatively low [27, 28].

Treatment

Pregnant women. Pregnant women with confirmed primary toxoplasmosis infection should be treated. The choice of therapy depends on whether or not fetal infection is identified. If fetal sonography is normal and amniotic fluid is PCR-negative, then spiramycin is the drug of choice [29]. Spiramycin can be obtained from the Food and Drug Administration (phone, 301-796-1600). The Food and Drug Administration works with the Palo Alto *Toxoplasma* Serology Laboratory, so testing and treatment should be coordinated with them as well as the local infectious diseases specialist.

Before 18 weeks' gestation, the mother should be treated with spiramycin. At 18 weeks' gestation, she can then be converted to pyrimethamine, sulfadiazine, and leucovorin—the same medications recommended for congenitally infected infants. Treatment should continue until term (37 weeks' gestation) if congenital infection is confirmed; if congenital infection is excluded with amniocentesis, therapy should revert to spiramycin [30].

Infants. Infants with congenital toxoplasmosis should be treated with combination therapy that includes pyrimethamine, sulfadiazine, and leucovorin (Table 2). Treatment markedly improves neurodevelopmental outcomes. In a remarkable cohort study spanning more than two decades, McLeod et al. [18] treated 121 infants with congenital toxoplasmosis with the regimen shown in Table 2 and compared their outcomes to historical controls. Treatment was associated with significant and substantial reductions in intellectual disability, eye lesions, visual impairment, hearing loss, and cerebral palsy. The benefits are most visible among the most severely affected infants. For infants with severe chorioretinitis or marked cerebrospinal fluid proteinosis (>1000 mg/dL), corticosteroid therapy should be included with the antiparasitic therapy.

Therapy generally lasts 1 year. However, if new ocular disease appears after treatment is discontinued, additional treatment should be given for 1–2 months. Given the length and complexity of treatment as well as the need for hematologic monitoring, therapy is best provided in coordination with a pediatric infectious diseases specialist.

Table 2 Recommended treatment of infants with congenital toxoplasmosis (Adapted from [18])

Intervention	Dose	Duration
Pyrimethamine	1 mg/kg PO q12 h × 2 days and then 1 mg/kg PO q24 h for 2–6 months and then 1 mg/kg PO three times a week	1 year
Sulfadiazine	50 mg/kg PO q12 h	
Leucovorin	10 mg PO three times a week	
Prednisone[a]	0.5 mg/kg q12 h	1 week after resolution
Fundoscopy	Q3 months in first year of life Q6 months in second year of life Annually thereafter	
Audiology[b]	Routine screening	
Neurodevelopmental surveillance	Routine screening	

[a]Prednisone is indicated if severe chorioretinitis is present or if cerebrospinal fluid protein levels are >1000 mg/dL. Prednisone should be continued until the indication resolves and then for 1 additional week

[b]The association between congenital toxoplasmosis and hearing loss is unclear; there is no recommendation for more aggressive screening

Prevention

At present, prevention of congenital toxoplasmosis is best accomplished by education so that pregnant women can avoid primary infection. Only about 40% of women in the United States are aware of the risks associated with exposure to cat feces, and far fewer are aware of the other exposures associated with *T. gondii* including raw or undercooked meat, unwashed fruits or vegetables, or soil exposure such as gardening [31]. Education on toxoplasmosis and prevention strategies intuitively should be effective, but the few randomized controlled trials have not shown a reduction in primary infection during pregnancy [32, 33].

Failing that, prompt diagnosis and treatment of pregnant women with primary infection has been shown to reduce the risk of congenital toxoplasmosis by approximately 50% [34]. However, the benefit is attenuated when maternal treatment is started later. In the United States, which does not prospectively screen pregnant women, it can become very difficult to identify primary toxoplasmosis quickly and initiate prompt therapy.

Universal antepartum screening is favored by many advocates, and the limited evidence available suggests that it could be cost-effective in the United States under the proper circumstances. However, there is currently no recommendation by either the American College of Obstetricians and Gynecologists or the US Preventive Health Task Force to screen pregnant women [35, 36].

References

1. Moncada PA, Montoya JG. Toxoplasmosis in the fetus and newborn: an update on prevalence, diagnosis, and treatment. Expert Rev Anti-Infect Ther. 2012;10:815–28.

2. Tamma P. Toxoplasmosis. Pediatr Rev. 2007;28:470–1.
3. Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of Toxoplasma gondii seroprevalence and implications for pregnancy and congenital toxoplasmosis. Int J Parasitol. 2009;39:1385–94.
4. Jones JL, Kruszon-Moran D, Rivera HN, Price C, Wilkins PP. Toxoplasma gondii seroprevalence in the United States 2009–2010 and comparison with the past two decades. Am J Trop Med Hyg. 2014;90:1135–9.
5. Roberts T, Frenkel JK. Estimating income losses and other preventable costs caused by congenital toxoplasmosis in people in the United States. JAMA. 1990;2:249–56.
6. Torgerson PR, Mastroiacovo P. The global burden of congenital toxoplasmosis: a systematic review. Bull World Health Organ. 2013;91:501–8.
7. Dubey JP, Bhatia CR, Lappin MR, Ferreira LR, Thorn A, Kwok OC. Seroprevalence of Toxoplasma gondii and Bartonella spp. Antibodies in cats from Pennsylvania. J Parasitol. 2009;95:578–80.
8. Boyer KM, Holfels E, Roizen N, et al. Risk factors for Toxoplasma gondii infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. Am J Obstet Gynecol. 2005;192:564–71.
9. Mahmoudvand H, Saedi Dezaki E, Soleimani S, et al. Seroprevalence and risk factors of Toxoplasma gondii infection among healthy blood donors in south-east of Iran. Parasite Immunol. 2015;37(7):362.
10. Bachmeyer C, Mouchnino G, Thulliez P, Blum L. Congenital toxoplasmosis from an HIV-infected woman as a result of reactivation. J Infect. 2006;52:e55–7.
11. Campos FA, Andrade GM, Lanna Ade P, et al. Incidence of congenital toxoplasmosis among infants born to HIV-coinfected mothers: case series and literature review. Braz J Infect Dis. 2014;18:609–17.
12. Kodjikian L, Hoigne I, Adam O, et al. Vertical transmission of toxoplasmosis from a chronically infected immunocompetent woman. Pediatr Infect Dis J. 2004;23:272–4.
13. Dunn D, Wallon M, Peyron F, et al. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counseling. Lancet. 1999;353:1829–33.
14. Desmonts G, Couvreur J. Congenital toxoplasmosis—a prospective study of 378 pregnancies. N Engl J Med. 1974;290:1110–6.
15. Saadatnia G, Golkar M. A review on human toxoplasmosis. Scand J Infect Dis. 2012;44:805–14.
16. Contini C. Clinical and diagnostic management of toxoplasmosis in the immunocompromised patient. Parassitologia. 2008;50:45–50.
17. Olariu TR, Remington JS, McLeod R, Alam A, Montoya JG. Severe congenital toxoplasmosis in the United States: clinical and serologic findings in untreated infants. Pediatr Inf Dis J. 2011;30:1056–61.
18. McLeod R, Boyer K, Karrison T, et al. Outcome of treatment for congenital toxoplasmosis, 1981–2004: the national collaborative Chicago-based, congenital toxoplasmosis study. Clin Inf Dis. 2006;42:1383–94.
19. Eichenwald HF. A study of congenital toxoplasmosis, with particular emphasis on clinical manifestations, sequelae, and therapy. In: Siim JC, editor. Human toxoplasmosis. Copenhagen: Munksgaard; 1960. p. 41–9.
20. Peyron F, Wallon M, Kieffer F, Garweg J. Toxoplasmosis. In: Wilson CB, Nizet V, Maldonado YA, Remington JS, Klein JO, editors. Infectious diseases of the fetus and newborn infant. 8th ed. Philadelphia, PA: Elsevier; 2016. p. 949–1042.
21. Arun V, Noble AG, Latkany P, et al. Cataracts in congenital toxoplasmosis. J AAPOS. 2007;11:551–4.
22. Pomares C, Montoya JG. Laboratory diagnosis of congenital toxoplasmosis. J Clin Microbiol. 2016;54:2448–54.
23. Rostami A, Karanis P, Fallahi S. Advances in serological, imaging techniques and molecular diagnosis of Toxoplasma gondii infection. Infection. Available online Jan. 2018;12:2018.
24. U.S. Department of Health and Human Services. Aidsinfo: Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. https://aidsinfo.

nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/322/toxo. Accessed 17 Feb 2018.
25. Robert-Gangneux F, Brenier-Pinchart MP, Yera H, et al. Evaluation of toxoplasma ELITe MGB real-time PCR assay for diagnosis of toxoplasmosis. J Clin Microbiol. 2017;55:1369–76.
26. Gilbert RE, Thalib L, Tan HK, et al. Screening for congenital toxoplasmosis: accuracy of immunoglobulin M and immunoglobulin A tests after birth. J Med Screen. 2007;14:8–13.
27. Olariu TR, Remington JS, Montoya JG. Polymerase chain reaction in cerebrospinal fluid for the diagnosis of congenital toxoplasmosis. Pediatr Infect Dis J. 2014;33:566–70.
28. Filisetti D, Cocquerelle V, Pfaff A, Villard O, Candolfi E. Placental testing for Toxoplasma gondii is not useful to diagnose congenital toxoplasmosis. Pediatr Infect Dis J. 2010;29:671–2.
29. Avci ME, Arslan F, Ciftci S, et al. Role of spiramycin in prevention of fetal toxoplasmosis. J Matern Fetal Neonatal Med. 2016;29:2073–6.
30. Chaudhry SA, Gad N, Koren G. Toxoplasmosis and pregnancy. Can Fam Physician. 2014;60:334–6.
31. Jeon J, Victor M, Adler SP, et al. Knowledge and awareness of congenital cytomegalovirus among women. Infect Dis Obstet Gynecol. 2006;2006:80383.
32. Breugelmans M, Naessens A, Foulon W. Prevention of toxoplasmosis during pregnancy—an epidemiologic survey over 22 consecutive years. J Perinat Med. 2004;32:211–4.
33. Di Mario S, Basevi V, Gagliotti C, et al. Prenatal education for congenital toxoplasmosis. Cochrane Database Syst Rev. 2015;23:CD006171.
34. Thiebaut R, Leproust S, Chene G, et al. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. Lancet. 2007;369:115–22.
35. American College of Obstetricians and Gynecologists. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015;125:1510–25.
36. Maldonado YA, Read JS, Committee on Infectious Diseases. Diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. Pediatrics. 2017;139:e20163860.

Tuberculosis in the Neonate

Gabriella S. Lamb and Jeffery R. Starke

Epidemiology

TB is the most common infectious disease in the world with an annual incidence of over one million cases [1]. Globally, the incidence of TB is increasing in women of reproductive age, and as a consequence, TB is relatively common during pregnancy. As a result, the incidence of perinatally acquired disease is increasing [2–4, 8–10]. Among those tested, nearly 50% of foreign-born pregnant women in the United States have TB infection [6].

Vertical transmission—true congenital TB—is rare as the major symptom of genitourinary TB in a woman is infertility. Prior to 1984, there were fewer than 300 cases reported, but more than 80 cases have been reported subsequently [8, 9, 11–13]. This rarity is likely because the placenta can protect the infant from bacterial penetration, making postpartum transmission via infected respiratory droplets much more common [11].

Pathogenesis

M. tuberculosis is transmitted via particles which may remain airborne for several hours after aerosolization from a cough or sneeze. After inhalation, *M. tuberculosis* reaches the alveoli. At that point, the clinical course depends on whether or not the immune system—including alveolar macrophages and T cell-mediated cellular immunity—is able to control the infection. The differences in transmission between congenitally and postnatally acquired diseases are shown in Fig. 1.

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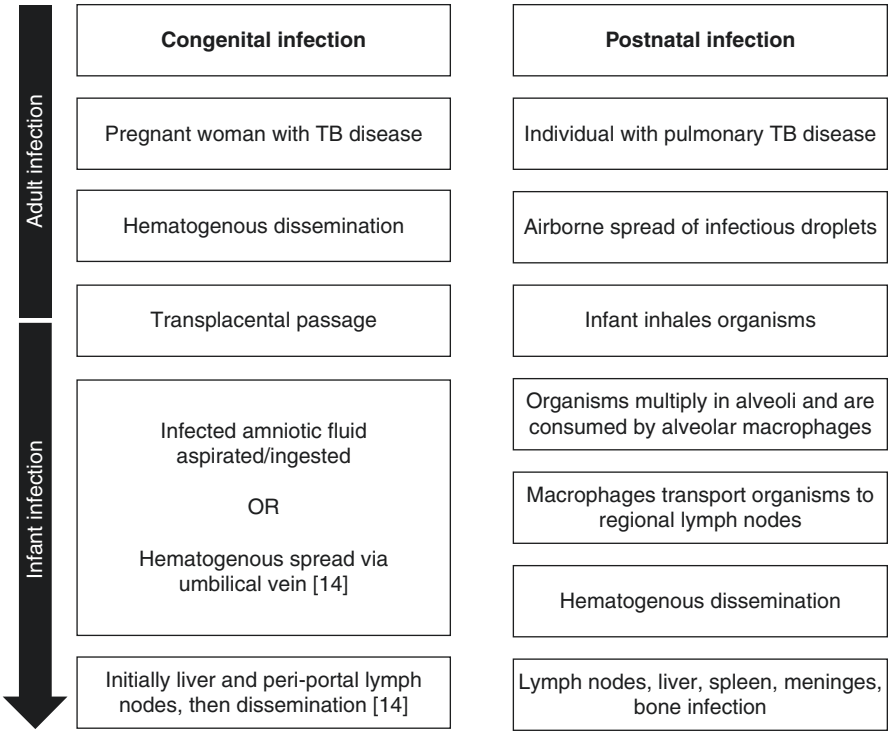

Fig. 1 Pathophysiology of congenital or postnatal tuberculosis infection in infants

TB infection. Patients who have immune control of their TB are defined as having "TB infection" (also known as latent TB infection). These patients are neither contagious nor symptomatic, but TST or IGRA tests for TB will be positive. Approximately 5–10% of patients with TB infection will go on to develop TB disease later in life.

TB disease. For patients whose immune system cannot control their initial infection, or for the fraction of patients with latent TB whose infection eventually escapes immune control, TB disease develops. TB disease includes primary or reactivated pulmonary disease or disseminated TB disease that may reach the liver, spleen, bones, and central nervous system.

Clinical Findings

Infants with TB acquired postnatally (via airborne droplets) or vertically (due to transplacental passage of *M. tuberculosis*) have a similar clinical presentation and should have the same diagnostic evaluation, medical management, and isolation precautions (Table 1) [15, 16]. The median age of presentation for infants with vertically transmitted disease is 24 days, with most cases presenting in the second or third week of life [15]. Infants with postnatally acquired TB tend to present at 1–4

Table 1 Signs and symptoms of perinatally acquired tuberculosis

Clinical features	Common	Fever, poor feeding with failure to thrive, irritability, jaundice, cough, respiratory distress, lymphadenitis, sepsis, developmental delay, and hearing loss [17, 18]
	Uncommon	Progressive liver dysfunction, spinal TB, and otitis media [19, 20]
Location of disease	Primary focus	Hepatic [congenital] or pulmonary [congenital or postnatal] with caseating granulomas
	Dissemination[a]	Bone and bone marrow, lymph nodes, gastrointestinal tract, spleen, kidneys, middle ear, meninges, brain, and skin [19]
Physical exam	Common	Growth delay, hepatosplenomegaly, abdominal distension, lethargy, seizures, increased head circumference [21]
	Uncommon	Ascites, otitis media with a draining ear, and facial nerve palsy [19, 22–25]

[a]Dissemination can occur rapidly and lead to significant morbidity and mortality in untreated infants, although prognosis is fair with timely and appropriate treatment [26, 27]

Table 2 Common laboratory and radiographic abnormalities of perinatally acquired tuberculosis

	General	CNS involvement
Laboratory abnormalities	Elevated white blood cell count with neutrophilic predominance	CSF studies: pleocytosis, elevated protein, moderately low glucose, positive AFB stain, mycobacterial culture or GeneXpert MTB/RIF PCR assay
	Thrombocytopenia	
	Elevated transaminases	
	Hyponatremia[a]	
	Elevated inflammatory markers	
Radiographic imaging	Early in disease CXR may be normal	Hydrocephalus, intraventricular hemorrhage, intracranial calcifications, bland infarction, tuberculoma
	Later the CXR is usually abnormal and can show miliary disease pattern, multiple pulmonary nodules, adenopathy, segmental atelectasis, or lobar pneumonia	

AFB acid-fast bacilli, *CXR* chest X-ray
[a]Hyponatremia, in particular, can be seen secondary to inappropriate antidiuretic hormone release or renal salt wasting [21]

months of age [15, 16]. Perinatally acquired TB can be difficult to distinguish clinically from other congenital infections, as the symptoms are nonspecific [12]. Infected infants are at significantly higher risk of progressing to symptomatic disease due to the immune system's immaturity [28, 29]. Immunocompromising conditions such as HIV and poor nutritional status also increase the risk of progression to disease [30, 31].

Infants with TB disease are at higher risk than other age groups for having disseminated disease, including hepatosplenic, osteoarticular, or central nervous system involvement. Morbidity and mortality are as high as 60% for infants with perinatally acquired disease [12]. However, infants with congenital disease who present after 3 weeks of age have a higher survival rate, likely related to a lower inoculum load [9]. Table 2 summarizes common laboratory and radiographic abnormalities of perinatally acquired tuberculosis.

Diagnosis

Diagnostic criteria for TB acquired vertically were first described in 1935 and updated in 1994. To diagnose congenital tuberculosis, the infant must have proven tuberculous lesions in the first week of life, a primary hepatic complex or caseating hepatic granulomas, or TB infection of the placenta or maternal genital tract; additionally, postnatal transmission must be excluded [9, 15, 32].

Acid-fast bacilli (AFB) culture. The sensitivity of culture for infants with vertically transmitted disease is quite high. However, for those with postnatally acquired disease, diagnosis can be more challenging as AFB stains are positive in less than 10% of cases and cultures require 1–3 weeks of incubation [33]. Appropriate samples for AFB microscopy, culture, and PCR include gastric aspirates, tracheal aspirates, ear discharge, ascites fluid, pleural fluid, or biopsies from skin lesions [12]. Cerebrospinal fluid (CSF) should always be evaluated for cell count and differential, glucose, protein, and AFB stains and culture, as there is high risk for meningitis even in neonates lacking specific neurologic symptoms [8].

PCR. GeneXpert MTB/RIF PCR assay (Xpert®, Cepheid Inc., Sunnyvale, CA) is a rapid, automated molecular nucleic acid amplification test that can detect the presence of *M. tuberculosis* within 2 hours [34]. Xpert MTB/RIF has improved sensitivity for detection of TB compared to smear microscopy for respiratory, gastric aspirate, lymph node, and CSF samples. As such, the WHO recommends its use for diagnosis of TB lung disease, lymphadenitis, and meningitis [35, 36].

Histopathology. Histopathologic examination of the placenta should be performed when vertical transmission is suspected; however, finding evidence of granulomas or AFB in the placenta does not prove neonatal infection nor does its absence prove lack of infection [30].

TST and IGRA. Skin testing or interferon release assays are predicated on recognition of *M. tuberculosis* antigens by the immune system. Unfortunately, the relatively immature cellular immunity of infants not only increases their risk for TB disease and dissemination but also impairs the sensitivity of TST and IGRA testing. Positive results are helpful, but negative results should be interpreted with caution and/or repeated due to the risk of false negatives during infancy.

Treatment

Treatment should be initiated as early as possible when TB is suspected [12, 37]. If there are no positive cultures from the infant, the drug regimen should be based on the drug susceptibilities of the cultures obtained from the infant's mother [38]. There are limited pharmacokinetic data for anti-TB drugs in neonates, so recommended doses (Table 3) are adapted from those used in older children [39]. Treatment should typically include isoniazid, rifampin, pyrazinamide, and ethambutol. If meningitis is suspected or confirmed, amikacin or ethionamide are often substituted for ethambutol [8, 12, 40]. Additionally, pyridoxine should be added if the infant is exclusively breastfed [38]. An initial four-drug regimen should be

Table 3 Medical therapy of suspected or proven tuberculosis (TB) disease in infants

Presentation	Treatment	Duration
TB disease without central nervous system involvement	Isoniazid (10–15 mg/kg/day)[a]	9–12 months
	Rifampin (15–20 mg/kg/day)	9–12 months
	Pyrazinamide (30–40 mg/kg/day)	First 2 months
	Ethambutol (15–25 mg/kg/day)[b]	First 2 months
TB disease involving central nervous system	As above, plus:	
	Amikacin (15–30 mg/kg/day)	First 2 months
	OR	
	Ethionamide (15–20 mg/kg/day)	First 2 months
	AND corticosteroids	First 4–6 weeks

[a]If exclusively breastfeeding, infant should also receive vitamin B6 supplement
[b]Ethambutol may be substituted for amikacin or ethionamide if central nervous system disease present

continued for 2 months, followed by treatment with isoniazid and rifampin for an additional 7–10 months for a total of 9–12 months of treatment if the child has drug-susceptible disease [12, 41]. Infants with meningitis should also receive 1–2 mg/kg/day of prednisone or an equivalent corticosteroid for the first 4–6 weeks followed by a taper to prevent hydrocephalus or cerebral infarction [8].

The health department should be notified, and directly observed therapy should be used for children treated for suspected or proven TB [4]. Though prognosis is guarded, within 2 weeks of initiation of appropriate therapy, most patients are expected to demonstrate clinical improvement [9].

Prevention

Prevention of TB disease in infants is based on successful screening programs that allow contacts with TB to be diagnosed and treated, immunization with Bacille Calmette-Guerin (BCG) vaccine in high-prevalence countries, and infection control and prevention to minimize horizontal transfer.

Screening: A high index of suspicion of TB in an infant's mother or household contacts is required to optimally detect and prevent TB disease in neonates. Many pregnant women with TB disease are symptomatic, though they may have nonspecific symptoms such as fever, lethargy, and respiratory distress. TB can also lead to genitourinary disease, which can present with a history of infertility, loss of pregnancy, and irregular menstrual bleeding [42]. Untreated TB disease in pregnant women can also lead to preterm delivery, low birthweight, or stillbirth [10]. Evaluation and treatment of the neonate depends on whether they have had exposure to a person with TB infection or disease (Table 4).

BCG immunization: Meta-analyses of BCG efficacy demonstrate a 60–90% decrease in TB meningitis and miliary TB in infants and toddlers, so BCG vaccination remains common in high-burden countries [46, 47]. In the United States, its use is very limited. The Centers for Disease Control and Prevention currently

Table 4 Management of the infant exposed to persons with tuberculosis (TB) infection or disease [43]

Exposure	Household contact with TB infection only (latent TB)	Household contact or healthcare worker with suspected or confirmed pulmonary TB disease
Next steps	Evaluate other household members	Report to health department
		Contact tracing
		Evaluate the infant for congenital TB
Separation required?	No	• Yes
		• Once congenital TB excluded and source case is appropriately treated, separation no longer needed
		• If the mother has TB disease, contact with the child should be brief, and mother should wear a mask until sputum negative
Treat infected individual?	Yes	Yes
Management of infant	No testing or treatment	3–6 months of isoniazid prophylaxis and then repeat testing
Breastfeeding?[a]	No contraindication	If mother infected, expressed breast milk safe
		Direct breastfeeding safe after 2 weeks of therapy

[a]Anti-TB medications are present in breast milk, though in low concentrations and with significant interindividual variability. Use of these medications is not a contraindication to feeding breast milk [44]. All pregnant or breastfeeding women taking isoniazid should also be given pyridoxine [45]

recommends considering BCG vaccination only for children with a negative TST who cannot be isolated from an adult with untreated, ineffectively treated, or multidrug-resistant pulmonary disease [48].

Infection control: Infants with postnatally acquired TB disease are unlikely to be contagious, as children rarely transmit the organism. However, infants with vertically acquired disease often have extensive pulmonary involvement and have transmitted the organism to healthcare workers, especially those who perform unprotected suctioning of the airway [49–54]. Direct infant-to-infant transmission has not been reported. In one NICU outbreak, there was one case of indirect infant-to-infant transmission which was attributed to contaminated respiratory equipment [54]. All neonates with perinatally acquired TB should be placed in airborne precautions (i.e., in a negative pressure room with anyone entering the room wearing an N95 respirator mask), and all visitors to the child should be screened with a chest X-ray [55].

There are several case reports of infants acquiring TB infection in NICUs with the source of infection being an adult (e.g., a parent, another family member, a healthcare worker) [50–53]. However, the risk of infection in neonates in a modern NICU is low because of frequent air exchanges and large air volumes [38]. Additionally, with appropriate treatment, the risk of developing infection is low.

The optimal management of infants exposed to TB in the nursery is unclear. In one study of a nursery exposure, infants were given prophylactic isoniazid for 3–6 months, and none of the infants had positive TSTs at the end of therapy [50].

References

1. Murray CJ, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990--2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:1005–70.
2. Hageman JR. Congenital and perinatal tuberculosis: discussion of difficult issues in diagnosis and management. J Perinatol. 1998;18:389–94.
3. Margono F, Mroueh J, Garely A, White D, Duerr A, Minkoff HL. Resurgence of active tuberculosis among pregnant women. Obstet Gynecol. 1994;83:911–4.
4. Starke JR. Tuberculosis. An old disease but a new threat to the mother, fetus, and neonate. Clin Perinatol. 1997;24:107–27.
5. Peker E, Bozdoğan E, Doğan M. A rare tuberculosis form: congenital tuberculosis. Tuberk Toraks. 2010;58:93–6.
6. Malhamé I, Cormier M, Sugarman J, Schwartzman K. Latent Tuberculosis in Pregnancy: A Systematic Review. PLoS One. 2016;11:e0154825.
7. Singh M, Kothur K, Dayal D, Kusuma S. Perinatal tuberculosis a case series. J Trop Pediatr. 2007;53:135–8.
8. Saramba MI, Zhao D. A perspective of the diagnosis and management of congenital tuberculosis. J Pathog. 2016;2016:8623825.
9. Peng W, Yang J, Liu E. Analysis of 170 cases of congenital TB reported in the literature between 1946 and 2009. Pediatr Pulmonol. 2011;46:1215–24.
10. Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax. 2001;56:494–9.
11. Espiritu N, Aguirre L, Jave O, Sanchez L, Kirwan DE, Gilman RH. Congenital transmission of multidrug-resistant tuberculosis. Am J Trop Med Hyg. 2014;91:92–5.
12. Sagar T, Gupta K, Rani M, Kaur IR. Disseminated tuberculosis in a newborn infant. J Family Med Prim Care. 2016;5:695.
13. Khorsand Zak H, Mafinezhad S, Haghbin A. Congenital tuberculosis: a newborn case report with rare manifestation. Iran Red Crescent Med J. 2016;18:e23572.
14. Mittal H, Das S, Faridi MM. Management of newborn infant born to mother suffering from tuberculosis: current recommendations & gaps in knowledge. Indian J Med Res. 2014;140:32–9.
15. Cantwell MF, Shehab ZM, Costello AM, et al. Brief report: congenital tuberculosis. N Engl J Med. 1994;330:1051–4.
16. Vallejo JG, Starke JR. Tuberculosis and pregnancy. Clin Chest Med. 1992;13:693–707.
17. Hageman J, Shulman S, Schreiber M, Luck S, Yogev R. Congenital tuberculosis: critical reappraisal of clinical findings and diagnostic procedures. Pediatrics. 1980;66:980–4.
18. Hatzistamatiou Z, Kaleyias J, Ikonomidou U, Papathoma E, Prifti E, Kostalos C. Congenital tuberculous lymphadenitis in a preterm infant in Greece. Acta Paediatr. 2003;92:392–4.
19. Ng PC, Hiu J, Fok TF, Nelson EAS, Cheung KL, Wong W. Isolated congenital tuberculosis otitis in a preterm infant. Acta Paediatr. 1995;84:955–6.
20. Aelami MH, Qhodsi Rad MA, Sasan MS, Ghazvini K. Congenital tuberculosis presenting as ascites. Arch Iran Med. 2011;14:209–10.
21. Vadivelu S, Effendi S, Starke JR, Luerssen TG, Jea A. A review of the neurological and neurosurgical implications of tuberculosis in children. Clin Pediatr. 2013;52:1135–43.
22. Raj P, Sarin YK. Congenital tuberculosis in a neonate: a diagnostic dilemma. J Neonatal Surg. 2014;3:49.

23. Berk DR, Sylvester KG. Congenital tuberculosis presenting as progressive liver dysfunction. Pediatr Infect Dis J. 2004;23:78–80.
24. Pejham S, Altman R, Li KI, Munoz JL. Congenital tuberculosis with facial nerve palsy. Pediatr Infect Dis J. 2002;21:1085–6.
25. Kumar A, Ghosh SB, Varshney MK, Trikha V, Khan SA. Congenital spinal tuberculosis associated with asymptomatic endometrial tuberculosis: a rare case report. Joint Bone Spine. 2008;75:353–5.
26. Smith KC. Congenital tuberculosis: a rare manifestation of a common infection. Curr Opin Infect Dis. 2002;15:269–74.
27. Stahelin-Massik J, Carrel T, Duppenthaler A, Zeilinger G, Gnehm HE. Congenital tuberculosis in a premature infant. Swiss Med Wkly. 2002;132:598.
28. Whittaker E, Kampmann B. Perinatal tuberculosis: new challenges in the diagnosis and treatment of tuberculosis in infants and the newborn. Early Hum Dev. 2008;84:795–9.
29. Miller F. Tuberculosis in children. Evolution-control-treatment. Harcourt-Brace: San Diego; 1963.
30. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9:737–46.
31. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011;24:351–76.
32. Beitzke H. Über die angeborene tuberkulöse Infektion. Ergeb Ges Tuberk Forsch. 1935;7:1–30.
33. Al-Zamel FA. Detection and diagnosis of Mycobacterium tuberculosis. Expert Rev Anti Infect Ther. 2009;7:1099–108.
34. Dunn JJ, Starke JR, Revell PA. Laboratory diagnosis of Mycobacterium tuberculosis infection and disease in children. J Clin Microbiol. 2016;54:1434–41.
35. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2014;44:435–46.
36. Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations. Geneva: World Health Organization; 2014.
37. Ray M, Dixit A, Vaipei K, Singhi PD. Congenital tuberculosis. Indian Pediatr. 2002;39:1167–8.
38. Hanekom W. Tuberculosis. In: Remington and Klein's infectious diseases of the fetus and newborn infant. 8th ed. Philadelphia: Elsevier; 2016.
39. Mlotha R, Waterhouse D, Dzinjalamala F, et al. Pharmacokinetics of anti-TB drugs in Malawian children: reconsidering the role of ethambutol. J Antimicrob Chemother. 2015;70:1798–803.
40. Patel S, DeSantis ERH. Treatment of congenital tuberculosis. Am J Health Syst Pharm. 2008;65:2027–31.
41. Skevaki CL, Kafetzis DA. Tuberculosis in neonates and infants: epidemiology, pathogenesis, clinical manifestations, diagnosis, and management issues. Paediatr Drugs. 2005;7:219–34.
42. Ghosh K, Chowdhury JR. Tuberculosis and female reproductive health. J Postgrad Med. 2011;57:307.
43. Red Book. Report of the Committee on Infectious Diseases, Elk grove Village: American Academy of Pediatrics; 2015.
44. Lamounier JA, Moulin ZS, Xavier CC. Recommendations for breastfeeding during maternal infections. J Pediatr (Rio J). 2004;80:s181–8.
45. Centers for Disease Control and Prevention. The role of BCG vaccine in the prevention and control of tuberculosis in the United States-a joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. Morb Mortal Wkly Rep. 1996;45:1–27.
46. Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. Health Technol Assess. 2013;17:1.
47. Roy A, Eisenhut M, Harris RJ, et al. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. BMJ. 2014;349:4643.

48. Geiter LJ, Huebner RE, Lanner AH, Villarino ME. The role of BCG vaccine in the prevention and control of tuberculosis in the United States; a joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices; 1995.
49. Grisaru-Soen G, Savyon M, Sadot E, et al. Congenital tuberculosis and management of exposure in neonatal and pediatric intensive care units. Int J Tuberc Lung Dis. 2014;18:1062–5.
50. Laartz BW, Narvarte HJ, Holt D, Larkin JA, Pomputius WF. Congenital tuberculosis and management of exposures in a neonatal intensive care unit. Infect Control Hosp Epidemiol. 2002;23:573–9.
51. Crockett M, King SM, Kitai I, et al. Nosocomial transmission of congenital tuberculosis in a neonatal intensive care unit. Clin Infect Dis. 2004;39:1719–23.
52. Lee LH, LeVea CM, Graman PS. Congenital tuberculosis in a neonatal intensive care unit: case report, epidemiological investigation, and management of exposures. Clin Infect Dis. 1998;27:474–7.
53. Winters A, Agerton TB, Driver CR, Trieu L, O'Flaherty T, Munsiff SS. Congenital tuberculosis and management of exposure in three neonatal intensive care units. Int J Tuberc Lung Dis. 2010;14:1641–3.
54. Reynolds DL, Gillis F, Kitai I, Deamond SL, Silverman M, King SM, et al. Transmission of Mycobacterium tuberculosis from an infant. Int J Tuberc Lung Dis. 2006;10:1051–6.
55. Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR Recomm Rep. 2005;54:1–141.

Varicella in the Peripartum Period

Chandana Ravikumar

Epidemiology

VZV is a highly communicable virus that was extremely common in the United States and Europe prior to the introduction of widespread varicella vaccination in 1995 [1]. Due to either vaccination or childhood history of chickenpox, more than >95% of adults in the United States are immune to varicella [2]. Correspondingly, the incidence of varicella in pregnant women is very low.

For regions of the world that do not have effective universal vaccination, there are distinct geographical differences and seasonal patterns to varicella outbreaks. Temperate regions have increased incidence during the winter and spring seasons, leading to periodic outbreaks affecting young children. In contrast, tropical regions have a lower incidence of outbreaks; as a result, adults in these regions are more likely to remain susceptible to infection [3, 4].

Pathogenesis

VZV is a member of the Herpesviridae family. VZV is transmitted by airborne respiratory droplets (during primary varicella) or by direct contact with skin lesions (during episodes of varicella or zoster) [5]. Airborne transmission of VZV is highly efficient, with attack rates exceeding 80%. VZV can also be acquired by transplacental transmission from a viremic mother to her fetus [6–9]. VZV rapidly reaches all fetal tissues but is particularly tropic for the central nervous system, eyes, and skin [10, 11]. Congenital and perinatal varicella are caused by hematogenous spread

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of VZV across the placenta to the fetus during the initial viremia; in contrast, postnatal VZV infection results from airborne or contact transmission to the newborn.

After infection, VZV incubates for approximately 2 weeks (range, 1–3), followed by viremia and ultimately the appearance of the rash [12]. The infected are considered contagious from 1 to 2 days preceding the rash until all lesions are crusted over. After primary varicella infection, the virus becomes latent in the dorsal root ganglion and may reactivate later in the form of herpes zoster (i.e., shingles). Infants with either congenital or postnatal VZV are also at risk for zoster during infancy and later life [13].

Clinical Findings

The spectrum of disease caused by varicella correlates with the timing of primary infection during pregnancy. The majority of infants born to mothers with primary varicella infection have uneventful deliveries [14]. Spontaneous abortion, preterm delivery, and fetal death do not seem to be increased among pregnancies complicated by varicella. However, complications of varicella infection in pregnancy do include congenital varicella syndrome, perinatal varicella, and postnatal varicella. In addition, pregnant women are at increased risk for varicella pneumonia due to attenuation of cellular immunity during pregnancy (see chapter "Varicella in the Peripartum Period") [15].

Congenital varicella syndrome. Congenital varicella syndrome occurs in approximately 1–2% of pregnancies complicated by varicella infection before 20 weeks gestation [16]. Characteristic scattered scarred skin lesions or "cicatrices" are the most common finding, occurring in 70% of cases [17]. Cicatrices may be dermatomal, clustered, or scattered. Ocular lesions (e.g., chorioretinitis, microphthalmia, cataracts), neurologic injury (e.g., microcephaly, seizures, cortical destruction), and limb abnormalities (e.g., hypoplasia, atrophy) are also present in >50% of cases. These signs are apparent at birth, but some infants are not diagnosed until later in infancy, especially if the skin lesions go unnoticed initially. Infants with congenital varicella syndrome, particularly those with neurologic impairment, may have developmental delay and increased risk for mortality [18].

Perinatal varicella. Perinatal varicella is defined as onset of rash within 10 days of delivery and is caused by transplacental transmission of VZV [19]. Maternal infection from 5 days antepartum to 2 days postpartum is associated with severe neonatal infection in approximately 25–50% of infants. The severity of perinatal varicella is presumably because when maternal infection is late, there is no opportunity for the development or transfer of passive maternal antibody to the infant. In addition, neonates have decreased T cell activity relative to older infants [13]. As a result, the case-fatality rate of perinatal varicella approaches 30%. In contrast, the attack rate of perinatal varicella when maternal infection is >5 days before delivery is 5–15%, and no neonatal deaths have been reported, presumably due to development of passive immunity from the mother [20, 21].

Postnatal varicella. Varicella acquired postnatally generally presents after age 10 days (median 15 days, range 10–28). As opposed to perinatal varicella, postnatal varicella is usually mild, although some neonatal deaths have been reported [20].

Maternal varicella pneumonia. Varicella pneumonia complicates 10–20% cases of varicella infection during pregnancy and can be severe; mortality due to varicella pneumonia is approximately 20% in pregnant women [15]. In areas where varicella is still endemic, varicella pneumonia represents a significant cause of morbidity and mortality in pregnant women. Onset of varicella pneumonia is 3–5 days after onset of rash; patients present with bilateral interstitial pneumonitis. *Streptococcus pyogenes* (group A *Streptococcus*) is associated with superinfection of varicella pneumonia or skin lesions and can markedly worsen prognosis [22].

Diagnosis

Diagnosis of maternal varicella in pregnancy can be made based on clinical findings of the classic vesicular pruritic rash or confirmatory laboratory testing. The following techniques can be used to confirm a varicella diagnosis.

Polymerase chain reaction (*PCR*). PCR amplifies the number of copies of VZV DNA, if any is present in a clinical sample. PCR is extremely sensitive and rapid and can be used on blood, cerebrospinal fluid, vesicular scrapings, amniotic fluid, and tissue, to name a few [23].

Viral culture. Viral culture may be used to diagnose varicella in mothers or infants. The base of the vesicles should be scraped, as the virus is present in epithelial cells but may not be in vesicular fluid. The culture is highly specific for varicella but less sensitive than PCR, and it may take up to a week for culture to yield results [24].

Direct fluorescent antigen staining. This laboratory test directly identifies the presence of VZV antigens (glycoproteins) in scrapings from a vesicle base by using tagged monoclonal antibodies. Direct fluorescent antigen staining is highly sensitive and specific and takes only a few hours to perform [24].

Serology. VZV IgG antibody usually appears ~5–7 days after the onset of rash (see perinatal and postnatal varicella, above). Therefore, serology is not particularly useful for diagnosing acute infection. However, serology is the gold standard for determining varicella immunity; patients with detectable IgG are considered immune to varicella. Of note, varicella immune globulin (VZIG, see Prevention, below) can persist for several months after administration and may complicate serologic evaluation.

Treatment

Antiviral treatment for varicella is generally accomplished with acyclovir or valacyclovir [25–27]. Both antivirals are pregnancy category B and can be used in pregnancy; the risk to the fetus is presumed to be low. The use of antiviral

Table 1 Clinical features and treatment of varicella in pregnant women and newborns

Condition	Clinical signs	Onset	Treatment	Mortality
Maternal varicella, uncomplicated	Pruritic vesicular lesions on erythematous base, in successive crops	Variable	Acyclovir, 800 mg PO q6 h until all lesions crusted	None
Maternal varicella, pneumonia	Interstitial pneumonitis	3–5 days after appearance of rash	Acyclovir, 10 mg/kg/dose IV q8 h	~20%
Congenital varicella syndrome	• Cicatrices (skin scarring) • Ocular lesions • Neurologic lesions • Limb lesions	Usually occurs before 20 weeks gestation following maternal varicella but rarely identified before birth	None unless active vesicles	~25%
Perinatal varicella	Pruritic vesicular lesions on erythematous base, in successive crops	≤10 days after delivery	Acyclovir, 10 mg/kg/dose IV q8 h, *OR* acyclovir, 500 mg/m^2/dose (1500/day) IV q8 h	~30%
Postnatal varicella		>10 days after delivery		<5%

therapy depends on the timing and severity of infection (Table 1). In general, pregnant women with primary varicella infection should be treated orally, although severe infections—including pneumonia—may prompt intravenous treatment. Infants with congenital varicella, for whom the actual infection is over by the time the infant is born and comes to clinical attention, do not require antiviral therapy unless they have reactivation (zoster) later in infancy. In contrast, perinatal or postnatal varicella disease should be treated with antiviral therapy.

Zoster in pregnant women or infants has not been as extensively studied, but oral therapy is generally recommended to speed resolution.

Prevention

Preexposure prophylaxis. VZV vaccine was introduced in 1995, and since 2007, a two-dose schedule is recommended as part of routine childhood immunization (at age 1 and 4 years) [28]. Women of childbearing age should be screened for a history of chickenpox or documentation of two doses of varicella vaccination to reduce risk of varicella infection during pregnancy [26, 27]. If a woman is seronegative, then two doses of the varicella vaccine should be administered 4–8 weeks apart. VZV vaccine is a live-attenuated vaccine and therefore contraindicated during pregnancy. Childbearing-age women who receive the vaccination should be counseled to avoid pregnancy for the following month. However, clinical registries have not identified congenital varicella syndrome or VZV-related adverse pregnancy outcomes among

Table 2 Recommendations for postexposure prophylaxis with varicella immune globulin (VZIG) following varicella exposure in nonimmune, high-risk patients [30]

Patient	VZIG dose
Pregnant woman	625 units IM
Infant whose mother has varicella 5 days before to 2 days after delivery	<2 kg: 62.5 units IM >2 kg: 125 units IM
Infant <28 weeks gestation regardless of maternal immunity to varicella	
Infant >28 weeks gestation only if mother is nonimmune	

VZIG should be given as soon as possible after exposure, but no more than 10 days later
Patients who develop varicella despite VZIG should be treated with antiviral therapy as per Table 1

women inadvertently vaccinated during pregnancy [29]. VZV vaccine can safely be administered to a breastfeeding mother.

Postexposure prophylaxis. Immune individuals exposed to varicella do not require any additional management. However, for nonimmune pregnant women or for infants at high risk of perinatal varicella, passive immunoprophylaxis can be accomplished with VZIG (Table 2) [30, 31]. The only available VZIG product in the United States currently is Varizig® (Cangene Corporation, Winnipeg, Canada). The only distributor of Varizig in the United States is FFF Enterprises (Temecula, California, 1-800-843-7477). VZIG is highly effective at reducing both attack rates and case-fatality rates of varicella infection in high-risk individuals.

References

1. Stagno S, Whitley RJ. Herpesvirus infections of pregnancy – herpes simplex virus and varicella-zoster virus infections. N Engl J Med. 1985;313:1327–30.
2. Lebo EJ, Kruszon-Moran DM, Marin M, et al. Seroprevalence of measles, mumps, rubella and varicella antibodies in the United States population, 2009-2010. Open Forum Infect Dis. 2015;20:ofv006.
3. Chen B, Sumi A, Wang L, Zhou W, Kobayashi N. Role of meteorological conditions in reported chickenpox cases in Wuhan and Hong Kong, China. BMC Infect Dis. 2017;17:538.
4. Mahmud AS, Metcalf CJ, Grenfell BT. Comparative dynamics, seasonality in transmission, and predictability of childhood infections in Mexico. Epidemiol Infect. 2017;145:607–25.
5. Asano Y. Clinicopathologic understanding and control of varicella-zoster virus infection. Vaccine. 2008;26(50):6487.
6. Hartung J, Enders G, Chaoui R, et al. Prenatal diagnosis of congenital varicella syndrome and detection of varicella-zoster virus in the fetus: a case report. Prenat Diagn. 1999;19:163–6.
7. Kawana K, Yoshikawa H, Sata T. Postpartum detection of varicella-zoster virus DNA in the placenta. Int J Gynaecol Obstet. 1996;55:165–6.
8. Sauerbrei A, Muller D, Eichhorn U, Wutzler P. Detection of varicella-zoster virus in congenital varicella syndrome: a case report. Obstet Gynecol. 1996;88:687–9.
9. Greenspoon JS, Masaki DI. Fetal varicella syndrome. J Pediatr. 1988;112:505–6.
10. Nikkels AF, Delbecque K, Pierard GE, et al. Distribution of varicella-zoster virus DNA and gene products in the tissues of a first-trimester varicella-infected fetus. J Infect Dis. 2005;191:540–5.
11. Arvin AM, Moffat JF, Sommer M, et al. Varicella-zoster virus T cell tropism and the pathogenesis of skin infection. Curr Top Microbiol Immunol. 2010;342:189–209.
12. Heininger U, Seward JF. Varicella. Lancet. 2006;368:1365–76.

13. Terada K, Kawano S, Yoshihiro K, et al. Varicella-zoster virus (VZV) reactivation is related to the low response of VZV-specific immunity after chickenpox in infancy. J Infect Dis. 1994;169:650–2.
14. Harger JH, Ernest JM, Thurnau GR, et al. Frequency of congenital varicella syndrome in a prospective cohort of 347 pregnant women. Obstet Gynecol. 2002;100:260–5.
15. Lamont RF, Sobel JD, Carrington D, et al. Varicella-zoster virus (chickenpox) in pregnancy. BJOG. 2011;118:1155–62.
16. Ahn KH, Park YJ, Hong SC, et al. Congenital varicella syndrome: a systemic review. J Obstet Gynaecol. 2016;36:563–6.
17. Borzyskowski M, Harris RF, Jones RW. The congenital varicella syndrome. Eur J Pediatr. 1981;137:335–8.
18. Gershon AA, Marin M, Seward JF. Varicella, measles, and mumps. In: Wilson CB, Nizet V, Maldonado YA, et al., editors. Remington and Klein's infectious diseases of the fetus and newborn infant. 8th ed. Philadelphia: Elsevier; 2016.
19. Berkoff MC, Brown WD. Varicella after the perinatal period. Pediatr Rev. 2013;34:537–8.
20. Meyers JD. Congenital varicella in term infants: risk reconsidered. J Infect Dis. 1974;129:215–7.
21. Gershon A. Commentary on VZIG in infants. Pediatr Infect Dis J. 1987;6:469.
22. Allard R, Pilon PA. Streptococcal infections and varicella. Clin Infect Dis. 2016;62:1056.
23. Mouly F, Mirlesse V, Meritet JF, et al. Prenatal diagnosis of fetal varicella-zoster virus infection with polymerase chain reaction of amniotic fluid in 107 cases. Am J Obstet Gynecol. 1997;177:894–8.
24. Coffin SE, Hodinka RL. Utility of direct immunofluorescence and virus culture for detection of varicella-zoster virus in skin lesions. J Clin Microbiol. 1995;33:2792–5.
25. Chiodo F, Manfredi R, Antonelli P, et al. Varicella in immunocompetent children in the first two years of life: role of treatment with oral acyclovir. Italian Acyclovir-Chickenpox study group. J Chemother. 1995;7:62–6.
26. Shrim A, Koren G, Yudin MH, et al. Management of varicella infection (chickenpox) in pregnancy. J Obstet Gynaecol Can. 2012;34:287–92.
27. American College of Obstetricians and Gynecologists. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015;125:1510–25.
28. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56:1–40.
29. Marin M, Willis ED, Marko A, et al. Closure of varicella-zoster virus-containing vaccines pregnancy registry – United States, 2013. MMWR Morb Mortal Wkly Rep. 2014;63:732–3.
30. Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG – United States, 2013. MMWR Morb Mortal Wkly Rep. 2013;62:574–6.
31. Huang YC, Lin TY, Lin YJ, Lien RI, Chou YH. Prophylaxis of intravenous immunoglobulin and acyclovir in perinatal varicella. Eur J Pediatr. 2001;160:91–4.

Zika Virus

Juan P. Calle and Eduardo López-Medina

Epidemiology

The first Zika virus disease outbreak in continental South America occurred in Brazil, where endemic transmission was confirmed in May 2015 [1]. Since then, up to November 2016, 10,056 cases of microcephaly or other neurologic disorders in newborn babies and infants have been reported in Brazil; 1950 of the microcephaly cases were confirmed to be infection-related. The maximum frequency of notified microcephaly in Brazil reached 49.9 cases per 10,000 newborn babies, a peak that is 24 times higher than the historical mean occurrence of microcephaly [2].

The first known cases of local Zika virus infection in the continental United States were reported in July, 2016 [3]. Soon after, the Centers for Disease Control and Prevention (CDC) established the Zika Pregnancy and Infants Registries to collect information about pregnancy and infant outcomes following laboratory evidence of ZIKV infection during pregnancy. By July 11, 2017, of 2945 completed pregnancies reported, 127 (4%) were live-born infants with birth defects, and 7 were pregnancy losses with birth defects [4].

Currently, ZIKV is a potential pandemic threat, circulating in the Americas, Pacific Islands, Southeast Asia, and the islands of Cape Verde off the coast of West Africa [5]. Although the number of cases in endemic areas different from the Americas is unknown, it is estimated that over two billion people inhabit in areas

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with proper environmental conditions for ZIKV, raising concerns about its final geographical range and ultimate clinical impact [6–8].

Pathogenesis

The exact pathogenic pathways of the immune response of the host and the molecular mechanisms involved in the complications associated with ZIKV infection are the subject of extensive research worldwide. Current knowledge of the physiopathology of the infection comes from multiple animal models, cell culture studies, postmortem evaluation of affected patients, and clinical/epidemiological studies.

ZIKV is transmitted to humans within their urban cycles mainly through bites of infected mosquitoes belonging to the *Aedes* genus (*A. aegypti*, *A. africanus*, *A. albopictus*) [9]. Perinatal infection occurs through vertical transmission from an infected expectant mother. The initial viral load allows transplacental passage, although the exact mechanisms have not been clarified [10]. Recent findings suggest that this is mediated by placental macrophages (Hofbauer cells) and cytotrophoblast cells. Thus, the virus reaches a direct pathway to fetal circulation, disseminating through developing tissue [11]. The virus has a tropism toward neuronal precursor cells over immature neurons or pluripotential stem cells [12]. There are multiple candidate receptors that could be responsible for the uptake of the virus into the developing neuron—among them the tyrosine kinase receptors of the families TYRO, AXL, and TAM—that allows this particular access to neuronal precursor cells [10]. The entrance of the virus to progenitor cells of the neural crest through the AXL receptor—a phagocytic phosphatidylserine widely shown in neuronal precursors—activates cell signaling pathways that result in the deregulation of the cell cycle and activation of apoptotic pathways [13]. Within NPCs, the virus quickly replicates, disseminating all over the underlying tissue. The result is a twofold depletion of NPCs: suppression of the proliferation of NPCs and increased cell death of both infected NPCs and non-infected cells.

After multiple replication cycles, there is a decrease in the neuronal volume and mass, leading to the clinical presentation of microcephaly. Other effects noted are the thinning of periventricular cell layers and structural disruption, which leads to alterations of the ventricular system. It has also been shown in animal models that infections during later pregnancy can lead to alterations in the neuronal differentiation and a decrease of the total number of neurons, which would also explain other neurocognitive manifestations seen in patients without microcephaly [12]. The cause of ocular and aural damage is not yet clear; however, widely accepted theories suggest direct cytotoxicity due to the virus or as a consequence of an inflammatory process. So far, it has not been possible to isolate the virus within ocular tissue [14]. It would also seem that the fetal compromise is associated with the viral strain. A study comparing different viral strains and their effect in the development of fetal brains in animal models and human neuronal organoids found that Brazilian virus strains cause a greater depletion of neuronal precursor cells and a higher disruption in neuronal monolayers when compared with African strains [15].

Clinical Findings

Adult Infection

In ZIKV, the ratio of symptomatic to asymptomatic patients is about 20% [16]. In symptomatic patients, the incubation period of ZVD ranges from 3.5 days for the human healthy volunteer to 6–10 days for returning travelers and blood donors [17–19]. Symptoms last for approximately 1 week [20]. During the Yap State, French Polynesia, and Brazil outbreaks, the described symptoms present in the majority of cases were maculopapular rash (present in 80–98%), fatigue (80%), fever (~70%), diffuse body aches (e.g., arthritis, arthralgia, or myalgia, ~60%), and conjunctivitis (50–60%) [20, 21]. In contrast to nonpregnant patients, fever is present in less than 30% of pregnant women with ZVD [22].

Congenital Infection

A causal relationship exists between prenatal ZIKV infection and microcephaly and other serious brain anomalies in offspring [23]. The spectrum of abnormalities is broad and includes neurological impairments, fetal akinesia deformation sequence (i.e., arthrogryposis), growth restriction, and ophthalmologic alterations—hence the term congenital Zika syndrome (CZS, Table 1) has been recommended [24]. The CDC has developed case definitions for congenital ZIKV infection and ZVD [25]. It should be noted that a large case series from Brazil showed that approximately 20% of infants with congenital ZIKV infection have normal head circumference

Table 1 Clinical characteristics of congenital Zika syndrome

Epidemiology	Approximately 6% of infants born to Zika virus-infected pregnant women[a]
Clinical Findings	Central nervous system • Microcephaly • Ventriculomegaly • Calcifications • Neuronal migration defects • Limb contractures/arthrogryposis Ophthalmic • Chorioretinitis • Macular injury • Atrophy Other • Sensorineural hearing loss • Congenital heart disease
Diagnosis	Pregnant woman: serum IgM, blood and urine PCR Infant: blood, urine, and cerebrospinal fluid PCR
Treatment	Supportive
Prevention	Mosquito control (DEET, netting, avoiding travel to endemic areas) Barrier contraception to prevent sexual transmission from infected partner

[a]In the United States, incidence during 2015–2016 Brazilian outbreak may have been much higher

[26]. Figure 1 shows an overlap between congenital ZIKV infection, rash during pregnancy, neuroimaging findings, and head size.

In Brazil, among 125 women who developed rash during pregnancy and had positive results for ZIKV on PCR testing, there were 58 adverse pregnancy outcomes (46%), including 9 cases of fetal death. The majority of these affected newborns had CNS abnormalities including microcephaly, cerebral calcifications, cerebral atrophy, ventricular enlargement, and hypoplasia of cerebral structures [22]. Preliminary data from the US Zika Pregnancy Registry shows that the impact of the Zika epidemic in the United States is lower than was reported from the Brazilian epidemic. Among 442 completed pregnancies in women with laboratory evidence of possible recent ZIKV infection, 271 pregnant women (61%) were asymptomatic, and 167 (38%) were symptomatic. Overall, there were 26 (6%) fetuses or infants with birth defects. The proportion of infants with birth defects was the same in mothers with or without symptoms. Unlike the Brazilian study, no birth defects were reported among pregnancies with maternal infection in the second or

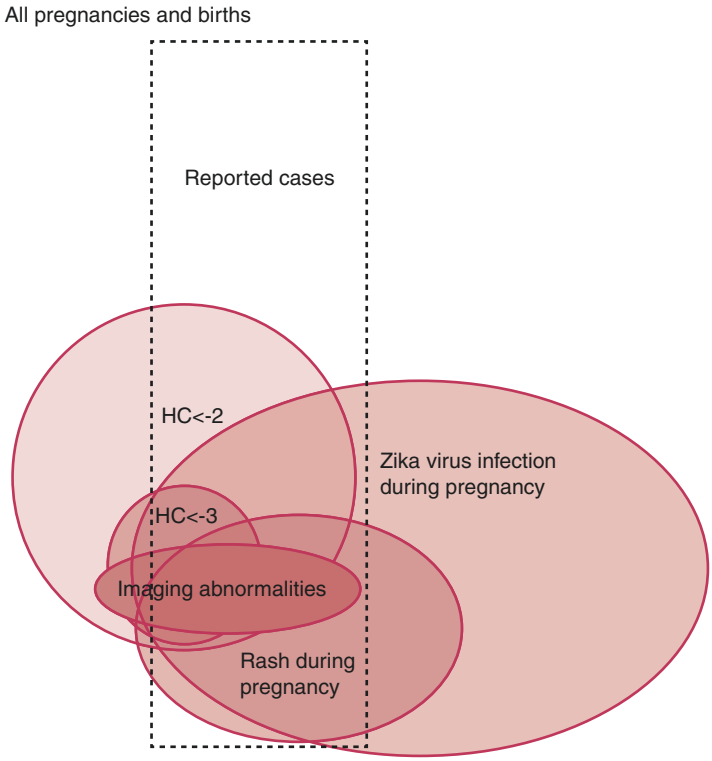

Fig. 1 Overlap between ZIKV, rash during pregnancy, neuroimaging findings, and head size [26]. França GVA, Schuler-Faccini L, Oliveira WK, Henriques CMP, Carmo EH, Pedi VD, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. The Lancet. 2016;388(10047):891-7. DOI: https://doi.org/10.1016/S0140-6736(16)30902-3. Creative Commons Attribution License (CC BY)

Table 2 Adverse pregnancy outcomes by trimester of maternal Zika virus infection

	Moderate[a] *n* (%)	Severe[b] *n* (%)	Overall *n* (%)
First trimester (*n* = 34)	0	11 (32.4%)	11/34 (32.4%)
Second trimester (*n* = 64)	1 (1.6%)	7 (10.9%)	8/64 (12.5%)
Third trimester (*n* = 47)	1 (2.1%)	2 (4.3%)	3/47 (6.3%)
Any trimester (*n* = 145)	2 (1.4%)	20 (13.8%)	22/145 (15.2%)

[a]Moderate adverse outcomes: severe osteomuscular impairment or 4–5 of 7 items affected in the Hammersmith Functional Motor Scale

[b]Severe adverse outcomes: pregnancy loss, microcephaly, or 6–7 items affected in the Hammersmith Functional Motor Scale

third trimester, while 11% of pregnancies with ZIKV infection during the first trimester presented with birth defects [27].

In Cali, Colombia, there is an ongoing follow-up of a cohort of infants born to mothers who consulted during pregnancy for Zika-related symptoms and were confirmed to have ZVD by blood PCR. Data for 145 infants has been obtained, 46% of whom had adverse outcomes, including 15% of infants with moderate or severe impairments (Table 2).

The contrasting findings between the epidemics in these three different regions were also reported in the distinct waves of ZIKV that occurred in Brazil, with incidences of infection-related microcephaly varying from 49.9 cases per 10,000 live births during the first wave in the northeast region to 3.2–15 cases per 10,000 live births during the second wave in other Brazilian regions. The reasons for the difference in the impact of ZIKV infection during pregnancy among different regions or countries are not clear [2].

Central nervous system findings. Neurologic impairment is the most common consequence of congenital infection. In an observational study from Brazil, 11 infants with congenital Zika virus infection were followed up from gestation to 6 months of age. Although most infants with CNS compromise had microcephaly, some patients had head circumference measurements that were consistent with their gestational age, as brain atrophy was compensated by an enlargement in ventricular size [24]. A common pattern of brain atrophy and changes associated with disturbances in neuronal migration were observed, resulting in findings such as microcephaly, a reduction in cerebral volume, ventriculomegaly, multifocal dystrophic calcifications, cerebellar hypoplasia, and lissencephaly [24, 28, 29].

Ophthalmic findings. Infants with congenital Zika frequently develop ocular manifestations. Of 29 Brazilian patients born with microcephaly with a presumed diagnosis of congenital ZIKV, 35% had ocular abnormalities [30]. Furthermore, the 43 Colombian and Venezuelan patients clinically diagnosed with congenital Zika syndrome had bilateral ophthalmic manifestations. The most common findings were focal pigmental mottling, with a predilection for the macular area, and chorioretinal atrophy and scars. Optic disk abnormalities as well as congenital glaucoma (12% of cases) were also described [31].

Other manifestations. As well as neurologic and ophthalmic abnormalities, other manifestations of CZS have been described. Congenital heart disease was present in

13.5% of 103 infants with presumed CZS. Sensorineural hearing loss was present in 5.8% of children born with microcephaly and laboratory evidence of congenital ZIKV infection [32]. Arthrogryposis, foveas in the knees or elbows due to limb contractures in utero, and redundant scalp skin in infants with normal head circumference are also common findings [22, 33].

Diagnosis

Maternal Diagnosis

Current diagnosis of ZIKV is based on molecular detection of viral RNA through polymerase chain reaction (PCR). Genetic material can be detected in serum or plasma from the expectant mother within 2 days of the beginning of the symptoms and up to 7 days after the symptomatology has started. In urine, it is detected up to 14 days later, but there are reports that have isolated the virus up to 20–39 days later [34]. Compared with serum, urine has shown higher responsiveness and a wider detection window. The CDC diagnosis protocol recommends taking both samples, as well as ZIKV IgM serology, as soon as possible through 12 weeks after symptom onset in pregnant women with recent possible ZIKV exposure and symptoms of ZVD [35].

Serological methods detect IgM-ELISA from 4 to 5 days after the start of the symptoms up to 12 weeks or more after the symptomatology has started. Even though false negatives occur, a negative result at least a week after the start of the symptoms is a strong evidence against ZIKV infection [36]. Due to the high degree of cross-reactivity with other flaviviruses, a positive or in conclusive IgM-antibody result must always be confirmed with a plaque reduction neutralization test (PRNT), generally only available in reference laboratories. This decreases the usefulness of serology, particularly in countries with high dengue endemicity [37]. With a confirmed diagnosis in an expectant mother or its high clinical suspicion, it is recommended to perform an amniocentesis and RT-PCR on the amniotic fluid to confirm the fetal infection.

Fetal Testing

Fetal diagnosis can be challenging; amniotic fluid samples can produce negative results in spite of fetal infection, and likewise, positive results can be obtained without fetal abnormalities. Thus, close monitoring through ultrasound and fetal magnetic resonance in the search of premature congenital malformations is recommended [38].

Newborn Testing

RT-PCR analysis of serum, urine, and CSF of the newborn suspected of having ZIKV infection is recommended during the first 2 days of life; however, there are multiple reports that reveal isolation of the virus for weeks to months after being

born [28]. If fetal or maternal infection is confirmed or highly suspected due to clinical manifestations, a thorough assessment of the newborn must be performed with neuroimaging (preferably brain magnetic resonance or ultrasound), ophthalmologic assessment and monitoring, hearing studies, and a detailed neurological examination. In symptomatic cases at birth, it is recommended to perform an echocardiogram, electroencephalogram, hepatic function testing, and exploration of possible musculoskeletal malformations. CDC has implemented a guide for infant neuroimaging and infant and placental Zika virus testing, which is currently being revised and updated [39].

Treatment

There is no specific treatment or antiviral drug for ZIKV infection. Recommendations include the treatment of symptoms with acetaminophen for fever or pain and an antihistaminic for pruritic rash and hydration [19]. For congenital Zika syndrome, multidisciplinary follow-up care, including infectious diseases, neurology, ophthalmology, audiology, speech, occupational therapy, and physical therapy, is important in order to maximize the functional outcome.

Prevention

Primary prevention of the ZIKV infection consists of avoiding mosquito bites and the performance of vector control. Among the recommended measures are clothing that covers exposed parts of the body, use of repellents, and adequate physical barriers such as closed windows, screens, and mosquito nets [40]. In expectant mothers who live or come from areas where the virus is circulating, consultation upon recent infection symptomatology must be emphasized, highlighting that for one third of congenital cases there was no history of rash during pregnancy [26].

In order to prevent sexually transmitted infections, it must be noted that viral particles have been isolated in semen up to 10 weeks after the beginning of the symptoms, within the female genital tract up to 2 days after the beginning of the symptoms, and that sexual transmission has been documented up to 44 days after the beginning of the symptoms [41, 42].

Transmission of virus by blood transfusion has also been documented [43]. Given that most of the infections are asymptomatic, the best strategies to prevent infections by transfusions are the evaluation of nucleic acids in the donor blood or inactivation of the pathogen [44]. There are about 40 vaccine candidates under development; however, they are not expected to be available for some years. It is unknown whether Zika infection produces a permanent immunity [45].

References

1. Zanluca C, Melo VC, Mosimann AL, Santos GI, Santos CN, Luz K. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz. 2015;110:569–72.

2. de Oliveira WK, de França GVA, Carmo EH, Duncan BB, de Souza Kuchenbecker R, Schmidt MI. Infection-related microcephaly after the 2015 and 2016 Zika virus outbreaks in Brazil: a surveillance-based analysis. Lancet. 2017;390:861–70.
3. Ventura CV, Albini TA, Berrocal AM. First locally transmitted Zika virus cases identified in the United States. JAMA Ophthalmol. 2016;134:1219–20.
4. Centers for Disease Control and Prevention. Outcomes of pregnancies with laboratory evidence of possible Zika Virus infection in the United States and the US territories. Available at https://www.cdc.gov/zika/reporting/pregnancy-outcomes.html. Accessed 5 Feb 2018.
5. European Centre for Disease Prevention and Control. Zika transmission. Available at http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/pages/zika-countries-with-transmission.aspx. Accessed 5 Feb 2018.
6. Baud D, Gubler DJ, Schaub B, Lanteri MC, Musso D. An update on Zika virus infection. Lancet. 2017;390:2099–109.
7. Messina JP, Kraemer MU, Brady OJ, et al. Mapping global environmental suitability for Zika virus. Elife. 2016;5:e16272.
8. Gatherer D, Kohl A. Zika virus: a previously slow pandemic spreads rapidly through the Americas. J Gen Virol. 2016;97:269–73.
9. Song BH, Yun SI, Woolley M, Lee YM. Zika virus: history, epidemiology, transmission, and clinical presentation. J Neuroimmunol. 2017;308:50–64.
10. Merfeld E, Ben-Avi L, Kennon M, Cerveny KL. Potential mechanisms of Zika-linked microcephaly. Wiley Interdiscip Rev Dev Biol. 2017;6(4):e273.
11. Relich RF, Loeffelholz M. Zika virus. Clin Lab Med. 2017;37:253–67.
12. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. Cell Stem Cell. 2016;18:587–90.
13. Faizan MI, Abdullah M, Ali S, Naqvi IH, Ahmed A, Parveen S. Zika virus-induced microcephaly and its possible molecular mechanism. Intervirology. 2016;59:152–8.
14. Marquezan MC, Ventura CV, Sheffield JS, et al. Ocular effects of Zika virus - a review. Surv Ophthalmol. 2017. Available online 13 June 2017.
15. Cugola FR, Fernandes IR, Russo FB, et al. The Brazilian Zika virus strain causes birth defects in experimental models. Nature. 2016;534:267–71.
16. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009;360:2536–43.
17. Bearcroft WG. Zika virus infection experimentally induced in a human volunteer. Trans R Soc Trop Med Hyg. 1956;50:442–8.
18. Kutsuna S, Kato Y, Takasaki T, et al. Two cases of Zika fever imported from French Polynesia to Japan, December 2013 to January 2014. Euro Surveill. 2014; 19(4). pii: 20683.
19. Musso D, Nhan T, Robin E, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill. 2014;19(14). pii: 20761.
20. Musso D, Gubler DJ. Zika virus. Clin Microbiol Rev. 2016;29:487–524.
21. Cerbino-Neto J, Mesquita EC, Souza TM, et al. Clinical manifestations of Zika virus infection, Rio de Janeiro, Brazil, 2015. Emerg Infect Dis. 2016;22:1318–20.
22. Brasil P, Pereira JP Jr, Moreira ME, et al. Zika virus infection in pregnant women in Rio de Janeiro. N Engl J Med. 2016;375:2321–34.
23. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika Virus and birth defects - reviewing the evidence for causality. N Engl J Med. 2016;374:1981–7.
24. Melo AS, Aguiar RS, Amorim MM, et al. Congenital Zika virus infection: beyond neonatal microcephaly. JAMA Neurol. 2016;73:1407–16.
25. Zika virus disease and Zika virus infection 2016 case definition. Approved June 2016. Available at: https://wwwn.cdc.gov/nndss/conditions/zika/case-definition/2016/06/. Accessed 5 Feb 2018.
26. França GVA, Schuler-Faccini L, Oliveira WK, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet. 2016;388:891–7.

27. Honein MA, Dawson AL, Petersen EE, et al. Birth defects among fetuses and infants of US women with evidence of possible Zika virus infection during pregnancy. JAMA. 2017;317:59–68.
28. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. N Engl J Med. 2016;374:951–8.
29. Vouga M, Baud D. Imaging of congenital Zika virus infection: the route to identification of prognostic factors. Prenat Diagn. 2016;36:799–811.
30. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol. 2016;134:529–35.
31. Yepez JB, Murati FA, Pettito M, et al. Ophthalmic manifestations of congenital Zika syndrome in Colombia and Venezuela. JAMA Ophthalmol. 2017;135(5):440.
32. Leal MC, Muniz LF, Ferreira TS, et al. Hearing loss in infants with microcephaly and evidence of congenital Zika virus infection - Brazil, November 2015–May 2016. MMWR Morb Mortal Wkly Rep. 2016;65:917–9.
33. van der Linden V, Filho EL, Lins OG, et al. Congenital Zika syndrome with arthrogryposis: retrospective case series study. BMJ. 2016;354:i3899.
34. Campos Rde M, Cirne-Santos C, Meira GL, et al. Prolonged detection of Zika virus RNA in urine samples during the ongoing Zika virus epidemic in Brazil. J Clin Virol. 2016;77:69–70.
35. Oduyebo T, Polen KD, Walke HT, et al. Update: Interim guidance for health care providers caring for pregnant women with possible Zika virus exposure — United States (including U.S. Territories), July 2017. MMWR Morb Mortal Wkly Rep. 2017;66:781–93.
36. Landry ML, St George K. Laboratory diagnosis of Zika virus infection. Arch Pathol Lab Med. 2017;141:60–7.
37. Felix AC, Souza NCS, Figueiredo WM, et al. Cross reactivity of commercial anti-dengue immunoassays in patients with acute Zika virus infection. J Med Virol. 2017;89:1477–9.
38. Baud D, Van Mieghem T, Musso D, Truttmann AC, Panchaud A, Vouga M. Clinical management of pregnant women exposed to Zika virus. Lancet Infect Dis. 2016;16:523.
39. Centers for Disease Control and Prevention. Placental testing guidance. Available at: https://www.cdc.gov/zika/pdfs/placental-testing-guidance.pdf. Accessed 29 July 2017.
40. Centers for Disease Control and Prevention. Zika virus - prevention. Available at: https://www.cdc.gov/zika/prevention/index.html. Accessed 29 July 2017.
41. Penot P, Brichler S, Guilleminot J, et al. Infectious Zika virus in vaginal secretions from an HIV-infected woman, France, August 2016. Euro Surveill. 2017;22(3). pii: 30444.
42. Moreira J, Peixoto TM, Siqueira AM, Lamas CC. Sexually acquired Zika virus: a systematic review. Clin Microbiol Infect. 2017;23:296–305.
43. Motta IJ, Spencer BR, Cordeiro da Silva SG, et al. Evidence for transmission of Zika virus by platelet transfusion. N Engl J Med. 2016;375:1101–3.
44. Musso D, Broult J, Bierlaire D, Lanteri MC, Aubry M. Prevention of transfusion-transmitted Zika virus in French Polynesia, nucleic acid testing versus pathogen inactivation. VOXS. 2017;12:254–9.
45. Thomas SJ, L'Azou M, Barrett AD, Jackson NA. Fast-track Zika vaccine development - is it possible? N Engl J Med. 2016;375:1212–6.

Part III

Support Services

Principles of Infection Prevention in the Nursery

Jacqueline M. Ryaboy and Jacqueline D. Julia

Standard Precautions

Standard precautions (Box 1) are a set of actions that are required of every healthcare provider for every patient, regardless of circumstances. Standard precautions include the use of personal protective equipment (PPE) such as eye shielding, masks, gowns, or gloves when in contact with body fluids (or when at risk for exposure). For example, when changing a wet diaper, gloves should be used to prevent contact with urine or feces.

Hand hygiene. Hand hygiene before and after patient contact is an important aspect of standard precautions. The positive effects of hand hygiene have been clear since the 1840s, when Ignaz Semmelweis demonstrated that handwashing

Box 1 Standard Precautions for All Healthcare Settings, Including the Nursery and the Neonatal Intensive Care Unit

1. Perform hand hygiene before and after every patient contact.
2. Use personal protective equipment (gloves, gowns, and/or masks) when in contact with body fluids (or when at risk for body fluid exposure).
3. Use and dispose of sharps safely.
4. Perform routine environmental cleaning.
5. Clean and process shared medical equipment between patients.
6. Follow respiratory hygiene and cough etiquette.
7. Use aseptic technique.
8. Handle and dispose of waste and soiled linen safely.

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dramatically reduced the incidence and mortality of childbed fever (i.e., puerperal sepsis) in Vienna's Allgemeines Krankenhaus maternity ward [1]. Hand hygiene is incredibly effective in prevention of horizontal transmission between patients, but perfect compliance is difficult to achieve and maintain [2, 3]. NICU-specific studies have shown significant reduction in sepsis and pneumonia as hand hygiene compliance improves [4]. Therefore, every individual entering the NICU—whether nursery provider, consultant, technician, or family visitor—should perform thorough handwashing before and after every patient contact. Efforts to support hand hygiene, such as "secret shoppers," written and verbal education and feedback, administrative support, family empowerment, and a culture of giving and accepting feedback are all strategies that have been used to improve hand hygiene compliance [5]. Of note, gloves are not a substitute for proper hand hygiene, and some studies suggest that hand hygiene compliance worsens when routine glove use is promoted [6]. Designing nurseries so that gel dispensers or sinks are readily available at entry to the unit as well as in every care area is an important step in improving hand hygiene compliance [7].

Respiratory etiquette. Respiratory etiquette involves covering coughs or sneezes, ideally with the proximal arm to avoid contaminating hands. However, respiratory etiquette also involves not introducing respiratory viruses to the unit in the first place. Respiratory viruses are a common cause of infection in the NICU setting (see chapter "Respiratory Viruses in the Neonatal Intensive Care Unit"). Visitors to the NICU should disclose active symptoms of illness and avoid visiting when symptomatic. Prior to entry, staff should inquire regarding active symptoms of infection such as cough, congestion, rhinorrhea, and fever [8]. Similarly, staff should avoid coming to work when actively sick with potentially transmissible infections, and administrators should ensure that staff members do not feel pressured to do so [9].

PPE. Gloves, gowns, masks, and other PPE should be worn as indicated by standard or transmission-based precautions (see section "Transmission-Based Precautions" below) by all healthcare personnel. However, the evidence is unclear as to whether family visitors should wear PPE. PPE can interfere with family bonding and prevent skin-to-skin kangaroo care and breastfeeding and is viewed negatively by many families [10]. According to the most recent recommendations by the Society for Healthcare Epidemiology in America, decisions regarding PPE for visitors should be based on the severity of the organism of concern, the healthcare status of the visitor, and the healthcare setting [11]. For example, the benefit of PPE for visitors for an infant with suspected varicella or parvovirus will vary based on immune status, pregnancy, et cetera. A NICU with an active outbreak may enforce PPE use, while a NICU with no ongoing transmission may be more relaxed. Research into the benefits and adverse consequences of visitor PPE use are needed to better inform these policies. Regardless of a given nursery's approach to visitor PPE, hand hygiene compliance should be paramount for all visitors.

Transmission-Based Precautions

Transmission-based precautions (Table 1) are used for certain infections when transmission is not completely interrupted using standard precautions alone. When used in addition to standard precautions, transmission-based precautions can reduce the risk for horizontal transmission and outbreaks (see chapter "Outbreak Control in the Nursery").

Contact precautions. Contact precautions (gown and gloves) are used to prevent transmission of infectious agents that are spread by direct or indirect contact with the patient or the patient's environment [12]. A single-patient room is preferred for infants in contact precautions; if one is not available, cohorting can be used (i.e., placing patients with the same colonization or infection in the same room) [13]. As much space as possible should be left between beds to reduce the opportunities for horizontal transmission between infants [12].

Droplet precautions. Droplet precautions (mask) are used to prevent transmission of pathogens that spread through infected droplets, which can be spread by expulsion during coughing or sneezing or by close contact with respiratory secretions. Droplet precautions are often used in combination with contact precautions, as most agents that can be spread by droplet can also be spread by indirect contact with droplets that land on nearby surfaces [12].

Table 1 Transmission-based precautions and common indications in the nursery setting

Precautions[a]	Equipment	Example pathogens
Contact	Gown and gloves	Methicillin-resistant staphylococci ESBL-producing gram negatives Vancomycin-resistant enterococci Herpes simplex virus Respiratory syncytial virus[b] Parainfluenza[b]
Droplet	Surgical mask	Influenza Rhinovirus Parvovirus Pertussis
Airborne	N95 mask Negative-pressure room with HEPA filter	Varicella Tuberculosis

[a]In addition to standard precautions

[b]Respiratory syncytial virus and parainfluenza require contact precautions rather than droplet. However, as part of standard precautions, surgical mask should be worn if contact with respiratory secretions is likely (e.g., if patient coughing or sneezing)Note that cytomegalovirus infection requires only standard precautions, since it is transmitted by body fluids (saliva, urine, etc.), and gloves should be worn for all potential body fluid contact as per standard precautions. Exclusion of pregnant caregivers is not specifically recommended (as it is for rubella or varicella nonimmune pregnant healthcare providers)A comprehensive list of pathogens and their recommended isolation precautions can be found in Appendix A of reference [12]

Airborne precautions. Airborne precautions (N95 mask, negative pressure room with HEPA filter) prevent transmission of pathogens by airborne particles. In contrast to droplets, which have a range of 3–6 ft before landing, airborne infections can remain suspended in air for long periods of time and can cover tremendous distances. Specialized negative pressure rooms prevent infectious airborne particles from spreading. Healthcare personnel should wear an N95 respirator when inside the negative pressure room [12, 14].

Surveillance Cultures

As opposed to clinical cultures, which are obtained when infection is suspected, surveillance cultures can be used to periodically ascertain whether or not infants are colonized with certain pathogens (Table 2) [15]. In clinical practice, surveillance cultures are usually used for two purposes—first, to determine whether specific transmission-based precautions are needed for a given infant (e.g., if the infant is found to be colonized with methicillin-resistant *Staphylococcus aureus* [MRSA], they are then placed in contact precautions) and second, to determine whether a given infant requires different empiric antibiotic treatment when infection is suspected (e.g., if an infant is colonized with an extended-spectrum beta-lactamase (ESBL)-producing gram-negative organism, they may need empiric carbapenem therapy). Conversely, surveillance cultures can support antibiotic stewardship—if an infant is known to be MRSA negative on surveillance cultures, then vancomycin can be safely withheld in most circumstances [16]. Examples of specific surveillance approaches are shown below.

MRSA. *S. aureus* is one of the more common causes of late-onset sepsis (see chapter "Late-Onset Sepsis") and causes significant morbidity and mortality. Approximately 25% of staphylococcal infections in US nurseries are due to MRSA

Table 2 Approach to surveillance cultures for common multidrug-resistant organisms encountered in the neonatal intensive care unit

	MRSA	ESBL	VRE
Source	Axilla and/or groin	Rectum	Rectum
Interventions	1. Contact precautions 2. Include vancomycin in empiric antibiotic therapy 3. Consider decolonization (nasal mupirocin and chlorhexidine bathing)	1. Contract precautions 2. Consider including meropenem in empiric antibiotic therapy	1. Contact precautions 2. Consider including linezolid in empiric antibiotic therapy
Evidence grade	A1	C2	C2

Frequency of screening depends on local epidemiology; higher incidence requires more frequent screening. Reported schedules range from monthly to as often as twice weekly during outbreaks. *MRSA* methicillin-resistant *Staphylococcus aureus*, *ESBL* extended-spectrum beta-lactamase-producing gram negatives, *VRE* vancomycin-resistant *Enterococcus*

rather than methicillin-susceptible strains [17]. Prematurity and prolonged NICU stay are major risk factors for MRSA colonization [18]. MRSA-colonized infants can be cohorted and decolonized (treated with intranasal mupirocin twice daily for 5 days along with chlorhexidine bathing), which has been shown to reduce the risk of infection and horizontal transmission [19].

ESBL-producing gram negatives. The prevalence of colonization with ESBL-producing gram negatives mirrors the community prevalence; infants born to mothers who are colonized are at increased risk. Most transmission occurs within the first 2–4 weeks after delivery but may occur at any point during the NICU stay [20]. Surveillance rectal or skin swabs to detect ESBL-producing gram negatives have been used during outbreaks [21]. However, data regarding the use of routine surveillance for ESBL producers is lacking. Given that colonization with a given organism is a risk factor for subsequent infection with that organism, and since ESBL-producing organisms usually require carbapenem therapy for treatment, the logical extension is that screening for these organisms could be beneficial. However, the implications for microbiology lab workflow, cost-effectiveness, and impact on infant outcome have not been well studied [22].

Vancomycin-resistant Enterococci (*VRE*). *Enterococcus* species are generally susceptible to ampicillin and/or vancomycin; enterococci that develop resistance to vancomycin are referred to as VRE. As with MRSA and ESBL producers, VRE most commonly colonizes and subsequently infects preterm infants. Vancomycin exposure is an unsurprising risk factor for VRE colonization [23]. Colonized infants should be placed in contract precautions, and linezolid should be considered as part of empiric antibiotic therapy when sepsis is suspected.

Device-Associated Infections

Central line-associated bloodstream infections. Central line-associated bloodstream infections (CLABSIs) are the most common hospital-acquired infection in the NICU and are associated with significant morbidity and mortality [24–26]. Central lines are commonly required for the administration of fluid, nutrition, and medications. The primary risk factors for CLABSIs include prematurity and catheter dwell time. The longer that a central line remains in place, the higher the risk for CLABSI. Each manipulation of the central line—such as infusions, tubing changes, opening or recapping the hub—will increase risk for CLABSI if proper technique is not followed. On average, preterm infants undergo catheter manipulation every 8 h [27]. Intra-abdominal pathology such as necrotizing enterocolitis or bowel perforation usually requires bowel rest and total parenteral nutrition through a central line, which increases catheter dwell time and therefore the risk for CLABSI. Histamine-2 receptor blockers and proton pump inhibitors are also associated with increased risk for necrotizing enterocolitis, sepsis, and CLABSIs [28, 29]. Presumably, this is due to lowered gastric acidity and increased central line requirement if the infant develops necrotizing enterocolitis.

CLABSI reduction can be achieved by combining evidence-based prevention strategies into "bundles." Bundles focus on avoiding central-line insertion whenever possible, minimizing dwell times, and careful attention to sterile line maintenance (Box 2). Unnecessary line placement can be avoided if specific criteria for insertion are used [30]. Having a dedicated team of providers (i.e., a central line team) who are specially trained in insertion and maintenance of central lines has been associated with decreased risk for CLABSI [31, 32]. Feeding guidelines that emphasize prompt feeding initiation and advancement will help to minimize line days. Bundles that focus on reaching 120 cc/kg/day of enteral feeds and then promptly removing the central line have been shown to reduce CLABSIs [33]. The CLABSI risk per line/day is higher with umbilical venous catheters than with other catheters once dwell times exceed 7–14 days [34, 35]. Therefore, a reasonable strategy is to exchange the umbilical venous catheter for a peripherally inserted central catheter within 7–10 days and to remove the central line as soon as it is no longer needed.

Ventilator-associated pneumonia. Ventilator-associated pneumonia (VAP) is defined as new lower respiratory tract infection in a mechanically ventilated infant occurring >48 h after intubation [36]. VAP is a difficult diagnosis to confirm, as the clinical criteria are subjective and the majority of intubated neonates have preexisting, noninfectious lower respiratory tract disease such as respiratory distress syndrome, transient tachypnea of the newborn, or bronchopulmonary dysplasia [37]. The primary risk factor for VAP is intubation. An endotracheal tube allows bacteria to avoid most of the innate defenses of the upper airway and directly communicate with distal airways and alveoli [38]. Another major risk factor for VAP is prematurity and concomitant lung immaturity. The most preterm infants generally require the longest duration of mechanical ventilation and therefore have the highest

Box 2 Evidence-Based Bundles to Prevent Central-Line Associated Bloodstream Infections in the Neonatal Intensive Care Unit

Insertion

- Avoid placement of unnecessary central lines
- Hand hygiene and maximal sterile barrier precautions before catheter insertion
- Povidone-iodine or 2% chlorhexidine skin preparation before insertion

Maintenance

- Disinfect catheter hubs and connectors before accessing ports
- Perform dressing changes *only* if dressing is loose or soiled

Removal

- Remove catheter promptly once no longer required

Box 3 Evidence-Based Bundles to Prevent Ventilator-Associated Pneumonia in the Neonatal Intensive Care Unit

Insertion

- Avoid intubation when possible
- Use sterile tube for intubation

Maintenance

- Elevate head of bed 30° if possible
- Oral care with sterile water or colostrum
- Change breathing circuit only when malfunctioning or visibly soiled
- Closed-circuit suctioning
- Avoid unplanned extubations

Removal

- Avoid oversedation
- Daily evaluation for readiness to extubate

incidence of VAP. As with CLABSI, antacid therapy has been linked to pneumonia and VAP [39–41].

Bundled prevention of VAP care (Box 3) includes careful insertion and maintenance of endotracheal tubes, closed suctioning systems, avoiding unplanned extubations, oral care with sterile water or breast milk, avoiding oversedation, and extubating infants as soon as feasible [42, 43]. In addition, as discussed in chapter "Late-Onset Sepsis," culture of the endotracheal tube should be avoided whenever possible. The upper airway is not sterile, and endotracheal tubes are rapidly colonized [44]. Therefore, bacteria recovered from the endotracheal tube are likely to represent colonization rather than infection, particularly if signs of lower respiratory tract disease are absent. Endotracheal tube cultures should only be considered when both clinical and radiographic evidence of pneumonia are present [45].

Ventricular shunt infection. Infants may require cerebrospinal fluid shunting due to congenital (e.g., aqueductal stenosis, Dandy-Walker malformation) or acquired (e.g., posthemorrhagic or postinfectious) hydrocephalus. Shunting can be accomplished with a ventriculoperitoneal shunt (VPS) or, for infants too small to undergo definitive VPS shunting, a temporizing measure such as a ventricular reservoir, subgaleal shunts, or serial lumbar punctures. Both definitive and temporizing shunts are associated with risk for shunt-associated meningitis or ventriculitis. The risk of shunt infection decreases as the age and size of the child increase [46]. Temporizing measures generally have a higher incidence of infection than VPS. Regardless of the type of shunt, risk is highest within a few weeks of shunt placement or revision and then decreases sharply over time, but never reaches zero [47].

Prevention of shunt infection requires striking a balance between higher-risk temporizing measures that allow growth until the lower-risk VPS is available. Careful insertion and maintenance technique is critical for temporizing measures. The optimal strategy is to standardize the approach to ventricular diversion at a given center, with input from pediatric neurosurgery, neonatology, infectious diseases, and infection prevention. Standardized surgical approaches to VPS placement are associated with lower infection rates [48]. Antibiotic-impregnated shunt catheters or injection of antibiotics into the shunt during placement has also been shown to reduce infection risk [49–51]. Double-gloving—where the neurosurgeon removes the first pair of gloves intraoperatively prior to handling the shunt catheter—also appears to be effective in reducing risk [52].

References

1. Noakes TD, Borrensen J, Hew-Butler T, Lambert MI, Jordaan E. Semmelweis and the aetiology of puerperal sepsis 160 years on: a historical review. Epidemiol Infect. 2008;136:1–9.
2. Derde LPG, Cooper BS, Goossens H, et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. Lancet Infect Dis. 2014;14:31–9.
3. Stewardson AJ, Sax H, Gayet-Ageron A, et al. Enhanced performance feedback and patient participation to improve hand hygiene compliance of health-care workers in the setting of established multimodal promotion: a single-centre, cluster randomised controlled trial. Lancet Infect Dis. 2016;16:1345–55.
4. Won SP, Chou HC, Hsieh WS, et al. Handwashing program for the prevention of nosocomial infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol. 2004;25:742–6.
5. Gould DJ, Moralejo D, Drey N, et al. Interventions to improve hand hygiene compliance in patient care. Cochrane Database Syst Rev. 2017;(9):CD005186.
6. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Lancet. 2000;356:1307–12.
7. Bartley J, Streifel AJ. Design of the environment of care for safety of patients and personnel: does from follow function or vice versa in the intensive care unit? Crit Care Med. 2010;38:S388–98.
8. Wittrock B, Lavin MA, Pierry D, Thomson R, Wurtz R. Parents as a vector for nosocomial infection in the neonatal intensive care unit. Infect Control Hosp Epidemiol. 2001;22:472.
9. Mitchell KJ, Vayalumkal JV. Sickness presenteeism: the prevalence of coming to work while ill among peadiatric resident physicians in Canada. Paediatr Child Health. 2017;22:84–8.
10. Flacking R, Lehtonen L, Thomson G, et al. Closeness and separation in neonatal intensive care. Acta Paediatr. 2012;101:1032–7.
11. Banach DB, Bearman GM, Morgan DJ, Munoz-Price LS. Infection control precautions for visitors to healthcare facilities. Expert Rev Anti Infect Ther. 2015;13:1047–50.
12. Siegel JD, Rhinehart E, Jackson M, et al. 2007 guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Am J Infect Control. 2007;35:S65–164.
13. Pammi M, Davis RJ, Gordon A, Starke J. Infant isolation and cohorting for preventing or reducing transmission of healthcare-associated infections in neonatal units. Cochrane Database Syst Rev. 2016;(12):CD012458.
14. Gammon J, Hunt J. A review of isolation practices and procedures in healthcare settings. Br J Nurs. 2018;27:137–40.
15. Cipolla D, Giuffre M, Mammina C, Corsello G. Prevention of nosocomial infections and surveillance of emerging resistances in NICU. J Matern Fetal Neonatal Med. 2011;24:23–6.

16. Chiu CH, Michelow IC, Cronin J, et al. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J. 2011;30:273–8.
17. Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible Staphylococcus aureus bacteremia and meningitis in preterm infants. Pediatrics. 2012;129:e914–22.
18. Washam M, Woltmann J, Haberman B, Haslam D, Staat MA. Risk factors for methicillin-resistant Staphylococcus aureus colonization in the neonatal intensive care unit: a systematic review and meta-analysis. Am J Infect Control. 2017;45:1388–93.
19. Pierce R, Lessler J, Popoola VO, Milstone AM. Methicillin-resistant Staphylococcus aureus acquisition risk in an endemic neonatal intensive care unit with an active surveillance culture and decolonization programme. J Hosp Infect. 2017;95:91–7.
20. Danino D, Melamed R, Sterer B, et al. Mother to child transmission of extended spectrum beta-lactamase producing Enterobacteriaceae. J Hosp Infect. 2018. Available online 9 Jan 2018. [In print].
21. Cantey JB, Sreeramoju P, Jaleel M, et al. Prompt control of an outbreak caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a neonatal intensive care unit. J Pediatr. 2013;163:672–9.
22. Folgori L, Tersigni C, Hsia Y, et al. The relationship between gram-negative colonization and bloodstream infections in neonates: a systematic review and meta-analysis. Clin Microbiol Infect. 2018;24:251–7.
23. Akturk H, Sutcu M, Somer A, et al. Vancomycin-resistant enterococci colonization in a neonatal intensive care unit: who will be infected? J Matern Fetal Neonatal Med. 2016;29:3478–82.
24. Hsu JF, Chu SM, Lee CW, et al. Incidence, clinical characteristics and attributable mortality of persistent bloodstream infection in the neonatal intensive care unit. PLoS One. 2015;10:e0124567.
25. Patel AL, Johnson TJ, Engstrom JL, et al. Impact of early human milk on sepsis and health-care costs in very low birth weight infants. J Perinatol. 2013;33:514–9.
26. Johnson TJ, Patel AL, Jegier BJ, Engstrom JL, Meier PP. Cost of morbidities in very low birth weight infants. J Pediatr. 2013;162:243–9.
27. Mahieu LM, De Muynck AO, Ieven MM, et al. Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit. J Hosp Infect. 2001;48:108–16.
28. Romaine A, Ye D, Ao Z, et al. Safety of histamine-2 receptor blockers in hospitalized VLBW infants. Early Hum Dev. 2016;99:27–30.
29. More K, Athalye-Jape G, Rao S, Patole S. Association of inhibitors of gastric acid secretion and higher incidence of necrotizing enterocolitis in preterm very low-birth-weight infants. Am J Perinatol. 2013;30:849–56.
30. Shahid S, Dutta S, Symington A, Shivananda S. Standardizing umbilical catheter usage in preterm infants. Pediatrics. 2014;133:e1742–52.
31. Krein SL, Kuhn L, Ratz D, Chopra V. Use of designated nurse PICC teams and CLABSI prevention practices among U.S. hospitals: a survey-based study. J Patient Saf. 2015. Available online 10 Nov 2015. [In print].
32. Taylor T, Massaro A, Williams L, et al. Effect of a dedicated percutaneously inserted central catheter team on neonatal catheter-related bloodstream infection. Adv Neonatal Care. 2011;11:122–8.
33. Fisher D, Cochran KM, Provost LP, et al. Reducing central line-associated bloodstream infections in North Carolina NICUs. Pediatrics. 2013;132:e1664–71.
34. Sanderson E, Yeo KT, Wang AY, et al. Dwell time and risk of central-line associated bloodstream infection in neonates. J Hosp Infect. 2017;97:267–74.
35. Butler-O'Hara M, D'Angio CT, Hoey H, Stevens TP. An evidence-based catheter bundle alters central venous catheter strategy in newborn infants. J Pediatr. 2012;160:972–7.
36. Mourani PM, Sonag MK. Ventilator-associated pneumonia in critically ill children: a new paradigm. Pediatr Clin North Am. 2017;64:1039–56.

37. Centers for Disease Control and Prevention. Pneumonia (ventilator-associated [VAP] and non-ventilator-associated pneumonia [PNEU]) event. Available at https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf. Accessed 28 Feb 2018.
38. Rouze A, Jaillette E, Poissy J, Preau S, Nseir S. Tracheal tube design and ventilator-associated pneumonia. Respir Care. 2017;62:1316–23.
39. Santana RNS, Santos VS, Ribeiro-Junior RF, et al. Use of ranitidine is associated with infections in newborns hospitalized in a neonatal intensive care unit: a cohort study. BMC Infect Dis. 2017;17:375.
40. Bianconi S, Gudavalli M, Sutija VG, et al. Ranitidine and late-onset sepsis in the neonatal intensive care unit. J Perinat Med. 2007;35:147–50.
41. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics. 2012;129:e40–5.
42. Azab SF, Sherbiny HS, Saleh SH, et al. Reducing ventilator-associated pneumonia in neonatal intensive care unit using "VAP prevention bundle": a cohort study. BMC Infect Dis. 2015;15:314.
43. Weber CD. Applying adult ventilator-associated pneumonia bundle evidence to the ventilated neonate. Adv Neonatal Care. 2016;16:178–90.
44. Willson DF, Conaway M, Kelly R, Hendley JO. The lack of specificity of tracheal aspirates in the diagnosis of pulmonary infection in intubated children. Pediatr Crit Care Med. 2014;15:299–305.
45. Cantey JB. Optimizing the use of antibacterial agents in the neonatal period. Paediatr Drugs. 2016;18:109–22.
46. Pople IK, Bayston R, Hayward RD. Infection of cerebrospinal fluid shunts in infants: a study of etiological factors. J Neurosurg. 1992;77:29–36.
47. Conen A, Walti LN, Merlo A, et al. Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. Clin Infect Dis. 2008;47:73–82.
48. Simon TD, Butler J, Whitlock KB, et al. Risk factors for first cerebrospinal fluid shunt infection: findings from a multi-center prospective cohort study. J Pediatr. 2014;164:1462–8.
49. Kestle JR, Riva-Cambrin J, Wellons JC, et al. A standardized protocol to reduce cerebrospinal fluid shunt infection: the Hydrocephalus Clinical Research Network Quality Improvement Initiative. J Neurosurg Pediatr. 2011;8:22–9.
50. Konstantelias AA, Vardakas KZ, Polyzos KA, Tansarli GS, Falagas ME. Antimicrobial-impregnated and -coated shunt catheters for prevention of infections in patients with hydrocephalus: a systematic review and meta-analysis. J Neurosurg. 2015;122:1096–112.
51. Klimo P, Thompson CJ, Baird LC, et al. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 7: Antibiotic-impregnated shunt systems versus conventional shunts in children: a systematic review and meta-analysis. J Neurosurg Pediatr. 2014;14(S1):53–9.
52. Rehman AU, Rehman TU, Bashir HH, Gupta V. A simple method to reduce infection of ventriculoperitoneal shunts. J Neurosurg Pediatr. 2010;5:569–72.

Outbreak Control in the Nursery

Joseph B. Cantey

Epidemiology

An outbreak refers to disease activity within a given population that is above the "normal" or expected endemic level [1]. Outbreaks that result from a brief, limited exposure (e.g., if a family member with active varicella visits the NICU) are called point-source outbreaks; in contrast, ongoing exposure over time leads to a longer outbreak called a common-source outbreak. Regardless of the source, outbreaks can be propagated by ongoing horizontal transmission from affected infants to unaffected infants. Pathogens associated with outbreaks in the NICU setting include multidrug-resistant organisms (MDROs), respiratory or gastrointestinal viruses, fungi, and parasites (Box 1). The most commonly reported causes of outbreaks in the NICU are MDROs, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) or extended-spectrum beta-lactamase (ESBL)-producing gram-negative organisms [2]. The incidence of MDROs has steadily climbed over the last two decades [3]. Active surveillance programs for MDROs allow identification of colonized infants so that isolation precautions can be instituted before horizontal transmission occurs. An increase in colonization rates relative to baseline is suggestive of an outbreak. Alternatively, outbreaks may be identified due to a cluster of infections [2]. Identifying an outbreak is a critical first step in controlling transmission. Preventing and controlling outbreaks promptly is critical, both to prevent the high costs associated with outbreak management and to prevent morbidity and mortality for affected infants [4].

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Box 1 Pathogens Reported to Have Caused Outbreaks in Nurseries or Neonatal Intensive Care Units

Bacteria

Methicillin-resistant *Staphylococcus aureus*
Extended-spectrum beta-lactamase-producing gram-negative organisms
Carbapenem-resistant gram-negative organisms
Vancomycin-resistant *Enterococcus*
Vancomycin-intermediate or resistant coagulase-negative *Staphylococcus*
Enterohemorrhagic *Escherichia coli*
Serratia sp.
Pertussis
Group B streptococci
Burkholderia sp.
Cronobacter sp.
Salmonella
Tuberculosis
Legionella pneumophila
Bacillus sp.
Ralstonia sp.
Pantoea sp.

Viruses

Respiratory viruses (influenza, respiratory syncytial virus, adenovirus, etc.)
Gastrointestinal viruses (rotavirus, norovirus, enteroviruses)
Hepatitis A
Varicella
Cytomegalovirus
Herpes simplex virus type 1
Mumps

Fungi

Candida sp.
Malassezia sp.
Aspergillosis
Rhizopus (mucormycosis)
Trichosporon asahii
Microsporum canis (ringworm)
Pichia sp.
Rhodotorula mucilaginosa

Parasites

Scabies
Cimex hemipterus (bedbugs)

Pathogenesis

The NICU setting often provides the perfect conditions for outbreaks to occur. These conditions include vulnerable hosts and environmental challenges.

Infant risks. The immune system of infants, especially preterm infants, is immature relative to older children. Although quantitatively normal in most cases, the innate and adaptive immune system is functionally impaired. This includes granulocyte chemotaxis, complement, opsonization, antibody production, and cell-mediated killing. In addition, preterm infants—particularly those born <28–30 weeks gestation—lack protective levels of transplacental maternal immunoglobulin [5, 6]. Finally, preterm infants have immature skin which is frequently breached by catheters and phlebotomy, allowing pathogens to enter the bloodstream. Therefore, while preterm infants are not classically "immunodeficient," they are at markedly increased risk for infection due to their immature immune system. Preterm infants also require the most indwelling support devices and have the longest length of stay in the NICU, factors that combine to maximize their risk of exposure. Unsurprisingly, preterm infants are the most commonly affected during NICU outbreaks.

Environmental risks. There are several environmental factors that have been associated with outbreaks. Approximately 150 ft^2 of NICU space is recommended for each intensive care infant [7]. Overcrowding has been linked to outbreaks, and decreasing patient density is a common step in outbreak control (see Management below). Nursing understaffing is also a risk factor for horizontal transmission [8, 9]. Presumably, more infants in a nursing assignment equates to less time and attention for standard precautions such as hand hygiene; higher density of infants in a given space equates to less distance needed for horizontal transmission of pathogens. Horizontal transmission is also facilitated by shared medical equipment such as ventilators, isolettes, and stethoscopes if not cleaned in between patients [10]. Finally, environmental sources such as contaminated formula or parenteral nutrition, water sources, air conditioning, or even particles from nearby construction have all been associated with NICU outbreaks [11–13].

Outbreak Detection

The initial step in outbreak detection is realizing that one is occurring. Detection usually follows one of two scenarios: a cluster of similar infections or an uptick in the detection of asymptomatic colonization on routine surveillance screening. Once detected, several actions should occur promptly (Fig. 1). For the purposes of this chapter, steps are divided into "outbreak detection" and "outbreak control," but in reality, these actions should be happening simultaneously.

- *Form a multidisciplinary team*. A multidisciplinary outbreak control team should be formed in order to rapidly collect and distribute information, review and reinforce existing protocols, and implement control measures (see section "Outbreak

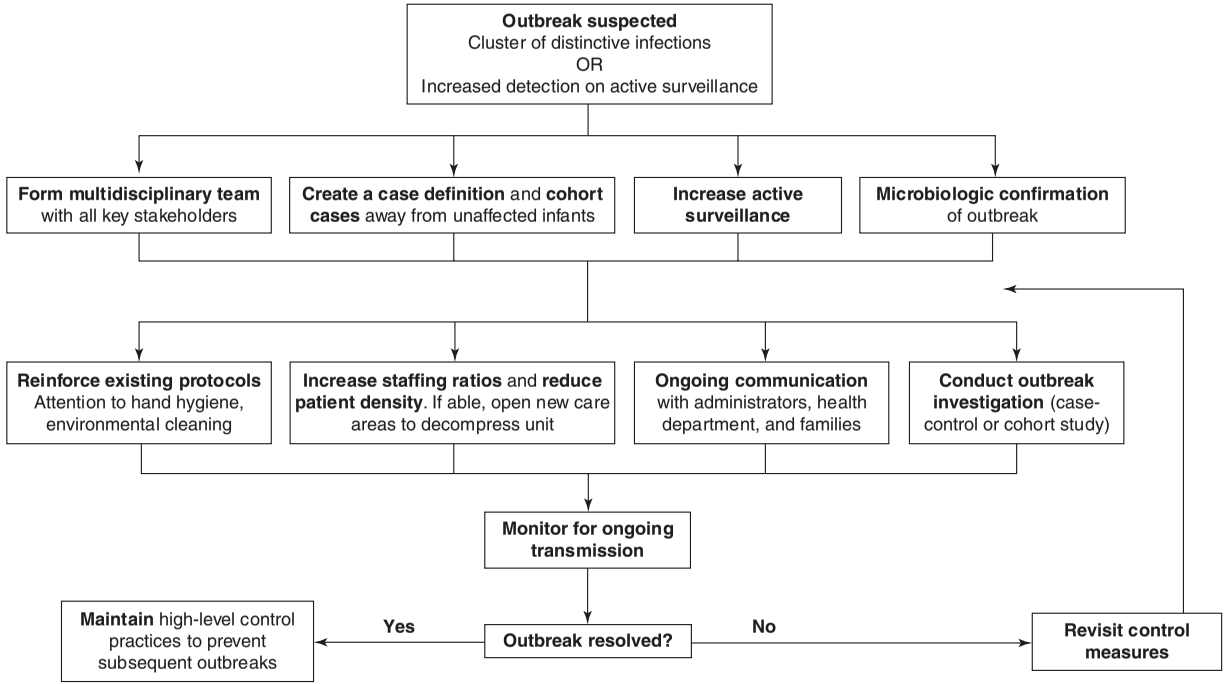

Fig. 1 General steps in outbreak management. Although every outbreak is different, the general principles remain constant. Initial steps (top row) include (1) formation of a multidisciplinary team, including key stakeholders such as infection prevention, nursery providers, microbiology, infectious diseases, environmental services, and hospital administration; (2) creating a case definition and then cohorting case infants separately from "control" infants, (3) beginning or increasing active surveillance for the pathogen in question, and (4) confirming the presence of an outbreak with strain typing. Control measures (second row) generally include (1) reinforcing strict hand hygiene and environmental cleaning policies; (2) decompressing the nursery by increasing available care areas, reducing census, and increasing nursing staffing ratios; (3) communicating openly and honestly with stakeholders, hospital administration, and patient families; and (4) conducting an outbreak investigation to help determine risk factors for ongoing transmission. If these measures prevent ongoing transmission and end the outbreak, the measures should be maintained to prevent subsequent outbreaks. If the outbreak does not resolve, then control measures should be revisited and additional interventions should be considered

Control" below) [14]. This team should consist of all stakeholders, including—but not limited to—infection preventionists, neonatologists, charge nurses, respiratory therapists, environmental services, microbiology, infectious disease specialists, and hospital administration. Administrators should be included whenever possible, as increased resources (physical space, laboratory time, materials, and labor) are virtually always needed to control an outbreak. In addition, local or state health departments should be involved for severe or complex outbreaks or ones that represent an extramural threat to the community [15].

- *Create a case definition*. A case definition should be developed, and infants should be screened if possible to determine whether they are "cases" (infected or colonized with the outbreak pathogen) or "controls" (exposed but unaffected) [16]. Infants should then be cohorted so that cases are isolated from controls. Optimally, providers should also be cohorted (e.g., a nurse would have only case infants or only control infants in their daily assignment, but not both). Providers who must see all infants should begin with control infants and finish with case infants to reduce the risk of horizontal transmission.
- *Increase active surveillance*. If possible, active surveillance should be started for the outbreak pathogen if not already in place, or the frequency of screening should be increased. For example, if a cluster of ESBL-producing *E. coli* infections are detected, then regular screening for ESBL producers should be initiated [15]. Similarly, if a NICU performs once-monthly MRSA screening and suddenly identifies a significant increase in colonization rates, then screening should be increased to every other week or weekly until the outbreak is under control [17]. Note that control infants may become cases over time if horizontal transmission is ongoing.
- *Microbiologic confirmation*. Routine clinical or surveillance cultures will generally report the species of bacteria and susceptibility information (e.g., methicillin-susceptible *S. aureus*). However, in an outbreak setting, it is usually valuable to identify the particular strain. Historically, this has been accomplished by pulsed-field gel electrophoresis, where the organism is lysed and then run on a gel using pulsed electricity to separate the DNA fragments into a distinct "fingerprint." Pulsed-field gel electrophoresis can determine the relatedness of different isolates of the same species and can confirm whether a single strain is spreading in the NICU [18]. Currently, whole-genome sequencing is increasingly used as a quick and efficient substitute for electrophoresis [19].

Outbreak Control

Once an outbreak has been detected and the initial steps have been taken, efforts should focus on controlling horizontal transmission and identifying the source of the outbreak. However, source control is not always possible; many outbreaks do not have a definitive "index patient" or point source identified [20, 21]. Instead, outbreak interventions should primarily center on ending patient-to-patient transmission.

Reinforcement of existing protocols. All staff, including personnel who consult in the NICU such as surgical personnel or other pediatric services, should be reminded to perform proper hand hygiene before and after patient contact [22]. Artificial nails, bracelets, watches, complex or multifaceted rings, and nail polish have all been associated with increased risk of horizontal transmission and should be prohibited if not already against unit policy [23, 24]. Auditing of compliance with hand hygiene will improve compliance rates and allow for reeducation of staff [25]. Parents and other visitors should also be reminded to perform proper hand hygiene before infant contact.

Environmental cleaning. Environmental service staff should be reeducated regarding proper bed space cleaning. Audits using ultraviolet markers can help identify environmental areas that may need re-cleaning and prompt additional training for personnel [26]. All equipment, particularly shared equipment, should be thoroughly cleaned at the time of outbreak recognition as well as before and after patient use [27]. The minimum amount of providers and equipment (e.g., computers on wheels, bedside trays, etc.) should be allowed in the rooms of infected or colonized infants. Finally, case infants should not be moved from their room or bay if at all possible; transfer from bed space to bed space leads to increased risk for environmental contamination and subsequent horizontal transmission.

Avoid overcrowding and understaffing. Increasing the available floor space per infant is critical [28–30]. In addition, cohorting infants into groups often reduces the available space for other infants (e.g., if two MRSA-colonized infants are using a bay normally meant for four infants). Working with nursing leadership and hospital administration to find additional space for uninfected infants is an important step in outbreak control. Reducing staff ratios can also decrease the risk for horizontal transmission. In rare cases, when additional space or staffing is not available, NICUs have closed to additional admissions [31, 32]. However, this is an extreme (and costly) step that is rarely necessary if other interventions are successfully implemented. Another measure that has been used for outbreak control is to perform surveillance cultures of staff [33]. However, this process is costly and potentially problematic. Asymptomatic carriers may have acquired infection from the infant and not vice versa, and the exclusion of colonized staff may contribute to understaffing [34]. Other MDROs that are not related to the outbreak strain may be identified [35]. Additionally, staff surveillance cultures are tremendously unpopular and—most importantly—unnecessary if proper hand hygiene is adhered to [36].

Communication. During an outbreak, honest and frequent communication with parents, other hospital staff, administrators, and the health department is critical. As with any adverse hospital outcome, there is an ethical obligation to inform families about their infant's involvement in an outbreak. If applicable, parents should be counseled about the distinction between colonization and infection. Nondisclosure is often related to embarrassment or concern for legal liability. However, disclosure and apology are not tantamount to admitting fault. There is also evidence that disclosure and apology may reduce the risk of subsequent litigation [37]. There have also been circumstances in which perceived nondisclosure of an outbreak has led to increased media attention [38].

Case control or cohort study. Methodical study of the outbreak cohort can identify risk factors associated with acquisition of the outbreak pathogen. The more variables that are analyzed, the more likely the source can be identified; however, more variables also mean more work, longer time to results, and a greater risk of making type 1 errors (i.e., finding an association between the outbreak and a variable when no such association really exists). The study should be informed by the timing and geography of the outbreak. An investigation may focus on different variables if all cases were clustered near a water leak, for example, than if the case infants are scattered randomly throughout the NICU. In addition, certain pathogens have been associated with particular routes of administration (e.g., *Cronobacter* in contaminated formula, *Legionella* in air conditioning systems, *Malassezia* in contaminated parenteral nutrition). Coordination with microbiology and infectious disease specialists can help guide the study and may lead to source control. These studies may be valuable for outbreak control, although if other steps are properly implemented, the outbreak is often controlled before study results are available. However, such studies are still important as they may identify a risk or a source that was not previously known, and they inform future prevention efforts that may help prevent the next outbreak.

Outbreak Prevention

Intermittent introduction of potential pathogens to the nursery is unavoidable. No amount of questionnaires or symptom screening will capture staff or visitors with asymptomatic infection or colonization with MDROs or viruses. Therefore, the best way to prevent the next outbreak is to continue high-level, "outbreak"-style prevention measures at all times [2, 4, 39], that is, high hand hygiene compliance, quality environmental cleaning, avoiding overcrowding or understaffing, and active surveillance for MDROs. Audit and feedback can provide objective evidence of how well NICU staff are adhering to hygiene procedures. Nurseries that encourage a culture of communication and respectful correction (e.g., "Excuse me, please remember to wash your hands before you touch my patient.") will have better adherence rates [40]. Maintaining outbreak-level precautions at all times is difficult, but when done properly, these steps can markedly reduce the risk for horizontal transmission.

References

1. Centers for Disease Control and Prevention. Principles of epidemiology in public health practice, third edition. Self-study course SS1978. Available online at https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section11.html. Accessed 28 Feb 2018.
2. Johnson J, Quach C. Outbreaks in the neonatal ICU: a review of the literature. Curr Opin Infect Dis. 2017;30:395–403.
3. Cantey JB, Milstone AM. Bloodstream infections: epidemiology and resistance. Clin Perinatol. 2015;42:1–16.
4. Decembrino L, Maini A, Decembrino N, Maggi I, Lacerenza S. Management of outbreak in neonatal intensive care units. Early Hum Dev. 2014;90:S54–6.

5. Strunk T, Currie A, Richmond P, Simmer K, Burgner D. Innate immunity in human newborn infants: prematurity means more than immaturity. J Matern Fetal Neonatal Med. 2011;24:25–31.
6. Cuenca AG, Wynn JL, Moldawer LL, Levy O. Role of innate immunity in neonatal infection. Am J Perinatol. 2013;30:105–12.
7. Kilpatrick SJ, Papile L, Macones GA, Watteberg KL, editors. Guidelines for perinatal care. 8th ed: Elk Grove, American Academy of Pediatrics; 2017.
8. Andersen BM, Lindemann R, Bergh K, et al. Spread of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit associated with understaffing, overcrowding and mixing of patients. J Hosp Infect. 2002;50:18–24.
9. Rogowski JA, Staiger D, Patrick T, et al. Nurse staffing and NICU infection rates. JAMA Pediatr. 2013;167:444–50.
10. Lemaitre D, Elaichouni A, Hundhausen M, Claeys G. Tracheal colonization with Sphingomonas paucimobilis in mechanically ventilated neonates due to a contaminated ventilator temperature probes. J Hosp Infect. 1996;32:199–206.
11. Campbell JR, Hulten K, Baker CJ. Cluster of Bacillus species bacteremia cases in neonates during a hospital construction project. Infect Control Hosp Epidemiol. 2011;32:1035–8.
12. Yiallouros PK, Papadouri T, Karaoli C, et al. First outbreak of nosocomial Legionella infection in term neonates caused by a cold mist ultrasonic humidifier. Clin Infect Dis. 2013;57:48–56.
13. Campos LC, Lobianco LF, Seki LM, Santos RM, Asensi MD. Outbreak of Enterobacter hormaechei septicemia in newborns caused by contaminated parenteral nutrition in Brazil. J Hosp Infect. 2007;66:95–7.
14. Haas JP, Trezza LA. Outbreak investigation in a neonatal intensive care unit. Semin Perinatol. 2002;26:367–78.
15. Cantey JB, Sreeramoju P, Jaleel M, et al. Prompt control of an outbreak caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a neonatal intensive care unit. J Pediatr. 2013;163:672–9.
16. Waldram A, McKerr C, Gobin M, Adak G, Stuart JM, Cleary P. Control selection methods in recent case-control studies conducted as part of infectious disease outbreaks. Eur J Epidemiol. 2015;30:465–71.
17. Gerber SI, Jones RC, Scott MV, et al. Management of outbreaks of methicillin-resistant Staphylococcus aureus infection in the neonatal intensive care unit: a consensus statement. Infect Control Hosp Epidemiol. 2006;27:139–45.
18. Kozyreva VK, Crandall J, Sabol A, et al. Laboratory investigation of Salmonella enterica serovar Poona outbreak in California: comparison of pulsed-field gel electrophoresis (PFGE) and whole genome sequencing (WGS) results. PLoS Curr. 2016;22:8.
19. Miller JM. Whole-genome mapping: a new paradigm in strain-typing technology. J Clin Microbiol. 2013;51:1066–70.
20. Stapleton PJ, Murphy M, McCallion N, et al. Outbreaks of extended spectrum beta-lactamase-producing Enterobacteriaceae in neonatal intensive care units: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2016;101:F72–8.
21. Carey AJ, Long SS. Staphylococcus aureus: a continuously evolving and formidable pathogen in the neonatal intensive care unit. Clin Perinatol. 2010;37:535–46.
22. Montagnani C, Cocchi P, Lega L, et al. Serratia marcescens outbreak in a neonatal intensive care unit: crucial role of implementing hand hygiene among external consultants. BMC Infect Dis. 2015;15:11.
23. Gupta A, Della-Latta P, Todd B, et al. Outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae in a neonatal intensive care unit linked to artificial nails. Infect Control Hosp Epidemiol. 2004;25:210–5.
24. Moolenaar RL, Crutcher JM, San Joaquin VH, et al. A prolonged outbreak of Pseudomonas aeruginosa in a neonatal intensive care unit: did staff fingernails play a role in disease transmission? Infect Control Hosp Epidemiol. 2000;21:80–5.
25. Lam BC, Lee J, Lau YL. Hand hygiene practices in a neonatal intensive care unit: a multimodal intervention and impact on nosocomial infection. Pediatrics. 2004;114:e565–71.

26. Gillespie E, Wright PL, Snook K, et al. The role of ultraviolet marker assessments in demonstrating cleaning efficacy. Am J Infect Control. 2015;43:1347–9.
27. Kanamori H, Rutala WA, Weber DJ. The role of patient care items as a fomite in healthcare-associated outbreaks and infection prevention. Clin Infect Dis. 2017;65:1412–9.
28. Haley RW, Bregman DA. The role of understaffing and overcrowding in recurrent outbreaks of staphylococcal infection in a neonatal special-care unit. J Infect Dis. 1982;145:875–85.
29. Harbarth S, Sudre P, Dharan S. Outbreak of Enterobacter cloacae related to understaffing, overcrowding, and poor hygiene practices. Infect Control Hosp Epidemiol. 1999;20:598–603.
30. Andersen BM, Linemann R, Bergh K, et al. Spread of methicillin-resistant Staphylococcus aureus in a neonatal intensive unit associated with understaffing, overcrowding and mixing of patients. J Hosp Infect. 2002;50:18–24.
31. Adler A, Solter E, Masarwa S, et al. Epidemiological and microbiological characteristics of an outbreak caused by OXA-48-producing Enterobacteriaceae in a neonatal intensive care unit in Jerusalem, Israel. J Clin Microbiol. 2013;51:2926–30.
32. Hernandez AR. Deadly bacteria closes NICU for second time in months at Md. hospital. Washington Post, 2 Nov, 2016. Available at https://www.washingtonpost.com/local/md-politics/deadly-bacteria-closes-nicu-for-second-time-in-months-at-local-hospital/2016/11/02/7af3b70c-a11c-11e6-8832-23a007c77bb4_story.html?utm_term=.759978af9b22. Accessed 2 March 2018.
33. Scheithauer S, Trepels-Kottek S, Hafner H, et al. Healthcare worker-related MRSA cluster in a German neonatology level III ICU: a true European story. Int J Hyg Environ Health. 2014;217:307–11.
34. Hawkins G, Stewart S, Blatchford O, Reilly J. Should healthcare workers be screened routinely for methicillin-resistant Staphylococcus aureus? A review of the evidence. J Hosp Infect. 2011;77:285–9.
35. Mangini E, Srinivasan P, Burns J, et al. Unrelated strain methicillin-resistant Staphylococcus aureus colonization of health care workers in a neonatal intensive care unit: findings of an outbreak investigation. Am J Infect Control. 2013;41:1102–4.
36. Cox RA, Conquest C. Strategies for the management of healthcare staff colonized with epidemic methicillin-resistant Staphylococcus aureus. J Hosp Infect. 1997;35:117–27.
37. McDonnell WM, Altman RL, Bondi SA, et al. Disclosure of adverse events in pediatrics. Pediatrics. 2016;138:e20163215.
38. Petersen M. Mother of baby who caught superbug says UC Irvine hospital didn't tell her about the outbreak. Los Angeles Times, 19 April 2017. Available online at http://www.latimes.com/business/la-fi-uc-irvine-outbreak-mom-20170418-story.html. Accessed 2 March 2018.
39. Curtis C, Shetty N. Recent trends and prevention of infection in the neonatal intensive care unit. Curr Opin Infect Dis. 2008;21:350–6.
40. Ling ML, How KB. Impact of a hospital-wide hand hygiene promotion strategy on healthcare-associated infections. Antimicrob Resist Infect Control. 2012;1:13.

Antibiotic Stewardship

Stephen D. Baird

Introduction

Neonates, especially those who are premature or have congenital malformations, are at increased risk for serious bacterial infections. It is therefore unsurprising that antibiotics are the most-prescribed medications within neonatal intensive care units. Appropriate antibiotic use for proven infection can be lifesaving. However, their inappropriate or excessive use must be guarded against. Mounting evidence has associated exposure to antibiotics with numerous adverse outcomes (Box 1) [1–10]. Therefore, clinicians must balance the benefits of antibiotics against short-term and long-term risk of their use. This balance can be achieved through an antibiotic stewardship program (ASP) [11]. The goal of this chapter is to demonstrate how providers can optimize antibiotic use while minimizing toxicity and adverse effects.

Box 1 Adverse Outcomes Associated with Antibiotic Use in Early Infancy

Early	*Candida* colonization and invasive candidiasis
	Multidrug-resistant organism colonization
	Late-onset sepsis
	Necrotizing enterocolitis
	Bronchopulmonary dysplasia
	Mortality
Late	Asthma
	Eczema
	Obesity

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Establishing an Antibiotic Stewardship Program

Personnel. Antibiotic stewardship programs (ASPs) should be multidisciplinary. Most ASPs involve at a minimum an infectious disease specialist or a clinical pharmacist whose sole or primary role is to oversee the ASP. However, remote monitoring by ASP personnel is not nearly as effective as when nursery personnel are invested stakeholders. Evidence suggests that neonatologists are more receptive to feedback if it originates from another nursery provider than from infectious diseases or pharmacy [12, 13]. In addition, nursery stakeholders can guide the ASP as to which interventions are likely to meet with the most buy-in from other nursery providers.

Strategies. There are several approaches that ASPs can use in the nursery setting, including audit and feedback, prior authorization, and guidelines.

- *Audit and feedback*. Prospective audit of antibiotic prescribing combined with timely feedback to individual providers, the nursery as a whole, or both, is a staple of antimicrobial stewardship. Prospective audit may be comprehensive, evaluating every dose of every antibiotic administered in the nursery, or it may be restricted to certain antimicrobials such as those that are broad spectrum or those that are most commonly used [14, 15]. Audit and feedback has several advantages. First, it is the most "passive" of the three core strategies and may be viewed more favorably by providers as a result. Secondly, prospective audit allows ASP providers and the nursery stakeholders to identify emerging patterns in real time. Finally, when audit and feedback has been compared head-to-head with prior authorization, audit and feedback has consistently been shown to be more effective [16–18].
- *Prior authorization*. Prior authorization refers to specific antimicrobials that can only be used after being "authorized" by a member of the ASP. Alternatively, a given agent could be used empirically for 24 or 48 h, but then would be stopped unless authorization to continue is given. Use of a given antimicrobial usually drops quickly once it is placed under prior authorization. However, prior authorization has also been associated with provider push-back, increased use of unrestricted antimicrobials, and delays in therapy [19]. The use of antibiotic "time-outs," where antibiotics may be started but then are reviewed at a certain point (usually the 48-h mark), is an equally effective and better-tolerated approach compared with prior authorization [20].
- *Guidelines*. Guidelines for common infections can improve both diagnostic and antimicrobial stewardship by minimizing the number of unnecessary evaluations and optimizing the diagnosis and treatment of suspected infections. In the NICU setting, protocols for early-onset sepsis, late-onset sepsis, and necrotizing enterocolitis may be beneficial. Suspected sepsis accounts for the majority of antibiotic use in the NICU. Chapters "Early-Onset Sepsis," "Late-Onset Sepsis," and "Necrotizing Enterocolitis" highlight suggested approaches to early- and late-onset sepsis and necrotizing enterocolitis, respectively.

Metrics. Another issue is how to report antibiotic usage in the nursery setting. A commonly used term for ASPs is days of therapy per 1000 patient-days [21]. This metric counts each day (or partial day) of a given antibiotic separately. For example, 2 days of ampicillin and gentamicin therapy would count as 4 days of therapy—2 days of ampicillin and 2 days of gentamicin. This is in contrast to "length of therapy," which refers to the number of calendar days that an infant receives antimicrobial therapy and is more consistent with how providers speak. When using length of therapy, 2 days of ampicillin and gentamicin therapy is 2 days. Although days of therapy is preferred by ASPs, and length of therapy is used by providers, the optimal metric has not been identified and both have weaknesses [22]. For example, providers can decrease their nursery's days of therapy by changing all infants from ampicillin and gentamicin to meropenem—significantly broadening coverage but reducing the days of therapy to 2 to 1.

Diagnostic Stewardship

Proper approach to the diagnosis of infection can ensure that antibiotics are used properly. This includes obtaining proper microbiologic studies when infection is suspected, interpreting the results correctly, and using ancillary tests properly to help guide cessation of antimicrobial use.

Cultures. The vast majority of antibiotic use within the NICU comes from the empiric or directed treatment of sepsis. Bacterial blood cultures remain the gold standard for diagnosing neonatal sepsis and are extremely sensitive when obtained properly. Studies have shown that septic neonates tend to have high bacterial concentrations in their bloodstreams, with a median value of 500 colony-forming units/mL [23]. Inoculation of 1 mL of blood is able to recover bacteria at concentrations as low as 4 colony-forming units/mL [24]. Sensitivity is lower at extremely low bacterial concentrations (<4 colony-forming units/mL), but the clinical significance of such low-level bacteremia is unknown. The recommendation is that a minimum of 1 mL of blood be obtained for culture when sepsis is suspected; unfortunately, collected volumes are frequently <1 mL [25, 26]. This issue could be improved with simple education of the providers obtaining the cultures.

Another major stewardship challenge is that clinicians may not trust sterile blood cultures. Reasons for this are multifactorial and include concern for improperly drawn specimens, institutional practices and habits, suspicion that intrapartum antibiotic prophylaxis may have "masked" a positive culture, and continued signs consistent with sepsis in an infant with sterile cultures. Whatever the reason, these behaviors may lead to treatment of "culture-negative" sepsis, often for prolonged periods [27]. The median course of therapy for culture-negative sepsis is 7–10 days. ASPs should evaluate the frequency of "culture-negative" sepsis courses and focus on timely discontinuation of antibiotics. This includes ensuring that appropriate blood cultures are drawn and then educating providers to trust those results [28].

Finally, cultures of non-sterile sites (e.g., trachea, skin, mucous membranes, etc.) must be interpreted cautiously. The infant's clinical state, imaging studies if

applicable, and culture results should be interpreted together to determine whether a positive culture represents infection or asymptomatic colonization.

Ancillary tests. A variety of ancillary blood tests have been evaluated against the gold standard of cultures to determine their sensitivity and specificity for detection of sepsis in infants. These biomarkers include complete blood cell counts with differential, C-reactive protein, procalcitonin, presepsin, interleukin-6, and more [29]. Although the particulars of the frequency, intervals, and cutoff values have varied between studies, the overall pattern is quite clear. The positive predictive value of these tests is generally poor. A variety of clinical scenarios can make these biomarkers abnormal even when cultures are sterile, including chorioamnionitis, perinatal asphyxia, preeclampsia, and even delivery itself [30, 31]. However, their negative predictive value is generally good, approaching 99% for serial neutrophil values. Therefore—if used at all—these studies are best used for their negative predictive value. Clinicians who are anxious about stopping antibiotic therapy in an infant with sterile blood cultures but continued signs of illness (e.g., hypotension, respiratory failure) may be reassured if biomarkers are also normal. However, it cannot be overstated that cultures are the gold standard, and properly obtained, sterile blood cultures should be trusted on their own merits. Additionally, these biomarkers do not have sufficient specificity or sensitivity to preclude the need for cultures or empiric antibiotic therapy.

Risk prediction models. Risk prediction models, also known as sepsis calculators, show tremendous promise in helping guide initiation of antibiotic therapy for early-onset sepsis. The best-studied model to date is the Kaiser sepsis calculator (available at https://neonatalsepsiscalculator.kaiserpermanente.org). This calculator uses the local epidemiology of early-onset sepsis, gestational age, maternal temperature, duration of rupture of membranes, and maternal group B streptococcal colonization status in combination with the infant's clinical appearance to recommend observation or cultures ± empiric antibiotic therapy. Large cohort studies have demonstrated that the use of these prediction models can safely reduce sepsis evaluations and empiric antibiotic use by 30–50% [32, 33]. However, these models have not yet been validated in more preterm infants.

Antimicrobial Stewardship

Once properly obtained cultures are obtained, antibiotics should be initiated, modified, and discontinued based on the results of those cultures and the infant's clinical status. Detailed recommendations for early-onset and late-onset sepsis, focal infections, and necrotizing enterocolitis are given in chapters "Early-Onset Sepsis," "Late-Onset Sepsis," and "Necrotizing Enterocolitis," respectively. However, antimicrobial selection should be tailored to a given center's antibiogram, which is available through the hospital microbiology lab and will inform nursery providers about rates of resistance seen locally.

Empiric selection. Empiric antibiotics provide adequate coverage for the likely pathogens while cultures are pending (Table 1).

Table 1 General empiric and definitive therapy guidelines for infants with suspected infection

Condition	Empiric therapy	Alternatives	Duration
Suspected infection			
Early-onset sepsis	Ampicillin and gentamicin		36–48 h pending culture results
Late-onset sepsis	Oxacillin and gentamicin	Vancomycin and gentamicin	
Meningitis	Cefotaxime and vancomycin		48 h pending culture results
Proven infection			
Necrotizing enterocolitis	Piperacillin/tazobactam	Ampicillin, gentamicin, and metronidazole	7–14 days depending on Bell's staging
Gram-positive	GBS—ampicillin CoNS—vancomycin MSSA—oxacillin MRSA—vancomycin *Enterococcus*—ampicillin		7–10 days for uncomplicated sepsis 10–14 days for meningitis
Gram-negative	Varies		10–14 days for uncomplicated sepsis 14–21 days for meningitis

CoNS coagulase-negative staphylococci, *GBS* group B streptococci, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *Staphylococcus aureus*

Early-onset sepsis. Common pathogens include group B streptococci and gram-negative *Enterobacteriaceae* such as *Escherichia coli*. Ampicillin and gentamicin are widely used and cover virtually all commonly encountered pathogens. However, if the proportion of gentamicin-resistant *E. coli* is high (>10–15%), an alternative aminoglycoside should be considered.

Late-onset sepsis. The range of pathogens capable of causing late-onset sepsis is broad, making it difficult to cover all the possibilities. In general, coagulase-negative staphylococci, *S. aureus*, and gram-negatives (primarily the *Enterobacteriaceae*) account for the majority of cases. A semisynthetic penicillin such as oxacillin, in combination with gentamicin or another aminoglycoside, is appropriate in most cases. For infants who are colonized with methicillin-resistant *S. aureus* (MRSA), or for NICUs who do not perform prospective surveillance for MRSA, vancomycin may be necessary in lieu of oxacillin. However, vancomycin reduction strategies have been shown to be safe and effective (see chapter "Late-Onset Sepsis") [34].

Necrotizing enterocolitis. Pathogens responsible for necrotizing enterocolitis include aerobic and anaerobic gram-negatives as well as the anaerobic gram-positives found in the infant gut. These organisms can be empirically covered with piperacillin/tazobactam monotherapy. Alternatively, ampicillin, gentamicin, and metronidazole can be given in combination, but this achieves the same general coverage as piperacillin/tazobactam at the expense of more line entry for dosing and more nephrotoxicity due to the inclusion of an aminoglycoside.

Definitive therapy. Once empiric therapy has been started, the selection and duration of therapy depend on culture results and the infant's clinical status. If sepsis is suspected but cultures are sterile, antibiotics should be stopped promptly within 48 h; 36 h may be sufficient for early-onset sepsis [35]. Positive cultures should be treated with definitive therapy that is the narrowest possible regimen that reaches the infected compartment (e.g., blood, urine, cerebrospinal fluid) and treats the responsible organism(s). General guidelines are shown in Table 1 but will vary depending on the clinical circumstances and the infant's response to therapy.

Reporting

Effective ASP programs use the strategies listed in 27.2 to improve antibiotic use. However, effective stewardship requires ongoing communication and reporting of data between the nursery and the ASP. This reporting serves as feedback and education and can also help to identify new or emerging areas that need to be addressed. Antibiotic stewardship can feel a little bit like Sisyphus rolling the boulder up the hill over and over again. However, antibiotic stewardship efforts are viewed favorably by nursery providers and ultimately can be remarkably effective in reducing unnecessary or unwarranted antibiotic exposure in vulnerable infants [12, 15].

References

1. Cotton CM, McDonald S, Stoll B, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics. 2006;118:717–22.
2. de Man P, Verhoeven BA, Verbrugh HA, et al. An antibiotic policy to prevent emergence of resistant bacilli. Lancet. 2000;355:973–8.
3. Cotton CM, Taylor S, Stoll B, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics. 2009;123:58–66.
4. Cantey JB, Huffman LW, Subramanian A, et al. Antibiotic exposure and risk for death or bronchopulmonary dysplasia in very low birth weight infants. J Pediatr. 2017;181:289–93.
5. Ting JY, Synnes A, Roberts A, et al. Association of antibiotic use and neonatal mortality and morbidities in very low-birth-weight infants without culture-proven sepsis or necrotizing enterocolitis. JAMA Pediatr. 2016;170:1181–7.
6. Sun W, Svendsen ER, Karmaus WJ, Kuehr J, Forster J. Early-life antibiotic use is associated with wheezing among children with high atopic risk: a prospective European study. J Asthma. 2015;52:647–52.
7. Lapin B, Piorkowski J, Ownby D, et al. The relationship of early-life antibiotic use with asthma in at-risk children. J Allergy Clin Immunol. 2014;134:728–9.
8. Schmitt J, Schmitt NM, Kirch W, Meurer M. Early exposure to antibiotics and infections and the incidence of atopic eczema: a population-based cohort study. Pediatr Allergy Immunol. 2010;21:292–300.
9. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics. 2015;135:617–26.
10. Korpela K, Zijlmans MA, Kuitunen M, et al. Childhood BMI in relation to microbiota in infancy and lifetime antibiotic use. Microbiome. 2017;5:26.

11. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159–77.
12. Cantey JB, Vora N, Sunkara M. Prevalence, characteristics, and perception of nursery antibiotic stewardship coverage in the United States. J Pediatric Infect Dis Soc. 2017;6:e30–5.
13. Patel S, Landers T, Larson E, et al. Clinical vignettes provide an understanding of antibiotic prescribing practices in neonatal intensive care units. Infect Control Hosp Epidemiol. 2011;32:597–602.
14. Kimura T, Uda A, Sakaue T, et al. Long-term efficacy of comprehensive multidisciplinary antibiotic stewardship programs centered on weekly prospective audit and feedback. Infection. 2018;46(2):215–24.
15. Cantey JB, Wozniak PS, Pruszynski JE, Sanchez PJ. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. Lancet Infect Dis. 2016;16:1178–84.
16. Mehta JM, Haynes K, Wileyto EP, et al. Comparison of prior authorization and prospective audit with feedback for antimicrobial stewardship. Infect Control Hosp Epidemiol. 2014;35:1092–9.
17. Chan S, Hossain J, DiPentima MC. Implications and impact of prior authorization policy on vancomycin use at a tertiary pediatric teaching hospital. Pediatr Infect Dis J. 2015;34:506–8.
18. Lukaszewicz Bushen J, Mehta JM, Hamilton KW, et al. Frequency of streamlining antimicrobial agents in patients with bacteremia. Infect Control Hosp Epidemiol. 2017;38:89–95.
19. Reed EE, Stevenson KB, West JE, Bauer KA, Goff DA. Impact of formulary restriction with prior authorization by an antimicrobial stewardship program. Virulence. 2013;4:158–62.
20. Graber CJ, Jones MM, Glassman PA, et al. Taking an antibiotic time-out: utilization and usability of a self-stewardship time-out program for renewal of vancomycin and piperacillin/tazobactam. Hosp Pharm. 2015;50:1011–24.
21. Ibrahim OM, Polk RE. Antimicrobial use metrics and benchmarking to improve stewardship outcomes: methodology, opportunities, and challenges. Infect Dis Clin North Am. 2014;28:195–214.
22. Cantey JB, Patel SJ. Antimicrobial stewardship in the NICU. Infect Dis Clin North Am. 2014;28:247–61.
23. Sabui T, Tudehope DI, Tilse M. Clinical significance of quantitative blood cultures in newborn infants. J Paediatr Child Health. 1999;35:578–81.
24. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996;129:275–8.
25. Polin RA, Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129:1006–15.
26. Connell TG, Rele M, Cowely D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. Pediatrics. 2007;119:891–6.
27. Cantey JB, Sanchez PJ. Prolonged antibiotic therapy for "culture-negative" sepsis in preterm infants: it's time to stop! J Pediatr. 2011;159:707–8.
28. Cantey JB, Baird SD. Ending the culture of culture-negative sepsis in the neonatal ICU. Pediatrics. 2017;140:e20170044.
29. Ng PC, Ma TP, Lam HS. The use of laboratory biomarkers for surveillance, diagnosis and prediction of clinical outcomes in neonatal sepsis and necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2015;100:F448–52.
30. Perron S, Lotti F, Longini M, et al. C reactive protein in healthy term newborns during the first 48 hours of life. Arch Dis Child Fetal Neonatal Ed. 2018;103:F163–6.
31. Jackson GL, Engle WD, Sendelbach DM, et al. Are complete blood cell counts useful in the evaluation of asymptomatic neonates exposed to suspected chorioamnionitis? Pediatrics. 2004;113:1173–80.
32. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr. 2017;171:365–71.

33. Warren S, Garcia M, Hankins C. Impact of neonatal early-onset sepsis calculator on antibiotic use within two tertiary health care centers. J Perinatol. 2017;37:394–7.
34. Chiu CH, Michelow IC, Cronin J, Ringer SA, Ferris TG, Puopolo KM. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J. 2011;30:273–8.
35. Vamsi SR, Bhat RY, Lewis LE, Vandana KE. Time to positivity of blood cultures in neonates. Pediatr Infect Dis J. 2014;33:212–4.

Immunizations in the Nursery

Johanna M. Ascher Bartlett

Overview

Immunization is one of the most important tools of pediatric preventative care. However, a tremendous number of infants are at risk of not being up-to-date on their vaccines at the time of nursery discharge. For well newborns, approximately 30–40% do not receive their birth dose of hepatitis B vaccine [1]. Under-immunization is even more common among preterm infants discharged from the neonatal intensive care unit (NICU); studies estimate that up to 50% of preterm infants are missing ≥1 immunization [2, 3].

Under-immunization in the nursery is problematic for several reasons:

1. Missed opportunity to prevent vertical transmission (hepatitis B).
2. Missed opportunity to prevent healthcare-associated infection (pertussis, influenza).
3. Restrictions on live virus vaccines may prevent infant from ever receiving rotavirus vaccine.
4. Time delay between hospital discharge and first well-child visit as outpatient increases the time window during which the infant is at risk for preventable infections.
5. Not giving immunizations on time in the nursery may "normalize" under-immunization to the family.

This chapter describes administration strategies for all routine childhood vaccines. In general, vaccines should be given at the normal chronologic ages to all

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infants (i.e., not corrected [post-menstrual] age). A 2-month-old former 23-week infant who is now 32 weeks corrected is due for the 2-month immunizations!

Hepatitis B Vaccine

Approximately 1000 new cases of perinatal hepatitis B virus (HBV) infection are diagnosed each year in the United States [4]. For neonates infected perinatally with HBV, more than 90% will become chronically infected, and >25% will develop hepatocellular carcinoma or liver cirrhosis [5]. In order to prevent perinatal infection, all pregnant women should be screened for the presence of hepatitis B surface antigen (HBsAg) in their blood prior to delivery (see chapter "Hepatitis B in the Perinatal Period").

The hepatitis B vaccine is approximately 85–95% effective when given in the first 12 h of life [6]. In addition, hepatitis B immune globulin (HBIG) provides passive immunoprophylaxis to infants with known perinatal exposure to HBV. The administration of hepatitis B vaccine, with or without HBIG, is determined by the infant's weight and HBV exposure status. In general, all infants should receive hepatitis B vaccine as soon as possible after delivery (Table 1). Prompt immunization is key to prevent vertical transmission from HBV-infected mothers and will also help protect infants born to mothers whose HBV status is either unknown or falsely negative. However, infants <2 kg born to HBsAg-negative mothers should be immunized at age 1 month—or at the time of discharge—in order to improve their immune response to immunization.

In addition to immunization, infants born to HBV-positive mothers should undergo confirmatory testing between ages 9 and 12 months, after completion of their three-dose hepatitis B vaccine series (at birth as well as ages 2 and 6 months). Providers should obtain HBsAg and anti-HBs to ensure that the infant is not infected (negative HBsAg) and has mounted a protective immune response. If the anti-HBs level is <10 mIU/mL, the infant is not considered protected and should receive additional dose(s) [7].

Table 1 Hepatitis B vaccine and immune globulin administration strategies

Maternal HBsAg status at delivery	Hepatitis B vaccine	Hepatitis B immune globulin
Positive	Within 12 h	Within 12 h
Negative	*≥2 kg*: Within 24 h	Not indicated
	<2 kg: At 1 month of age or discharge, whichever comes first	
Unknown/ pending	Within 12 h	*≥2 kg*: If mother's HBsAg test is positive *OR* at age 7 days or hospital discharge if mother's HBsAg status still unknown
		<2 kg: Within 12 h unless mother's HBsAg testing is negative by then

2-, 4-, and 6-Month Vaccines

The collection of vaccines due at ages 2, 4, and 6 months accounts for the majority of immunizations administered in the NICU, and are second only to the hepatitis B vaccine in terms of total doses administered in US nurseries. These vaccines include diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio virus (IPV), *Haemophilus influenzae* type b (Hib), and 13-valent pneumococcal vaccine (PCV-13). Rotavirus is included in the 2-4-6-month schedule but is discussed separately below.

Delay or absence of these 2-4-6-month vaccines accounts for a substantial fraction of nursery under-immunization [3]. Providers are often concerned about the increased frequency of apneas and bradycardia surrounding immunizations. Randomized controlled trials have confirmed that immunization is associated with an increase in inflammation, including C-reactive protein and prostaglandins, which can trigger apnea, bradycardia, respiratory decompensation, and other signs of clinical instability [8–10]. Unsurprisingly, the incidence of sepsis evaluations (e.g., cultures and empiric antibiotic administration) more than triples in the 3 days following immunization as a result [10]. Therefore, providers may delay immunizations until the infants are older, larger, or closer to discharge. However, vaccine-preventable illnesses—most notably pertussis—are capable of causing fatal nosocomial infections [11]. In addition, immunization near the time of discharge can still cause transient inflammation, which is associated with discharge delays and readmission for apneic events [12]. Additionally, infants who are immunized late may acquire vaccine-preventable infections after discharge, but before they have mounted a protective antibody response [13].

In general, 2-4-6-month immunizations should be administered promptly (Box 1). Rare exceptions can be made for infants being supported with noninvasive ventilation with tenuous respiratory status, who may require re-intubation with further respiratory decompensation. However, these infants should be immunized as soon as is feasible. Of note, active or recent administration of glucocorticoids does not seem to meaningfully affect vaccine response and is not a reason to delay immunization [14, 15]. Routine administration of antipyretics (e.g., ibuprofen, acetaminophen) has been associated with decreased antibody response to immunizations in infants and should be avoided in general [16].

Box 1 Approach to 2-, 4-, and 6-Month Vaccines in Preterm Infants

Immunizations should be given promptly at age 2, 4, and 6 months for all preterm infants

- Active or recent corticosteroid use *does not* meaningfully affect vaccine response
- Routine use of acetaminophen or ibuprofen post-immunization can reduce vaccine response and should be avoided

- Combination vaccines (e.g., DTaP/IPV/hepatitis B) have similar safety profiles to individual vaccines and can be used to minimize required injections
- Live-attenuated oral rotavirus vaccine should be included in the 2-4-6-month schedule

Absolute contraindications:

- Anaphylaxis to a vaccine component (not reported in preterm infants)
- History of intussusception (rotavirus)

Post-immunization monitoring

- Vaccine-associated events[a] occur within 72 h of immunization
- Sepsis evaluations—but not sepsis risk—increased within 72 h of immunization
- Discharge <72 h post-immunization associated with increased risk for readmission

[a]Apnea, bradycardia, desaturation, respiratory decompensation, temperature instability, feeding intolerance

Rotavirus Vaccine

Rotavirus vaccine, a live-attenuated virus vaccine, is indicated at ages 2, 4, and 6 months. Since live-attenuated viruses can be transmitted horizontally, and because wild-type rotavirus is associated with necrotizing enterocolitis and other intra-abdominal pathology among neonates [17, 18], the majority of neonatal providers historically have been hesitant to adopt routine administration of this vaccine in the nursery [19]. Unfortunately, the first dose of rotavirus vaccine must be administered by age 104 days (<15 weeks), and therefore many infants are too old for rotavirus immunization by the time of NICU discharge [20]. This is concerning, as preterm infants have a higher risk of hospitalization and death from wild-type rotavirus infection than term infants [21]. Infants with congenital gastrointestinal pathology or short-gut syndrome are also especially vulnerable to rotavirus [22]. Fortunately, safety data for the rotavirus immunization in the NICU continues to grow.

Safety Profile

Current studies suggest that there is no increased risk for feeding intolerance, necrotizing enterocolitis, or poor weight gain following rotavirus immunization

[23, 24]. This remains true for infants with congenital gastrointestinal anomalies or short-gut syndrome [25, 26]. A history of intussusception is an absolute contraindication to rotavirus vaccine for all infants, but rotavirus vaccine-associated intussusception has not been reported in preterm infants.

Shedding

Immunized infants begin shedding vaccine-strain rotavirus within 24 h of immunization. Shedding lasts for up to 2 weeks, with a median of 8 days with the first dose of rotavirus vaccine and 5 days after the second [27]. With proper handwashing hygiene, transmission between immunized and unimmunized infants should not occur [27]. In a study of preterm twins, in which one twin was immunized with rotavirus and the other was not, 29% of the unvaccinated twins acquired rotavirus immunity, but none had clinical signs of infection [28]. Illness from horizontal transmission of the vaccine strain has not been reported in the nursery setting and is extremely rare in older children [29].

In conclusion, the limited available evidence supports routine rotavirus immunization in the NICU setting. Standard precautions, including close attention to handwashing hygiene, are sufficient; contact precautions are not necessary post-immunization.

Influenza Vaccine

Infants Age ≥6 Months

Influenza immunization should be given for all infants age ≥6 months. As with any infant, preterm infants receiving their first dose of influenza vaccine should receive a second dose 1 month later [30]. The same risk exists for post-vaccine events following influenza vaccine as after 2-4-6 month vaccines.

Infants Younger Than Age 6 Months

Although there is no formal recommendation to administer influenza vaccine to infants age <6 months, there are units that will selectively administer influenza vaccine to high-risk infants (e.g., those with severe bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency) before discharge, even if age <6 months; this approach has not been rigorously studied [31]. A more proven approach to infants age <6 months is passive protection from maternally derived antibody. Immunization of pregnant women against influenza prevents more than 50% of influenza-associated morbidity among their infants during the first 6 months of life [32].

Palivizumab Prophylaxis

Palivizumab (Synagis®) provides passive protection against lower respiratory tract infections caused by respiratory syncytial virus (RSV). Palivizumab is a monoclonal antibody against a surface glycoprotein on RSV that causes fusion with respiratory epithelial cells [33]. By blocking the F (fusion) protein, palivizumab can prevent infection with RSV. However, once RSV infection is acquired, the virus can spread cell to cell without relying on the F protein, so palivizumab is minimally effective for treatment of RSV infection.

Palivizumab is given as monthly 15 mg/kg intramuscular injections during RSV season. This regimen reduces RSV-related hospitalizations by >50% and clinic visits by >80% [34, 35]. However, due to the cost of palivizumab (approximately $9000 per patient per season) and the relatively mild benefit seen in larger preterm infants, the most recent recommendations from the American Academy of Pediatrics narrowed the range of infants for whom palivizumab is recommended [36]. The current recommendations are summarized in Table 2.

At present, palivizumab is not recommended for prevention of hospital-acquired RSV and therefore is not recommended for infants with ongoing NICU admission. Many NICUs will administer the first dose of palivizumab near the time of hospital discharge; however, evidence supporting NICU administration of the first dose rather than outpatient administration is limited [37]. In contrast to vaccines, palivizumab administration does not seem to be associated with a subsequent increase in cardiopulmonary events.

Table 2 Recommendations for palivizumab prophylaxis in the first 2 years of life, adapted from reference 36

Indication	First year of life	Second year of life
Gestational age ≤28 weeks	Yes	Yes, if BPD still being treated[a]
Gestational age 29–31 weeks with BPD[b]	Yes	Yes, if BPD still being treated
Gestational age 29–31 weeks without BPD	No	No
Gestational age ≥32 weeks	No	No
Hemodynamically significant congenital heart disease[c]	Yes	No
Severe pulmonary or neuromuscular disease that impairs airway clearance	Yes	No
Profound immunocompromise[d]	Yes	Yes

BPD bronchopulmonary dysplasia

[a]Ongoing treatment including systemic corticosteroids, supplemental oxygen, or bronchodilators within 6 months of the start of RSV season (which is generally November in the United States)

[b]BPD defined as requirement for supplemental oxygen ≥28 days after birth

[c]Includes acyanotic heart disease requiring medication and/or surgical correction, moderate to severe pulmonary hypertension, and cyanotic heart disease. Does not include hemodynamically insignificant acyanotic heart disease or lesions that have been successfully surgically corrected

[d]No standard definition; generally includes severe combined immunodeficiency, DiGeorge syndrome, etc. Best determined in consultation with pediatric immunology providers

References

1. Zhao Z, Murphy TV. Which newborns missed the hepatitis B birth dose vaccination among U.S. children? Prev Med. 2013;57:613–7.
2. Meleth S, Dahlgren LS, Sankaran R, Sankaran K. Vaccination of infants discharged from a neonatal intensive care unit. CMAJ. 1995;153:415–9.
3. Navar-Boggan AM, Halsey NA, Escobar GJ, Golden WC, Klein NP. Underimmunization at discharge from the neonatal intensive care unit. J Perinatol. 2012;32:363–7.
4. Ko SC, Fan L, Smith EA, et al. Estimated annual perinatal hepatitis B virus infections in the United States, 2000-2009. J Pediatric Infect Dis Soc. 2016;5:114–21.
5. Stevens CE, Toy P, Kamili S, et al. Eradicating hepatitis B virus: the critical role of preventing perinatal transmission. Biologicals. 2017;50:3–19.
6. Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ. 2006;332:328–36.
7. Schillie S, Murphy TV, Fenlon N, Ko S, Ward JW. Update: shortened interval for postvaccination serologic testing of infants born to hepatitis B-infected mothers. MMWR Morb Mortal Wkly Rep. 2015;64:1118–20.
8. Ben Jmaa W, Hernandez AI, Sutherland MR, et al. Cardiorespiratory events and inflammatory response after primary immunization in preterm infants <32 weeks gestational age: a randomized controlled study. Pediatr Infect Dis J. 2017;36:988–94.
9. Montague EC, Hilinski JA, Williams HO, et al. Respiratory decompensation and immunization of preterm infants. Pediatrics. 2016;137:e20154225.
10. DeMeo SD, Raman SR, Hornik CP, et al. Adverse events after routine immunization of extremely-low-birth-weight infants. JAMA Pediatr. 2015;169:740–5.
11. Maltezou HC, Ftika L, Theodoridou M. Nosocomial pertussis in neonatal units. J Hosp Infect. 2013;85:243–8.
12. Klein NP, Massolo ML, Greene J, et al. Risk factors for developing apnea after immunization in the neonatal intensive care unit. Pediatrics. 2008;121:463–9.
13. Yasmin S, Sunenshine R, Bisgard KM, et al. Healthcare-associated pertussis outbreak in Arizona: challenges and economic impact, 2011. J Pediatric Infect Dis Soc. 2014;3:81–4.
14. Robinson MJ, Heal C, Gardener E, Powell P, Sims DG. Antibody response to diphtheria-tetanus-pertussis immunization in preterm infants who receive dexamethasone for chronic lung disease. Pediatrics. 2004;113:733–7.
15. Tsuda K, Iwasaki S, Horiguchi H, et al. Immune response to Haemophilus influenzae type b conjugate vaccine in preterm infants. Pediatr Int. 2012;54:64–7.
16. Wysocki J, Center KJ, Brzostek J, et al. A randomized study of fever prophylaxis and the immunogenicity of routine pediatric vaccinations. Vaccine. 2017;35:1926–35.
17. Sharma R, Hudak ML, Premachandra BR, et al. Clinical manifestations of rotavirus infection in the neonatal intensive care unit. Pediatr Infect Dis J. 2002;21:1099–105.
18. Rotbart HA, Nelson WL, Glode MP, et al. Neonatal rotavirus-associated necrotizing enterocolitis: case control study and prospective surveillance during an outbreak. J Pediatr. 1988;112:87–93.
19. Jaques S, Bhojnagarwala B, Kennea N, Duffy D. Slow uptake of rotavirus vaccination in UK neonatal units. Arch Dis Child Fetal Neonatal Ed. 2014;99:F252.
20. Stumpf KA, Thompson T, Sanchez PJ. Rotavirus vaccination of very low birth weight infants at discharge from the NICU. Pediatrics. 2013;132:e662–5.
21. Newman RD, Grupp-Phelan J, Shay DK, Davis RL. Perinatal risk factors for infant hospitalization with viral gastroenteritis. Pediatrics. 1999;103:E3.
22. Anagnostropoulos D, Valioulis J, Sfougaris D, Maliaropoulos N, Spyridakis J. Morbidity and mortality of short bowel syndrome in infancy and childhood. Eur J Pediatr Surg. 1991;1:273–6.
23. Thrall S, Doll MK, Nhan C, et al. Evaluation of pentavalent rotavirus vaccination in neonatal intensive care units. Vaccine. 2015;33:5095–102.

24. Monk HM, Motsney AJ, Wade KC. Safety of rotavirus vaccine in the NICU. Pediatrics. 2014;133:e1555–60.
25. Fang AY, Tingay DG. Early observations in the use of oral rotavirus vaccination in infants with functional short gut syndrome. J Paediatr Child Health. 2012;48(6):512.
26. Javid PJ, Sanchez SE, Jacob S, et al. The safety and immunogenicity of rotavirus vaccination in infants with intestinal failure. J Pediatric Infect Dis Soc. 2014;3:57–65.
27. Hiramatsu H, Suzuki R, Nagatani A, et al. Rotavirus vaccination can be performed without viral dissemination in the neonatal intensive care unit. J Infect Dis. 2018;217:589–96.
28. Rivera L, Pena LM, Stainier I, et al. Horizontal transmission of a human rotavirus vaccine strain – a randomized, placebo-controlled study in twins. Vaccine. 2011;29:9508–13.
29. Payne DC, Edwards KM, Bowen MD, et al. Sibling transmission of vaccine-derived rotavirus (RotaTeq) associated with rotavirus gastroenteritis. Pediatrics. 2010;125:e438–41.
30. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations from the committee on immunization practices – United States, 2017-18 influenza season. MMWR Recomm Rep. 2017;66:1–20.
31. Tinnion RJ, Berrington JE. Flu vaccination for ex-preterms and infants under 6 months – are we getting it right? Arch Dis Child. 2010;95:400–1.
32. Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med. 2014;371:918–31.
33. McLellan JS, Ray WC, Peeples ME. Structure and function of RSV surface glycoproteins. Curr Top Microbiol Immunol. 2013;372:83–104.
34. The Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics. 1998;102:531–7.
35. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med. 2013;368:1791–9.
36. Brady MT, Byington CL, Davies HD, et al. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134:415–20.
37. Geskey JM, Ceneviva GD, Brummel GL, Graff GR, Javier MC. Administration of the first dose of palivizumab immunoprophylaxis against respiratory syncytial virus in infants before hospital discharge: what is the evidence for its benefit? Clin Ther. 2004;26:2130–7.

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