Congenital Infections

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LEARNING OBJECTIVES

1. Given maternal and neonatal factors, design a pharmacologic regimen for the newborn with congenital syphilis or at risk of hepatitis B virus infection.
2. Analyze maternal and neonatal factors to implement an appropriate pharmacotherapeutic regimen for the neonate exposed to HIV.
3. Construct a treatment algorithm for managing congenital cytomegalovirus.
4. Evaluate maternal and neonatal factors to develop a treatment and monitoring plan for the infant born to a mother with possible or proven herpes simplex virus.

ABBREVIATIONS IN THIS CHAPTER

AAP	American Academy of Pediatrics
Anti-HBc	Antibody to hepatitis B core antigen
Anti-HBs	Antibody to hepatitis B surface antigen
ART	Antiretroviral therapy
ARV	Antiretroviral
CMV	Cytomegalovirus
HBeAg	Hepatitis B e-antigen
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HSV	Herpes simplex virus
NAT	Nucleic acid test
PJP	*Pneumocystis jirovecii* pneumonia (formerly *Pneumocystis carinii* pneumonia)
RPR	Rapid plasmin reagin (nontreponemal test)
SEM	Skin, eyes, and/or mouth
TORCH	*Toxoplasma gondii*, other viruses, rubella virus, cytomegalovirus, and herpes simplex virus
VDRL	Venereal disease research laboratory (nontreponemal test)

Table of other common abbreviations.

INTRODUCTION

Congenital infections in the neonate can lead to significant morbidity and mortality. The acronym "ToRCH," first described in 1971, included the perinatal infections *Toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), and herpes simplex virus (HSV) (Nahmias 1971). Since then, the "O" in "TORCH" has expanded to "Other" and includes hepatitis B virus (HBV), varicella zoster virus, and HIV, among others. Consistent with the original definition, though, is the recognition that these congenital infections must be diagnosed early to provide prevention and treatment strategies that improve the newborn's prognosis.

Transmission of congenital infections may occur in utero, peripartum, or after delivery, and clinical manifestations of the infection may vary depending on the time of transmission. Prenatal transmission occurs through the transplacental passage of organisms, and perinatal transmission occurs through contact with blood and vaginal secretions of the mother, whereas postnatal transmission may occur through exposure to breast milk or other body fluids.

Diagnosis should ideally begin with detection of the infection in the prospective mother before pregnancy. Preventive measures may reduce the likelihood of transmission in utero and during delivery. Routine prenatal care involves screening for many of the TORCH infections, providing obstetricians and neonatologists with early opportunities to reduce morbidity and mortality in the neonate. If a maternal history is incomplete and a TORCH infection is suspected, a prompt diagnostic workup, including maternal and neonatal testing, should be completed to allow for the most targeted treatment approach. Specifics related to more common congenital infections with targeted prevention or treatment strategies are discussed in this chapter, including congenital syphilis, HBV, HIV, CMV, and HSV.

CONGENITAL SYPHILIS

Despite effective treatment strategies, the WHO estimates that syphilis affects 1.86 million pregnancies worldwide (Gomez 2013). Congenital syphilis rates in the United States declined in the 1990s; however, rates began to increase again in the mid-2000s, correlating with increasing syphilis rates among women (CDC 2015b). Similarly, a small decline in syphilis rates occurred in the late 2000s; however, the incidence increased by 2014 to 11.6 cases per 100,000 live births, which was the highest rate reported since 2001. Risk factors associated with congenital syphilis include teenage mothers, insufficient prenatal care, illegal drug use, sexual promiscuity, other sexually transmitted infections, sexual contact with others with sexually transmitted infections, and living in areas with a low socioeconomic status. Although maternal treatment with penicillin is 98% effective at preventing transmission to the newborn (Alexander 1999), lack of appropriate prenatal care still contributes to the prevalence of this disease. Over 20% of U.S. congenital syphilis cases are associated with little to no prenatal care, causing this to remain a concern for neonatal clinical pharmacists.

Route of Infection

Syphilis is a type of sexually transmitted infection caused by the spirochete *Treponema pallidum*. Transmission to the mother may occur through direct contact with a spirochete-containing lesion or sexually. Transmission to the offspring usually occurs in utero. Syphilis in the mother is completely treatable, which means this congenital infection may be preventable with appropriate management.

Clinical Manifestations

Infections occurring in utero may result in stillbirth, hydrops fetalis, or preterm birth. However, almost 75% of live newborns remain asymptomatic at birth. Clinical manifestations may be present at birth or early (usually within the first 4–8 weeks of life and until 2 years of age) or may develop later (usually after 2 years of age) (Box 1). Late manifestations may occur in untreated newborns who are asymptomatic and never have any early clinical manifestations.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:
- General knowledge of the pharmacokinetic and pharmacodynamic changes in neonates and infants
- Drug knowledge of the mechanism of actions of pharmacologic agents used to treat bacterial and viral infections

Table of common pediatric laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:
- CDC. Recommendations for congenital syphilis.
- CDC. Recommendations for hepatitis B.
- DHHS. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. 2018.
- CDC. Recommendations for congenital cytomegalovirus.
- American Academy of Pediatrics. Recommendations for asymptomatic neonates born to mothers with active genital herpes lesions.

Box 1. Clinical Manifestations of Congenital Syphilis

Early
- Condyloma lata
- Edema (nephrotic syndrome)
- Hemolytic anemia
- Hepatosplenomegaly
- Hydrops fetalis
- Intrauterine growth restriction
- Jaundice (syphilitic hepatitis)
- Lymphadenopathy
- Mucocutaneous lesions
- Osteochondritis
- Pneumonia
- Premature birth
- Pseudoparalysis
- Rash
- Snuffles (syphilitic rhinitis)
- Stillbirth
- Thrombocytopenia

Late
- Anterior bowing of the shins
- Clutton's joints
- Eighth cranial nerve deafness
- Epilepsy
- Frontal bossing
- Higoumenakia sign
- Hutchinson teeth
- Hydrocephalus
- Intellectual disability
- Interstitial keratitis
- Mulberry molars
- Optic nerve atrophy
- Rhagades (perioral fissures)
- Saddle nose deformity

Information from: American Academy of Pediatrics (AAP). Syphilis. In: Kimberlin DW, Brady MT, Jackson MA, et al., eds. Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL: AAP, 2015:755-68.

Diagnosis

Routine screening, including serologic testing, should occur during the first prenatal visit (AAP 2015e; CDC 2015a). For women at high risk, further serologic screening should be done at 28 weeks' gestation and again at delivery. Screening should occur at delivery for all mothers who have received little to no prenatal care or when the mother's medical history cannot be obtained. For mothers treated for syphilis during pregnancy, follow-up serologic testing is needed to confirm the effectiveness of therapy.

The diagnosis of congenital syphilis is complicated because both maternal treponemal and nontreponemal immunoglobulin G (IgG) antibodies may cross the placenta. Treponemal antibodies are a direct result of infection and are thus highly specific for syphilis. Treponemal antibodies remain present for life even after treatment, however, so a nontreponemal test must be done afterward to differentiate between an active infection and simply a history of treated syphilis. Alternatively, nontreponemal tests result from biomarkers that are released during cellular damage from syphilis and other conditions and are thus highly sensitive for active infections. Their nonspecificity for syphilis may cause false-positive results, however, and a confirmatory treponemal test should be done. Several serologic tests fall into each category (Box 2).

If the mother has reactive treponemal and nontreponemal tests, the neonate should be evaluated with a quantitative nontreponemal serologic test (rapid plasma reagin [RPR] or venereal disease research laboratory [VDRL]), which must be obtained from the neonate's serum (AAP 2015e; CDC 2015a). Umbilical cord blood cannot be used because it may be contaminated with maternal blood, leading to a false-positive result, or alternatively, Wharton's jelly in the umbilical cord may lead to a false-negative result. In addition, neonates born to mothers with a known history of syphilis should be examined for any early clinical manifestations. Pathologic examination of the placenta or umbilical cord should be considered, and darkfield microscopic examination or PCR testing of suspicious lesions or body fluids should also be done. For stillborn infants, diagnosis may be aided by a skeletal survey revealing characteristic osseous lesions of congenital syphilis.

Additional workup for congenital syphilis may include liver function tests, CBC, Plt, long-bone and chest radiography, and an ophthalmologic examination. A CSF analysis to evaluate for neurosyphilis should be completed when the mother was not adequately treated, the mother received adequate treatment less than 4 weeks before delivery, or the neonate has an abnormal physical examination.

Treatment

Because of the complexity of interpreting diagnostic results, treatment decisions for the neonate must be based on the following information: (1) identification of maternal syphilis; (2) determination of adequacy of maternal treatment; (3) clinical, laboratory, or radiographic evidence of syphilis in the neonate; and (4) comparison of maternal and neonatal nontreponemal serologic titers using the same test around the time of delivery (AAP 2015e; CDC 2015a). Determining the adequacy of maternal treatment includes a history of an appropriate treatment course in addition to a sustained 4-fold decrease in nontreponemal titer (e.g., from 1:32 to 1:8). Alternatively, a 4-fold increase in nontreponemal titer (e.g., from 1:8 to 1:32) indicates reinfection or relapse.

Treatment of neonates born to mothers with syphilis includes four distinct scenarios: (1) proven or highly probable congenital syphilis, (2) possible congenital syphilis, (3) congenital syphilis less likely, and (4) congenital syphilis unlikely (AAP 2015e; CDC 2015a). The CDC and the American Academy of Pediatrics (AAP) *Red Book* on infectious diseases provide similar recommendations for managing these scenarios. The treatment algorithm and recommended regimens can be found in Figure 1.

Syphilis has remained susceptible to penicillin therapy, and all congenital syphilis treatment strategies include some formulation of penicillin: aqueous penicillin G, procaine penicillin G, or benzathine penicillin G. The aqueous formulation is given intravenously, and the procaine and benzathine formulations are given intramuscularly. Adverse events associated with penicillin administration include localized phlebitis and thrombophlebitis, rash, neutropenia, anaphylaxis and hypersensitivity reactions, Jarisch-Herxheimer reaction, and injection-site reactions. High doses have been associated with drowsiness, seizures, and other neurologic abnormalities. Monitoring values for penicillin include periodic renal and hematologic function tests with prolonged therapy and observation for injection-site or hypersensitivity reactions. If an infant has an allergic reaction during treatment, a desensitization protocol should be followed because data are currently insufficient to support treatment of congenital syphilis with other agents (CDC 2015a). In addition, if more than a day of therapy is missed or delayed, the entire treatment should
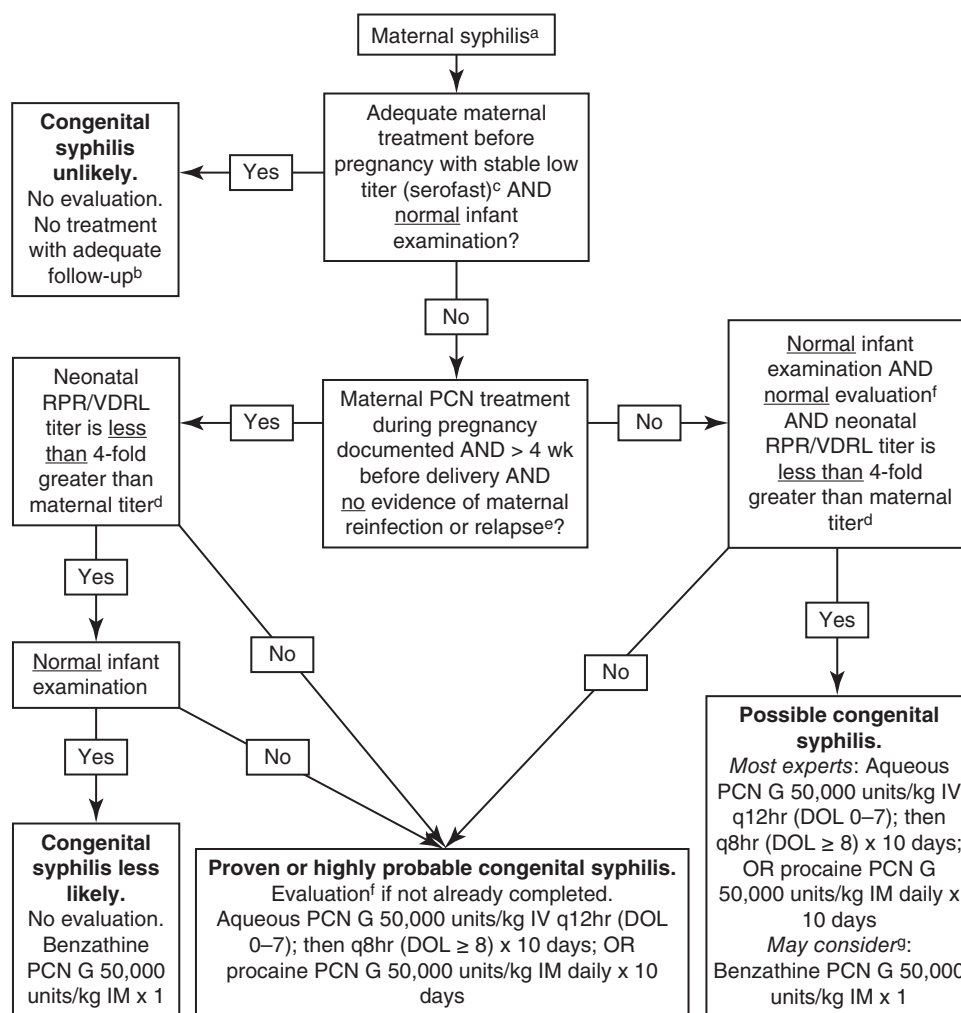

Box 2. Serologic Tests for Syphilis

Nontreponemal tests
- Rapid plasmin reagin (RPR)
- Venereal disease research laboratory (VDRL)

Treponemal tests
- Chemoluminescence immunoassay (CIA)
- Enzyme immunoassays (EIAs)
- Fluorescent treponemal antibody absorption (FTA-ABS)
- Microhemagglutination assay (MHA-TP)
- *T. pallidum* particle agglutination assay (TP-PA)

Information from: American Academy of Pediatrics (AAP). Syphilis. In: Kimberlin DW, Brady MT, Jackson MA, et al., Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL: AAP, 2015:755-68.

Figure 1. Evaluation and treatment of infants born to mothers with syphilis.

Maternal syphilis[a]

Adequate maternal treatment before pregnancy with stable low titer (serofast)[c] AND <u>normal</u> infant examination?

Congenital syphilis unlikely. No evaluation. No treatment with adequate follow-up[b] ← Yes

No

Maternal PCN treatment during pregnancy documented AND > 4 wk before delivery AND <u>no</u> evidence of maternal reinfection or relapse[e]?

Yes → Neonatal RPR/VDRL titer is <u>less than</u> 4-fold greater than maternal titer[d]

No → <u>Normal</u> infant examination AND <u>normal</u> evaluation[f] AND neonatal RPR/VDRL titer is <u>less than</u> 4-fold greater than maternal titer[d]

Neonatal RPR/VDRL titer is less than 4-fold greater than maternal titer[d] → Yes → <u>Normal</u> infant examination

No

Normal infant examination → Yes → **Congenital syphilis less likely.** No evaluation. Benzathine PCN G 50,000 units/kg IM x 1

No

Proven or highly probable congenital syphilis. Evaluation[f] if not already completed. Aqueous PCN G 50,000 units/kg IV q12hr (DOL 0–7); then q8hr (DOL ≥ 8) x 10 days; OR procaine PCN G 50,000 units/kg IM daily x 10 days

Yes → **Possible congenital syphilis.** *Most experts*: Aqueous PCN G 50,000 units/kg IV q12hr (DOL 0–7); then q8hr (DOL ≥ 8) x 10 days; OR procaine PCN G 50,000 units/kg IM daily x 10 days. *May consider[g]*: Benzathine PCN G 50,000 units/kg IM x 1

[a]Requires a reactive nontreponemal test with a confirmatory reactive treponemal test.

[b]Some experts would give benzathine penicillin G 50,000 units/kg IM as a single dose in patients when follow-up cannot be guaranteed.

[c]Women who maintain a VDRL titer of ≤ 1:2 or an RPR of ≤ 1:4 beyond 1 yr after successful treatment are considered serofast.

[d]Maternal and neonatal titers should be with the same type of nontreponemal test. For example, 4-fold greater would be a maternal titer of 1:4 with a neonatal titer ≥ 1:16.

[e]Relapse or reinfection would be indicated by a ≥ 4-fold increase in maternal titers with the same type of nontreponemal test.

[f]Evaluation includes a CBC and Plt; CSF examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (e.g., chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, auditory brain stem response).

[g]Benzathine penicillin G 50,000 units/kg IM as a single dose should <u>only</u> be considered if the infant is fully evaluated, full evaluation is normal, CSF analysis is interpretable and normal, and follow-up can be guaranteed.

DOL = day of life; IM = intramuscular(ly); IV = intravenous(ly); PCN = penicillin; q = every; RPR = rapid plasmin reagin (nontreponemal test); VDRL = venereal disease research laboratory (nontreponemal test).

Information from: American Academy of Pediatrics (AAP). Syphilis. In: Kimberlin DW, Brady MT, Jackson MA, et al., eds. Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL: AAP, 2015:755-68; and CDC. Congenital Syphilis. 2015.

be restarted. A full 10-day course of penicillin should be given when indicated, even if ampicillin was initiated at birth for possible sepsis.

Neonates born to mothers with a history of syphilis should receive follow-up examinations and serologic testing with a nontreponemal test every 2–3 months until the test becomes nonreactive or the nontreponemal titer decreases by 4-fold (AAP 2015e; CDC 2015a). Neonates in the congenital syphilis less-likely and unlikely groups should usually have a decline in their titers by 3 months of age with a nonreactive result by 6 months of age, indicating the original result occurred because of a passive transfer of maternal IgG antibodies. If the infant was nonreactive at birth with a confirmatory nonreactive result at 3 months or was initially reactive but nonreactive by 6 months, no further testing is warranted. If the infant is still reactive at 6 months, this indicates likely infection, and the infant should be treated. If treated infants are still reactive at 6–12 months of age, a full CSF analysis should be done, and retreatment with a 10-day course of penicillin is likely needed. Any infant with an abnormal CSF analysis at birth or later should have repeated CSF testing every 6 months until testing is normal. Treponemal tests should not be used in place of nontreponemal tests because of the potential for passive transfer of maternal IgG antibodies, which may persist until 15 months of age. A reactive treponemal test at 18 months of age or later is confirmatory for congenital syphilis.

PERINATAL HBV

Over 250 million people worldwide are estimated to be living with HBV infection (WHO 2017a). The highest prevalence is in the African and Western Pacific regions of the world. In addition, most infections in these areas occur during the perinatal period or in early childhood (Alter 2003). In the United States, most new infections and acute disease occur in adults; however, chronic infection has a higher incidence when infection occurs in infancy or early childhood (Table 1). Chronic infection increases the risk of cirrhosis and hepatocellular carcinoma. A vaccine against HBV has been available since 1982. The Advisory Committee on Immunization Practices has published a comprehensive immunization strategy with a goal of eliminating HBV in the United States. From 1990 to 2004, the incidence of acute HBV in the United States decreased by 75%, which represented a 94% decline in children and young adolescents. However, lack of adequate prenatal care and parental decisions not to vaccinate continue to contribute to HBV exposure among newborns. Because of the need for prompt intervention, rapid assessments of maternal HBV status and neonatal factors should be used by the neonatal clinical pharmacist to determine appropriate management.

Route of Infection

Although HBV is a bloodborne pathogen, it also spreads through other body fluids, including saliva, menstrual, vaginal, and seminal fluids. Most maternal transmission of HBV occurs perinatally, with prenatal transmission accounting for only 2%–4% of all cases (Bleich 2014). Transmission during delivery occurs through exposure to blood and vaginal secretions during labor, whereas transmission in utero is postulated to be caused by transplacental transfer, inhalation/ingestion of infected amniotic fluid, or fetal exposure to maternal blood during procedures such as amniocentesis. The maternal transmission rate in untreated newborns is 10%–40% in hepatitis B surface antigen (HBsAg)-positive/hepatitis B e-antigen (HBeAg)–negative mothers compared with 70%–90% in HBsAg-positive/HBeAg-positive mothers (Tran 2012). Children who are infected perinatally may have a high viral burden for the first few years of life and be highly contagious during that time.

Clinical Manifestations

Because HBV transmission often occurs perinatally, infants are usually asymptomatic at birth and during the neonatal period. Children may develop mildly increased ALT concentrations with minimal to mild histologic abnormalities of the liver starting at 2–6 months of age. Evidence of clinical hepatitis, which includes jaundice, feeding intolerance, anorexia, vomiting, and malaise, is age-dependent: less than 1% of infants, 5%–15% of children 1–5 years, and 30%–50% of children older than 5 years (AAP 2015b). Long-term clinical manifestations occur as a result of the high incidence of chronic HBV in infants who acquire HBV perinatally, leading to an increased lifetime risk of cirrhosis and hepatocellular carcinoma. These include extrahepatic manifestations such as arthralgia, arthritis, macular rashes, thrombocytopenia, polyarteritis nodosa, glomerulonephritis, and papular acrodermatitis (Gianotti-Crosti syndrome).

Diagnosis

Hepatitis as a clinical diagnosis cannot differentiate HBV from other viruses. As such, various blood tests are used to diagnose HBV infection. These tests also distinguish acute and chronic infections. Laboratory diagnosis of HBV infection focuses on detecting HBsAg. Routine screening of expectant

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Table 1. Chronic HBV Infection by Age

Age at Infection	% Likelihood of Chronic HBV Infection
Infants in first year of life	80–90
Children 1–6 yr	30–50
Adults	< 5

HBV = hepatitis B virus.
Information from: WHO. Hepatitis B: Fact Sheet. 2017.

mothers for HBsAg should occur during the first prenatal visit (Mast 2005). For mothers with minimal to no prenatal care or when medical records are unavailable, HBsAg should be obtained at the time of delivery. For mothers who are HBsAg positive, further testing for HBV DNA should be completed.

Acute HBV infection is characterized by the presence of HBsAg and immunoglobulin M (IgM) antibody to the hepatitis B core antigen. Because HBeAg is usually a marker of high levels of replication of the virus, it is usually found during the initial infection phase. As noted previously, HBeAg indicates a high degree of communicability and increased likelihood of maternal-to-neonatal transmission. Chronic HBV infection is characterized by the presence of HBsAg for at least 6 months (with or without concurrent HBeAg). Assessment of HBsAg, HBs antibody, total antibody to hepatitis B core antigen (anti-HBc), and IgM anti-HBc can help determine HBV infection (Table 2).

Treatment

No specific treatment exists for acute HBV infection. Several medications have been FDA approved for managing chronic HBV in children. These include interferon for children 1 year and older, lamivudine for children 3 months and older, adefovir for children 12 years and older, telbivudine for children 16 years and older, and entecavir for children 16 years and older. There are also current studies of pediatric patients using telbivudine, tenofovir, pegylated interferon, and entecavir. Online guidelines describe the treatment of children with HBV and HIV coinfection.

The primary management strategy in newborns focuses on preventing transmission from the mother during the perinatal period. Ideally, the maternal HBV status is known before delivery. However, when maternal HBV status is unknown, prompt testing for maternal status should be completed to guide management. Immunoprophylaxis of HBV after birth includes the administration of single-antigen HBV vaccine (Recombivax-HB 5 mcg/0.5 mL or Engerix-B 10 mcg/0.5 mL) as well as hepatitis B immune globulin (HBIG) 0.5 mL for high-risk scenarios. Combination vaccines may be used in infants older than 6 weeks. Recommendations from the CDC Advisory Committee on Immunization Practices for treating neonates on the basis of maternal HBV status can be found in Figure 2.

Both the HBV vaccine and HBIG are given intramuscularly. Adverse reactions associated with the HBV vaccine and HBIG include flushing, pain, headache, drowsiness, fatigue, irritability, malaise, rash, decreased appetite, diarrhea, vomiting, and injection-site reactions. Monitoring values are usually limited to laboratory values associated with maternal HBV exposure, including obtaining HBsAg and antibody to HBsAg

Table 2. Interpretation of Serologic Test Results for HBV Infection

HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	HBV DNA	How to Interpret
−	−	−	−	−	Never infected with HBV
+	−	−	−	±	Early acute HBV infection; transient for up to 18 days after vaccination
+	+	+	−	+	Acute HBV infection
−	+	+	±	±	Acute resolving HBV infection
−	+	−	+	−	Recovered from past HBV infection and now immune
+	+	−	−	+	Chronic HBV infection
−	+	−	−	±	False-positive (i.e., susceptible) OR past infection OR "low-level" chronic HBV infection OR passive transfer of anti-HBc to infant from HBsAg-positive mother
−	−	−	+	−	Immune if anti-HBs concentration ≥ 10 mIU/mL after completion of vaccine series OR passive transfer after HBIG administration

Anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to HBsAg; HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen.

Information from: Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(RR1):1-31.
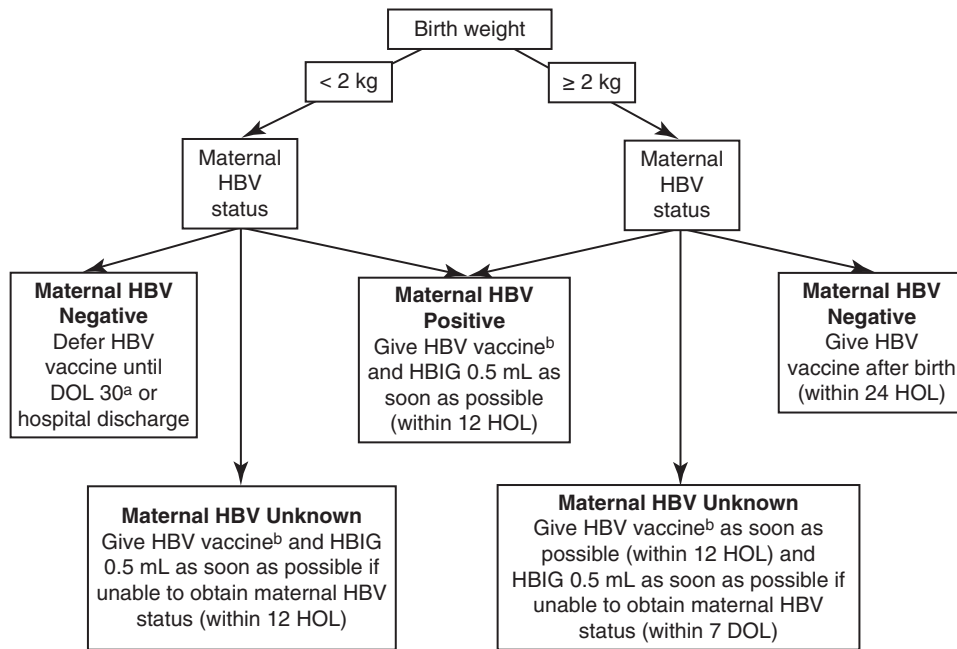
Figure 2. Evaluation and treatment of infants born, according to maternal HBV status.

[a]Preterm infants weighing < 2 kg at birth have a decreased response to HBV vaccine. However, data support that all medically stable preterm infants regardless of initial gestational age or birth weight have a response to vaccination at 1 mo of age similar to full-term infants.

[b]If HBV vaccine is given to newborns weighing < 2 kg at birth due to maternal HBV-positive or unknown status, this does not count toward the primary vaccination series because of decreased response to HBV vaccine (see footnote a).

DOL = days of life; HBIG = hepatitis B immune globulin; HBV = hepatitis B virus; HOL = hours of life.

Information from: Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(RR1):1-31.

(anti-HBs) at 9–18 months of age or 1–2 months after completing the HBV vaccination series.

HIV-EXPOSED NEONATES

Around 36.7 million people worldwide are living with HIV, of which an estimated 1.8 million were newly infected in 2016 (WHO 2017b). Because HIV attacks and destroys CD4 T lymphocytes, the immune system is weakened. Untreated HIV may lead to AIDS, placing patients at risk of opportunistic infections and cancers. Mortality secondary to HIV-related causes remains a high concern, with over 1 million deaths in 2016. Mortality is especially high for infants with untreated HIV infection in the first year of life. Although HIV has no cure, antiretroviral therapy (ART) has significantly improved morbidity and mortality. This is especially true for the role of appropriate screening and use of ART for preventing mother-to-child HIV transmission. An estimated 8700 women living with HIV (95% CI, 8400−8800) give birth annually in the United States (Whitmore 2011). The risk of infection without interventions to prevent mother-to-child transmission is estimated to

be 25% (AAP 2015d). However, when all the appropriate recommendations are followed, the likelihood of perinatal transmission has been reduced to 2% or less (Townsend 2014). The CDC has a goal of completely eliminating perinatal HIV transmission in the United States; to accomplish this, the Department of Health and Human Services issued recommendations for the management of HIV in the prenatal, perinatal, and postnatal periods. The pharmacist can play a key role during each phase by selecting appropriate and timely ART for the mother and child.

Route of Infection

HIV is part of the genus *Lentivirus* within the family of Retroviridae and is classified as HIV-1 or HIV-2. HIV consists of two identical single-stranded RNA molecules within the core of the virus particle. Proviral DNA is generated by reverse transcription of the viral RNA genome into DNA, RNA degradation, and integration of the double-stranded HIV DNA into the human genome.

HIV is transmitted through body fluids, including blood, semen, and vaginal secretions. Transmission from mother to

child may occur during pregnancy, perinatally, or even postnatally through breast milk. Transmission during pregnancy has been shown as early as 12 weeks' gestation; however, over 90% of prenatal transmission occurs during the third trimester, usually during labor and delivery.

Clinical Manifestations

Perinatal HIV transmission is divided into two categories before progression to AIDS: early and late. Early progression has a median onset of 4 months, and late progression has a median onset of 6 years of age. The usual age of symptom onset without treatment is 12–18 months, with 20%–30% of perinatal infections classified as early progression (HHS 2017; AAP 2015d). The common presenting symptom of early progression is usually a more severe diagnosis such as *Pneumocystis jirovecii* pneumonia (PJP; formerly *Pneumocystis carinii* pneumonia) or encephalopathy, and early progression is associated with a worse prognosis than late progression. Early ART and PJP prophylaxis can greatly improve outcomes in these patients; in fact, some patients with early ART have prolonged control of their HIV viral load, seroreversion, and preserved immune function. A study in California reviewed 205 children with perinatal HIV transmission up to age 3 years or HIV-related death (Berk 2005). The authors found that children who received early ART with triple-drug therapy were less likely to present with a category C diagnosis (Table 3). The median age to a category C diagnosis was 4 months without treatment, 8 months with only PJP prophylaxis, and 16 months with mono or dual ART regardless of PJP prophylaxis. This is contrasted with no children in the triple ART group developing a category C diagnosis before age

3 years. Studies like this support current recommendations for prompt and early management to improve outcomes.

In addition, normal CD4 T-lymphocyte values vary depending on age. Many practitioners are familiar with the thresholds for risk of opportunistic infections in adult patients with HIV; however, pediatric practitioners should be aware that normal CD4 counts are higher in infants and young children. For example, a CD4 count of less than 200 cells/mm^3 in adults correlates with a CD4 count of less than 750 cells/mm^3 (or less than 20%) in infants and of less than 500 cells/mm^3 (or less than 14%) in children 1–5 years of age.

Diagnosis

The three types of HIV tests are antibody, combination antibody/antigen, and nucleic acid tests (NATs). The window when HIV can first be detected after infection varies for each test. Antibody tests detect HIV antibodies in the blood or fluids from the mouth, and the window is usually 3–12 weeks from the time of infection. Combination tests detect both HIV antibodies and antigens in the blood and thus have a shorter window of 2–6 weeks. Nucleic acid tests detect HIV in the blood and have the shortest window of 7–28 days after infection; however, NATs are also the most expensive tests and are not routinely used. Most "rapid" HIV tests are antibody tests, though there is a "rapid" antibody/antigen test as well. If a patient tests positive for a rapid HIV test, confirmatory testing should be done to ensure the correct diagnosis.

Ideally, maternal HIV status is known before conception so that appropriate management strategies can be determined before pregnancy. Routine HIV testing is also recommended for all pregnant women early in their prenatal care, with additional testing during the third trimester for mothers at high risk of developing HIV. Universal HIV testing is recommended as the standard of care for all pregnant women in the United States by AAP, the CDC, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force. If HIV status is unknown, expedited HIV testing should occur during labor or delivery to help determine intra- and postpartum management. If a mother's rapid HIV test is positive, follow-up testing for the mother is recommended to confirm her diagnosis. However, treatment of the infant would follow the presumption that the mother is HIV positive until proved otherwise. Recommendations for diagnostic testing of HIV-exposed neonates can be found in Table 4.

Treatment

The first successful trial using ART to prevent mother-to-child HIV transmission included the use of single-drug zidovudine prophylaxis (Connor 1994). This treatment has since evolved to include recommendations for triple-drug therapy during pregnancy, zidovudine perinatally in high-risk patients, and the provision of ART to the newborn. The complete online

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Table 3. Examples of Category C (severely symptomatic) Diagnoses for HIV Infection[a]

Infectious	Noninfectious
Candida	Encephalopathy
CMV	Immunoblastic lymphoma
Mycobacterium avium	Progressive multifocal
PJP	leukoencephalopathy
Recurrent bacterial infections	Wasting

[a]For a complete list of all clinical categories of children < 13 yr with HIV infection, see: Centers for Disease Control and Prevention (CDC). 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Recomm Rep 1994;43(RR12):1-19.

CMV = cytomegalovirus; PJP = *P. jirovecii* pneumonia.

Information from: Berk DR, Falkovitz-Halpern MS, Hill DW, et al. Temporal trends in early clinical manifestations of perinatal HIV infection in a population-based cohort. JAMA 2005;293:2221-31.

Table 4. Selected Recommendations for Managing HIV in Pregnancy and for Neonates Born to Mothers with HIV

Selected Perinatal Recommendations

Intrapartum Care	• Continue maternal antepartum combination ART during labor and before scheduled cesarean delivery
	• IV zidovudine use is based on HIV RNA during late pregnancy/near delivery:
	  ◦ HIV RNA > 1000 copies/mL (or unknown HIV): administer IV zidovudine
	  ◦ HIV RNA 50-999 copies/mL: may consider IV zidovudine
	  ◦ HIV RNA < 50 copies/mL and good adherence to ART: not required
	  ◦ Zidovudine resistance does not affect the indications for use
	• Scheduled cesarean delivery at 38 wk gestation is recommended for women who have HIV RNA > 1000 copies/mL near delivery
	  ◦ Not routinely recommended in women adherent to ART with HIV RNA ≤ 1000 copies/mL
	• Women in labor with unknown HIV status should have expedited antigen/antibody HIV testing
	  ◦ If the results are positive, an HIV-1/HIV-2 antibody differentiation test and an HIV-1 RNA assay should be done as soon as possible
	  ◦ Maternal (IV zidovudine)/infant (combination ARV prophylaxis) ARV drugs should be initiated pending results of the differentiation test (see "Postnatal" in the section that follows for infant treatment)
	  ◦ If the maternal HIV differentiation test and HIV RNA test are negative, maternal and infant ARV drugs should be discontinued
	• Women with positive initial testing should not start breastfeeding until HIV infection is definitively ruled out

Selected Postnatal Recommendations

Infant ARV Prophylaxis	• All newborns with perinatal HIV exposure should receive postpartum ARV drugs as soon after birth as possible, preferably within 6–12 hr of delivery • Detailed recommendations for postnatal ARV management according to risk of HIV infection can be found in Table 5 • Only zidovudine, lamivudine, and nevirapine are recommended for any indication in premature newborns because of a lack of dosing and safety data for other agents
Postpartum Management	• The mother/caregiver should be given ARV medications before hospital discharge for her newborn to take at home • Breastfeeding is not recommended for women with confirmed or presumed HIV infection in the United States

Diagnosis of HIV Infection in Infants and Children	• Virologic assays (i.e., HIV RNA and HIV DNA NATs) must be used to diagnose HIV infection in infants and children < 18 mo. Do not use HIV antibody tests
	• RNA or DNA PCR testing is recommended equally for most patients; however, RNA PCR is recommended for known maternal non–subtype B virus
	• Virologic diagnostic testing is recommended for perinatally HIV-exposed infants at the following ages:
	  ◦ 14–21 days
	  ◦ 1–2 mo
	  ◦ 4–6 mo
	• Higher-risk infants may be considered for additional virologic diagnostic testing at birth and 2–4 wk after completing ARV prophylaxis
	• A positive virologic test should be confirmed as soon as possible by a repeat virologic test
	• Non-breastfed infants are considered to have definitive exclusion of HIV infection after ≥ 2 negative virologic tests, with one obtained at age ≥ 1 mo and one at age ≥ 4 mo, or two negative HIV antibody tests from separate specimens obtained at age ≥ 6 mo

ART = antiretroviral therapy; ARV = antiretroviral; IV = intravenous(ly); NAT = nucleic acid test.

Information from: NIH. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

Table 5. Newborn ARV Management According to Risk of HIV Infection

Risk of Perinatal HIV Transmission	Description	Neonatal ARV Management[a,b]
Low risk	• Mothers with adherence to ART during pregnancy with viral suppression near delivery	• 4 wk of zidovudine prophylaxis
High risk	• Mothers who did not receive antepartum ARV drugs • Mothers receiving ARV drugs who have a detectable viral load near delivery • Mothers with acute or primary HIV infection during pregnancy or breastfeeding[c]	• Combination ARV prophylaxis with 6 wk of zidovudine and three doses of nevirapine (*prophylaxis* dosage) OR • Empiric HIV therapy with 6 wk of zidovudine in addition to lamivudine and nevirapine (*treatment* dosage)[d]
Presumed exposure	• Mothers with unknown HIV status who test positive at delivery or postpartum • Newborn with a positive HIV antibody test	• ARV management as described in the "High risk" section within table • ARV management should be discontinued if supplemental testing is negative for maternal HIV
Confirmed HIV[e]	• Newborn with a confirmed positive HIV virologic test/NAT	• Three-drug combination ARV regimen at *treatment* dosage

[a]ARV drugs should be initiated as close to the time of birth as possible, preferably within 6–12 hr of delivery.

[b]See Table 6 for dosing specifics.

[c]Most experts would opt to administer empiric HIV therapy to infants with acute HIV during pregnancy because of the high risk of in utero infection. If acute HIV is diagnosed during breastfeeding, the mother should stop breastfeeding.

[d]Optimal empiric HIV therapy duration in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 wk of combination therapy; others opt to discontinue nevirapine and/or lamivudine after the return of negative newborn testing. Zidovudine should be continued for 6 wk.

[e]Most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing.

Information from: NIH. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

NIH recommendations are summarized in Table 4, Table 5, and Table 6. In addition, a federally funded service known as the National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation to providers and serves as an expert resource for individual cases.

The NICHD-HPTN 040/PACTG 1043 trial is currently the only randomized controlled trial of combination antiretroviral (ARV) prophylaxis for high-risk infants (Nielsen-Saines 2012). This study analyzed 1746 neonates born to mothers with HIV who did not receive ART during pregnancy. Newborns received 6 weeks of zidovudine, 6 weeks of zidovudine with three doses of nevirapine as described in Table 5, or 6 weeks of zidovudine with 2 weeks of lamivudine/nelfinavir. The authors found that the risk of intrapartum transmission was significantly lower with both the two- and three-drug regimens than with zidovudine alone (2.2% and 2.5% vs. 4.9%, respectively; p=0.046); however, the three-drug regimen was associated with higher neutropenia rates than the two-drug regimen (27.5% vs. 15%, p<0.0001). Although other observational studies have tried to analyze combination ARV prophylaxis, either as a comparison to zidovudine monotherapy or between different combination ARV prophylaxis regimens, interpretation of these studies is complicated by several variabilities: definition of combination ARV prophylaxis, determination of ARV dosing, and heterogeneous combination regimens. As such, variability still exists regarding the preference for two- or three-drug regimens in treating high-risk HIV-exposed newborns.

As mentioned earlier, the most-used ARV drugs in infants include zidovudine, nevirapine, and lamivudine. Of these, only zidovudine is available intravenously, whereas all three are available as oral liquids. Adverse events associated with zidovudine in neonates and children include anemia, granulocytopenia, neutropenia, thrombocytopenia, malaise, irritability, rash, diarrhea, abdominal pain, anorexia, hematuria, hepatomegaly, cough, and fever. Nevirapine-related adverse reactions include neutropenia, fatigue, headache, rash, diarrhea, abdominal pain, hepatic disease, and fever. Similarly, adverse reactions associated with lamivudine include anemia, neutropenia, thrombocytopenia, fatigue, headache, irritability,

Table 6. Newborn ARV Dosing Recommendations

Drug	Dosing

Zidovudine	≥ 35 wk gestation:
	• 0 to 4−6 wk:
	  ○ 4 mg/kg/dose enterally q12hr
	  ○ 3 mg/kg/dose IV q12hr
	30 to 34 + 6 wk gestation:
	• 0−2 wk:
	  ○ 2 mg/kg/dose enterally q12hr
	  ○ 1.5 mg/kg/dose IV q12hr
	• 2 to 4−6 wk:
	  ○ 3 mg/kg/dose enterally q12hr
	  ○ 2.25 mg/kg/dose IV q12hr
	< 30 wk gestation:
	• 0−4 wk:
	  ○ 2 mg/kg/dose enterally q12hr
	  ○ 1.5 mg/kg/dose IV q12hr
	• 4−6 wk:
	  ○ 3 mg/kg/dose enterally q12hr
	  ○ 2.25 mg/kg/dose IV q12hr

Nevirapine[a,b] (*prophylaxis* dosage)	Three enteral doses per course:
	• Doses:
	  ○ Birth weight > 2 kg: 12 mg x 3 doses
	  ○ Birth weight 1.5−2 kg: 8 mg x 3 doses
	  ○ Birth weight < 1.5 kg: No definitive recommendation
	• Timing of doses:
	  ○ First dose: Within 0−48 hr
	  ○ Second dose: 48 hr after the first dose
	  ○ Third dose: 96 hr after the second dose

Nevirapine[a,b] (*treatment* dosage)	≥ 37 wk gestation:
	• 0−6 wk: 6 mg/kg/dose enterally q12hr
	34 to 36 + 6 wk gestation:
	  ○ 0−1 wk: 4 mg/kg/dose enterally q12hr
	  ○ 1−6 wk: 6 mg/kg/dose enterally q12hr
	< 34 wk gestation: No definitive recommendation

Lamivudine[a,b]	≥ 32 wk gestation: • 0−4 wk: 2 mg/kg/dose enterally q12hr • 4−6 wk: 4 mg/kg/dose enterally q12hr < 32 wk gestation: No definitive recommendation

[a]Lamivudine and nevirapine have no IV formulation.

[b]For dosing recommendation for newborns below the gestational age or weight recommendations provided, call the National Perinatal HIV Hotline (1-888-448-8765) for assistance.

hr = hour; q = every

Information from: NIH. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

diarrhea, abdominal pain, pancreatitis, vomiting, increased liver function tests, myalgia, cough, and fever. Monitoring values include routine HIV laboratory tests, as mentioned in Table 4; CBC with differential; liver function tests; BUN; SCr; electrolytes; and glucose.

Since recommendations in the past several years have allowed for presumptive exclusion of HIV infection in exposed newborns by 4 weeks of age, use of sulfamethoxazole/trimethoprim for PJP prophylaxis in HIV-exposed newborns has greatly decreased. Infection with HIV can presumptively be excluded in non-breastfed infants with two or more negative virologic tests (i.e., negative RNA or DNA NAT) at age 14 days and older and at age 4 weeks and older, one negative virologic test at age 8 weeks and older, or one negative HIV antibody test at age 6 months and older. Sulfamethoxazole/trimethoprim should be initiated at 4−6 weeks of age in HIV-exposed newborns without adequate testing for presumptive exclusion or in those with confirmed HIV infection at a dose of 150 mg of trimethoprim/m^2/day or 5−10 mg of trimethoprim/kg/day (maximum 320 mg of trimethoprim) for 3−7 days per week. Doses should be reduced for impaired renal function. Sulfamethoxazole/trimethoprim should not be initiated before 4 weeks of age, even in newborns with confirmed HIV infection, because of the risk of kernicterus, which outweighs the likelihood of PJP within the first month of life. Prophylaxis of PJP in infants with confirmed HIV should be continued until at least 1 year of age and then reassessed on the basis of CD4 count or percentage. Additional adverse reactions of sulfamethoxazole/trimethoprim include rash, hyperkalemia, hyponatremia, diarrhea, agranulocytosis, hemolysis with glucose-6-phosphate dehydrogenase deficiency, neutropenia, thrombocytopenia, cholestatic jaundice, hepatotoxicity, and renal toxicities. Infants receiving sulfamethoxazole/trimethoprim should have routine monitoring of their CBC, renal function tests, liver function tests, and bowel frequency.

CONGENITAL CMV

CMV is still underrecognized worldwide, even though it is the most common congenital viral infection in the United States and the most common infectious cause of sensorineural hearing loss and neurodevelopmental abnormalities in infants (Kenneson 2007). The prevalence of congenital CMV is estimated at 0.2%−2% of pregnancies (Manicklal 2013); however, there is still a low level of awareness by expectant parents and minimal routine testing during pregnancy. Several current and future interventions are promising to reduce the burden of congenital CMV, including effective preventive strategies, potential vaccines, antiviral therapies, and early intervention for children with sensorineural hearing loss. Because patient outcomes can improve with timely diagnosis and intervention, the pharmacist can play a major role in treating newborns with congenital CMV by optimizing treatment strategies.

Patient Care Scenario

A newborn, 39 weeks' gestation boy (birth weight 3.4 kg) was just admitted to your neonatal ICU for respiratory distress and suspected transient tachypnea of the newborn. Maternal history is scarce, and little to no prenatal care was obtained. Infectious diagnostic workups include an RPR, rapid HIV test, and HBsAg. What would be best to recommend for this newborn patient while awaiting maternal laboratory results?

ANSWER

Both the RPR and HIV tests are rapid assays, which should provide important information to the provider in a timely fashion regarding concerns for maternal syphilis and HIV infection. Depending on the laboratory, HBsAg may take longer to result. However, because this patient weighed more than 2 kg at birth, assessment for administering HBIG may be deferred for up to 7 days while results are pending.

If the RPR returns positive, treatment should be determined using the recommendations in Figure 1. Because this mother would not have been treated during pregnancy, this patient would be classified as having either "possible congenital syphilis" or "proven or highly probable congenital syphilis," depending on patient symptoms and diagnostic tests. The newborn should receive a full evaluation, including a CBC and Plt; CSF examination for cell count, protein, and quantitative VDRL test; and other tests as clinically indicated (e.g., chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brain stem response). Because the maternal test was an RPR, the newborn should also receive an RPR to compare titers. Treatment would include either aqueous penicillin G 50,000 units/kg/dose intravenously every 12 hours (day of life 0–7), followed by every 8 hours (day of life 8 or greater) × 10 days, or procaine penicillin G 50,000 units/kg/dose intramuscularly daily x 10 days.

If the rapid HIV test returns positive, maternal testing should be repeated to confirm the diagnosis. Until then, it should be assumed that maternal HIV is present and without adequate treatment. Breastfeeding should be withheld, and combination antiretroviral prophylaxis should be initiated. This includes 6 weeks of zidovudine 4 mg/kg/dose enterally every 12 hours plus either nevirapine 12 mg × three doses in the first week or nevirapine/lamivudine at treatment dosing (see Table 6). Virologic diagnostic testing should be done at 14–21 days of life, 1–2 months of life, and 4–6 months of life. Additional virologic diagnostic testing at birth should be considered and at 2–4 weeks after cessation of antiretroviral prophylaxis because of the high risk in this patient.

Hepatitis B virus vaccine should be given soon after birth regardless of maternal HBV status because this patient weighed more than 2 kg at birth. If maternal HBV status returns positive, HBIG 0.5 mL should be given as soon as possible and no more than 7 days after birth. Monitoring for the newborn should include HBsAg and anti-HBs at 9–18 months of age or 1–2 months after completing the HBV vaccination series.

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3. 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. MMWR Recomm Rep 2005;54:1-31.
4. NIH. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

Route of Infection

Human CMV is a member of the herpesvirus family (*Herpesviridae*), the beta-herpesvirus subfamily (*Betaherpesvirinae*), and the *Cytomegalovirus* genus. Human CMV is a very prevalent virus that usually leads to only mild disease in the general population. CMV is commonly acquired during early childhood through "saliva sharing," with an estimated infection rate of 30%–70% of young children and infants at child care centers (AAP 2015a). Vertical transmission of CMV from mother to infant may occur in utero through transplacental passage, perinatally by passage through the maternal genital tract, or postnatally through CMV-positive human milk or transfusions. From 0.5% to 1% of all live-born infants are infected in utero and excrete CMV at birth. In utero infection may occur during a maternal primary or nonprimary infection; nonprimary infection accounts for two-thirds of congenital CMV cases in the United States. More severe sequelae are associated with primary maternal infections which occur during the first half of pregnancy. However, damaging fetal infections after nonprimary maternal infection have also been reported, usually because the mother was infected with a different viral strain during pregnancy. This is generally contracted via young children at child care centers or infected sexual partners. The relative immunocompromised state of pregnancy may also lead to virus reactivation and asymptomatic viral excretion, which is an additional concern for congenital CMV in these cases.

Clinical Manifestations

Most congenital CMV cases are asymptomatic at birth. Only about 10% of newborns with congenital CMV have noticeable clinical findings, which includes intrauterine growth

restriction, jaundice, hepatosplenomegaly, conjugated/direct hyperbilirubinemia, thrombocytopenia with petechiae/purpura ("blueberry muffin" spots), microcephaly, small for gestational age, intracerebral calcifications, and chorioretinitis. Developmental delays may be noted in later infancy and early childhood. Overall mortality from congenital CMV occurs in only 0.3%–1% of all cases; however, the risk is higher at 3%–10% for symptomatic patients.

The most common clinical manifestation of congenital CMV is sensorineural hearing loss, occurring in up to 15% of newborns with asymptomatic congenital CMV at birth and up to 50% of those who initially present with symptoms. However, most cases are late onset (55% and 75% of symptomatic and asymptomatic cases, respectively) and cannot be detected within the first month of life. In addition, almost half of sensorineural hearing loss cases are progressive, leading to continued deterioration of hearing loss. As such, the universal newborn hearing screen provides inadequate screening for hearing loss, and regular evaluations should be done in patients with symptomatic and asymptomatic congenital CMV.

Critical illnesses in preterm infants who acquired CMV postnatally through maternal breast milk or CMV-positive blood donors have been reported. This includes hepatitis, interstitial pneumonia, thrombocytopenia, leukopenia, and viral sepsis syndrome. However, intrapartum and postnatal transmissions through human milk have not resulted in critical illness in term infants.

Diagnosis

CMV can be isolated in urine, oral fluids, peripheral blood leukocytes, human milk, semen, cervical secretions, and other body tissues and fluids. Diagnosing CMV disease can be difficult because of high prevalence, high rate of asymptomatic excretion, reactivation of infections, development of IgM CMV-specific antibodies after reactivation, reinfection with different strains of CMV, and concurrent infections with other organisms. When maternal CMV infection is suspected in a previously seronegative pregnant woman, diagnostic testing should include de novo CMV-specific IgG in the serum. When CMV status is unknown, both CMV IgG and IgM antibodies should be obtained to help determine whether the CMV infection is primary or secondary. Several assays that detect antibodies to CMV are available, including immunofluorescence, latex agglutination, and enzyme immunoassays.

A presumptive diagnosis of CMV infection can be made after the neonatal period when there is a 4-fold antibody titer increase in paired serum specimens or there is virus excretion. Recovery of CMV from a target organ also provides strong evidence that the disease is caused by CMV infection. Viral DNA can be detected by PCR assay in tissues and fluids such as blood, CSF, urine, and saliva. If congenital CMV is suspected, CMV PCR testing should occur within 2–4 weeks of birth. Although PCR testing may occur from a neonatal dried blood spot, this assessment is only specific and not sensitive for congenital CMV infection. A strongly positive CMV-specific IgM during early infancy suggests congenital CMV infection; however, false-positive results are commonly reported. Thus, serologic diagnosis still poses a challenge.

Treatment

Studies of maternal prevention and treatment of CMV infection have included vaccinations and administration of CMV hyperimmunoglobulin and antiviral medications. Phase II trials for vaccinations have shown almost 50% efficacy for preventing maternal seroconversion; however, immunization waned over time (Bernstein 2016; Pass 2009). Additional vaccination trials are ongoing (ClinicalTrials.gov trial registry NCT02594566, NCT02396134, NCT02506933, and NCT01877655). Because of insufficient data showing efficacy and safety, hyperimmunoglobulin and antiviral medications to prevent vertical transmission are not currently recommended. Current randomized controlled trials may provide further guidance on use of these medications in the future (ClinicalTrials.gov registry NCT01376778 for hyperimmunoglobulin and NCT02351102 for antiviral therapy). Hygienic and behavioral interventions have reduced maternal seroconversion in several studies; thus, pregnant mothers should be educated on these preventive measures.

In 2015, an informal International Congenital Cytomegalovirus Recommendations Group was organized to provide a consensus on CMV prevention, diagnosis, and treatment (Rawlinson 2017). This group's recommendations for treating and monitoring congenital CMV are found in Table 7.

Both intravenous ganciclovir and enteral valganciclovir have been studied for the treatment of congenital CMV. The initial study was conducted with intravenous ganciclovir (Whitley 1997). Later, a phase III randomized trial found that treatment may have prevented hearing deterioration at 6–12 months and potentially improved neurologic outcome but increased the risk of neutropenia (Oliver 2009; Kimberlin 2003). In addition, case reports and observational studies confirmed the initial findings of improved hearing outcomes with intravenous ganciclovir (Lackner 2009; Tanaka-Kitajima 2005; Michaels 2003; Nigro 1994). Early studies with enteral valganciclovir simply compared the pharmacokinetics with intravenous ganciclovir in neonates (Kimberlin 2008; Acosta 2007). These studies established the current equivalent dosing of intravenous ganciclovir 6 mg/kg/dose every 12 hours with enteral valganciclovir 16 mg/kg/dose every 12 hours. A recent randomized trial showed that neonates of at least 32 weeks' gestation and weighing at least 1800 g receiving 6 months of enteral valganciclovir had a 2- to 6-fold increased likelihood of improved total hearing at 24 months of age compared with those who received only 6 weeks of enteral valganciclovir followed by placebo (Kimberlin 2015). Valganciclovir was associated with a risk of neutropenia; however, no difference was found between the valganciclovir and

Table 7. Recommendations for Treatment and Monitoring of Congenital CMV Infection

Neonates indicated for treatment	• Moderately to severely symptomatic congenital CMV disease
Timing of initiation of treatment	• Within the first month of life
Drug	• Valganciclovir 16 mg/kg/dose enterally twice daily[a]
Treatment duration	• 6 mo
Monitoring	• ANC weekly x 6 wk; then at 8 wk; then monthly during therapy • Transaminases monthly during therapy
Follow-up	• Ophthalmologic examination early; then as recommended by the ophthalmologist • Audiologic testing q6mo for the first 3 yr of life; then annually through adolescence • Developmental assessments beginning at the first year of life on a case-by-case basis for children with symptomatic congenital CMV

[a]If unable to provide enterally, may give ganciclovir IV 6 mg/kg/dose q12hr.

ANC = absolute neutrophil count.

Information from: 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:e177-88.

placebo groups after the first 6 weeks of treatment (21% and 27%, respectively), indicating that drug-induced neutropenia is a larger concern early in treatment. The incidence of neutropenia with enteral valganciclovir (one-fifth) is lower overall than the reported rates with intravenous ganciclovir (two-thirds) (AAP 2015a). Therefore, the International Congenital Cytomegalovirus Recommendations Group recommends treatment with enteral valganciclovir 16 mg/kg/dose twice daily for 6 months for neonates with moderate to severe congenital CMV. Benefit in patients with mild disease is unclear. No specific recommendation was made by the group delineating differences in treating term and preterm neonates; however, the AAP provides further guidance.

Preterm infants with congenital CMV infection can have symptomatic, end-organ disease such as pneumonitis, hepatitis, or thrombocytopenia. Antiviral treatments have not been studied in this population; thus, recommendations are limited. The AAP states that a reasonable approach is to treat symptomatic premature neonates for 2 weeks with intravenous ganciclovir 6 mg/kg/dose twice daily and then to reassess responsiveness to therapy. If treatment seems to be beneficial according to clinical data, an additional 1–2 weeks of intravenous ganciclovir can be considered if symptoms do not resolve. Enteral valganciclovir is not mentioned as a potential treatment option in preterm neonates, and minimal data currently exists for neonates younger than 32 weeks' gestation.

In addition to neutropenia, adverse reactions of intravenous ganciclovir and enteral valganciclovir include chills, diarrhea, vomiting, anemia, leukopenia, thrombocytopenia, sepsis, increased SCr, increased transaminases, sepsis, and fever. Monitoring values should include a periodic CBC with differential, Plt, urinary output, SCr, ophthalmologic examinations, liver enzyme tests, and blood pressure.

NEONATAL HSV

The incidence of neonatal HSV is estimated at 1 in 3000 to 1 in 20,000 live births (AAP 2015c), which correlates with about 1500 cases annually in the United States. Although this number is low, the prevalence of genital herpes in the general adult population is high, with 20%–25% of the population infected with genital HSV-2. Although neonatal HSV infection may be uncommon, management of potential exposure is quite common. Neonatal HSV usually results as an HSV-2 infection, which is the primary type associated with genital infections. However, HSV-1 infections do occur and may still result in significant morbidity and mortality. Because many people living with HSV infection may be asymptomatic for long periods, expectant mothers may not know they are infected. Viral shedding can still occur in asymptomatic patients, thus making it difficult for providers to identify newborns at risk of HSV infection. The pharmacist can play a key role in helping providers determine the need for treatment of neonatal HSV infection, treatment duration, and long-term management.

Route of Infection

HSV is an enveloped, double-stranded DNA virus with two distinct types: HSV-1 and HSV-2. Infections with HSV-1 usually involve the face and skin of the upper body; however, an increasing number of genital herpes cases have occurred with HSV-1. Infections with HSV-2 usually involve the genitalia and skin below the waist in sexually active adolescents and adults. Both HSV-1 and HSV-2 cause disease in neonates.

Although transmission may occur at any stage, intrapartum transmission accounts for about 85% of cases (Kimberlin 2013). Intrapartum HSV transmission usually occurs through an infected maternal genital tract; however, it may also occur by an ascending infection through ruptured or apparently intact amniotic membranes. Postpartum and intrauterine infections represent only 10% and 5% of cases, respectively. Although uncommon, postnatal transmission usually occurs from a parent or caregiver by the mouth or hands.

The risk of mother-to-child transmission depends on whether it is a first or recurrent infection and whether the infection is primary or nonprimary. A primary infection occurs when HSV-1 or HSV-2 is acquired in an individual without antibodies to either type. A nonprimary infection occurs when an individual with HSV-1 antibodies acquires HSV-2 or vice versa. The risk of transmission is greatest in mothers who have a primary first-episode genital herpes infection at the time of delivery, with an estimated rate of 50%. This risk is reduced to 25% in nonprimary first-episode infections and is only 2% of recurrent infections in seropositive mothers (Brown 2003).

Clinical Manifestations

HSV infection in newborns is divided into three categories: disseminated disease, localized CNS disease with or without skin involvement, and disease localized to the skin, eyes, and/or mouth (SEM). Disseminated disease has multiorgan involvement, usually the liver and the lungs, and CNS involvement occurs in 60%–75% of cases. About 25% of neonatal HSV infection cases present as disseminated disease, 30% as localized CNS disease, and 45% as SEM disease. If left untreated, SEM disease progresses to disseminated disease in over 70% of cases (AAP 2015c).

Skin vesicles are extremely useful in diagnosing neonatal HSV disease; however, they are absent in almost 20% of SEM disease and in 30%–40% of disseminated or CNS disease (AAP 2015c). In the absence of skin lesions, disseminated HSV infection should be considered in neonates with sepsis syndrome, signs and symptoms of serious infections with negative bacterial culture results, severe liver dysfunction, consumptive coagulopathy, fever, vesicular rash, or abnormal CSF findings in the presence of seizures. Nonspecific presentations include poor feeding, lethargy, apnea, and respiratory distress.

Morbidity and mortality associated with neonatal HSV infection are high. One retrospective study found a 26% fatality rate in infants having a diagnosis of HSV infection (Lopez-Medina 2015). Estimates for mortality in disseminated disease are even higher at 50% and 70% of HSV-2 and HSV-1, respectively. Although HSV is normally thought to occur at 1–3 weeks of life, it may in fact present at any time between birth and 6 weeks. The authors found that most infants with HSV infection who died developed signs of infection and were hospitalized during the first week of life (median

4 days; range 0–23 days), indicating that HSV as a cause of infectious symptoms should remain as part of the differential diagnosis, even soon after birth. In addition, recurrence of skin lesions is common, occurring in an estimated 50% of surviving infants only 1–2 weeks after completing appropriate treatment with intravenous acyclovir. Long-term sequelae are more common in neonates presenting with seizures at or before initiation of therapy.

Diagnosis

Diagnosis of neonatal HSV disease is complicated, given that an estimated 75% of neonates with HSV infection are born to mothers with no history or findings of genital HSV infection either before or during delivery. All infants should be examined after delivery, and any skin vesicles should be noted. When HSV infection is suspected, several tests should be done: (1) viral cultures after 12–24 hours after birth from various sites, including the mouth, nasopharynx, conjunctivae, rectum, skin vesicles, urine, stool, blood, and CSF; HSV-PCR assays may also be done on specimens from these sites, if desired, (2) whole-blood HSV-PCR assays, (3) whole-blood ALT concentrations, and (4) HSV-PCR testing from the CSF.

Of importance, all recommended diagnostic workups should be completed to help identify neonatal HSV disease. Ideally, viral cultures should not be obtained before 12–24 hours after birth from the various surface sites because positive results may indicate contamination from intrapartum exposure and limit interpretation of results. Conversely, positive cultures taken more than 12–24 hours after birth show viral replication and thus neonatal HSV infection. Whole-blood assays help diagnose neonatal HSV disease, but these should not be done in lieu of surface cultures and CSF PCR testing because positive results do not clarify the extent of disease or thus treatment duration. The gold standard for diagnosing HSV encephalitis is HSV-PCR testing from the CSF because CSF viral cultures in patients with HSV encephalitis are often negative. Of note, false negatives with HSV-PCR testing of CSF are possible, especially early in the disease course; thus, if clinical presentation still supports HSV encephalitis, treatment should be continued.

Recommendations for testing of pregnant mothers in labor with visible genital lesions that are characteristic of HSV have been made by the AAP (Kimberlin 2013). This testing includes swabbing lesions for HSV PCR and culture. Positive tests should further be analyzed to determine whether the virus is HSV-1 or HSV-2. These results allow for determining maternal infection classification (Table 8).

Treatment

Treatment of neonatal HSV infection includes intravenous acyclovir. Enteral acyclovir should not be used for acute management because of unreliable bioavailability. The recommended dosage is 20 mg/kg/dose intravenously every
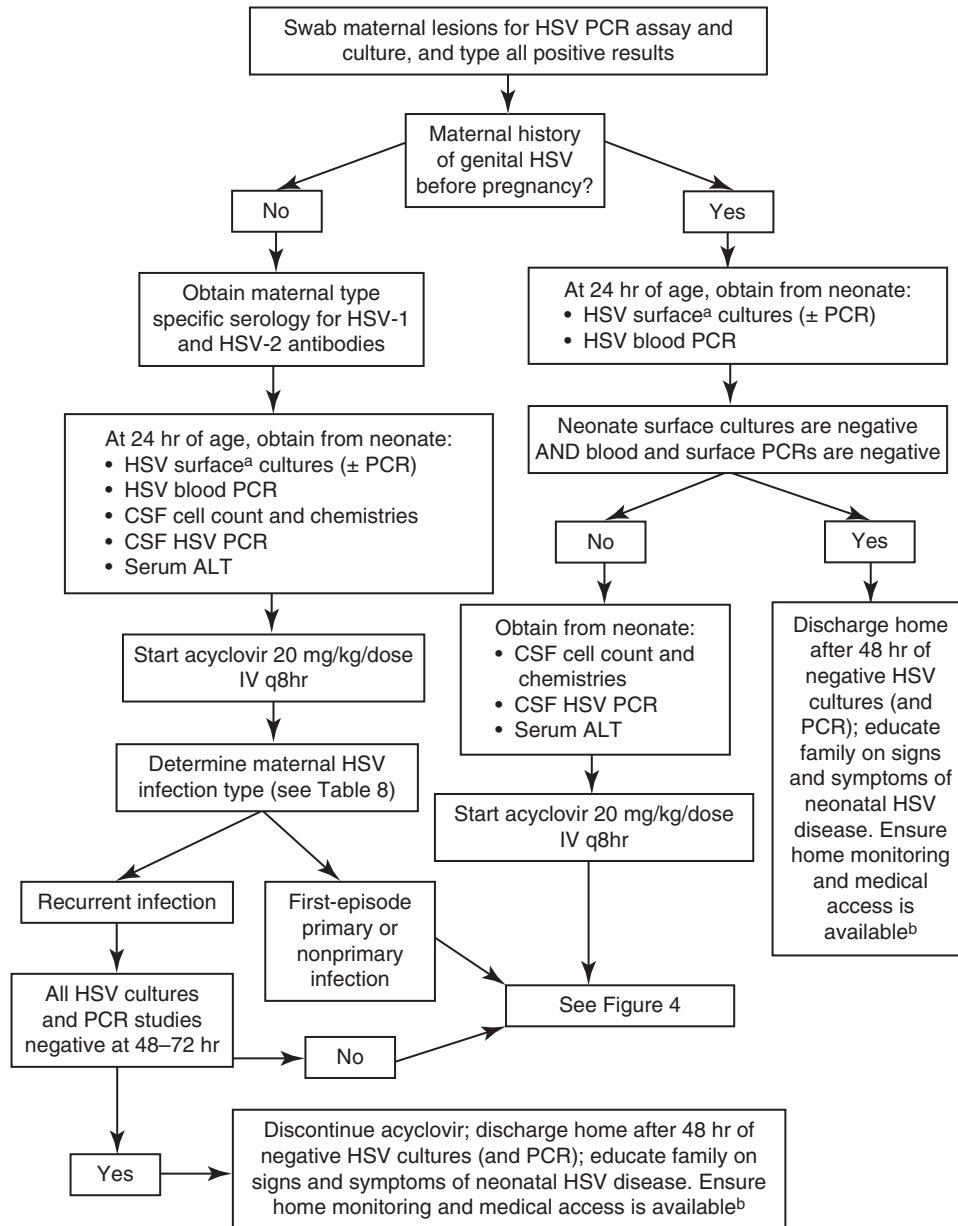
Figure 3. Treatment of asymptomatic neonates born to mothers with active genital herpes lesions: part 1.

[a]HSV surface cultures include conjunctivae, mouth, nasopharynx, rectum, and scalp electrode, if present.

[b]If unable to ensure that patient has ready access to medical care or that family is able to fully adhere to instructions for home observation, the infant should be observed in the hospital until HSV cultures are finalized as negative or are negative at 96 hr after being set up in cell culture, whichever is shorter.

HSV = herpes simplex virus.

Information from: Kimberlin DW, Baley J, Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidance on the management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics 2013;131:e635-46.

Table 8. Maternal Infection Classification by Genital HSV Viral Type and Maternal Serology for Women with No History of Genital HSV

Classification of Maternal Infection	PCR/Culture from Genital Lesion	Maternal HSV-1 and HSV-2 IgG Antibody Status
Documented first-episode primary infection	Positive, either virus	Both negative
Documented first-episode nonprimary infection	Positive for HSV-1	Positive for HSV-2 AND negative for HSV-1
	Positive for HSV-2	Positive for HSV-1 AND negative for HSV-2
Assume first-episode (primary or nonprimary infection)	Positive for HSV-1 OR HSV-2	Not available
	Negative OR not available[a]	Negative for HSV-1 and/or HSV-2 OR not available
Recurrent infection	Positive for HSV-1	Positive for HSV-1
	Positive for HSV-2	Positive for HSV-2

[a]When a genital lesion is strongly suggestive of HSV, clinical judgment should supersede the virologic test results for the conservative purposes of this neonatal management algorithm. Conversely, if, in retrospect, the genital lesion was unlikely caused by HSV and the PCR assay result or culture is negative, departure from the evaluation and management in this conservative algorithm may be warranted.

HSV = herpes simplex virus.

Information from: Kimberlin DW, Baley J, Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidance on the management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics 2013;131:e635-46.
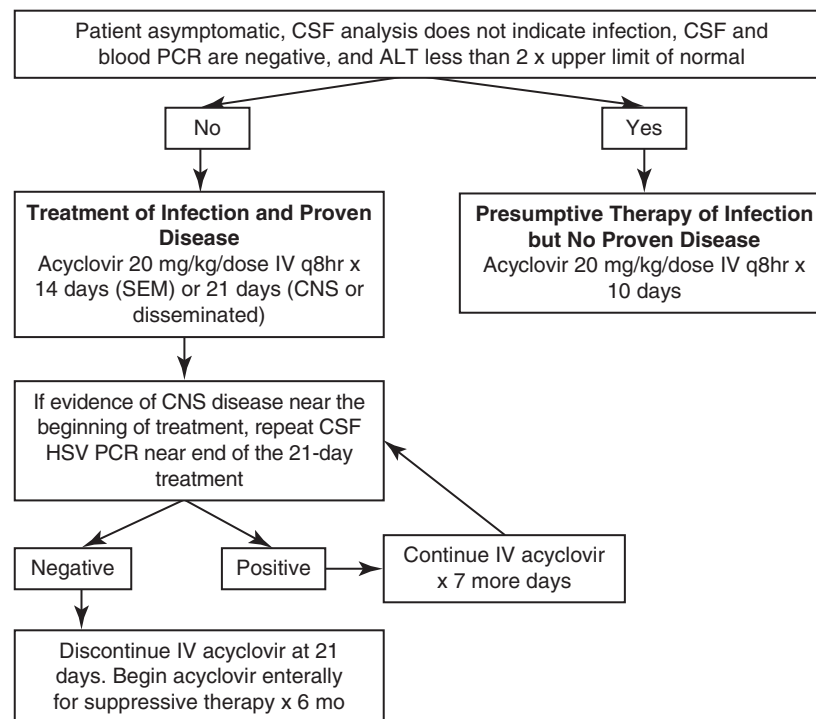
Figure 4. Treatment of asymptomatic neonates born to mothers with active genital herpes lesions: part 2.

CNS = localized central nervous system HSV; SEM = skin, eyes, and/or mouth disease.

Information from: Kimberlin DW, Baley J, Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidance on the management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics 2013;131:e635-46.

8 hours; however, recent literature has questioned whether the same frequency is appropriate from a pharmacokinetic standpoint for all neonates (see the Interactive Case on Neonatal Sepsis in the PedSAP Book for more information). Treatment duration depends on the type of neonatal HSV infection. Figure 3 and Figure 4 present the AAP recommendations for asymptomatic neonates born to mothers with active lesions at the time of delivery.

Practice Points

The pharmacist faces many challenges in recognizing and appropriately managing congenital infections. New data continue to emerge regarding how to treat various TORCH infections. As a result, guidelines/recommendations, new therapeutic entities, and safety issues continue to evolve:

- **The AAP *Red Book* and the CDC both provide recommendations for treating congenital syphilis. Four major categories are delineated: (1) congenital syphilis unlikely, (2) congenital syphilis less likely, (3) possible congenital syphilis, and (4) proven or highly probable congenital syphilis. Penicillin remains the mainstay of treatment for congenital syphilis. Recommended regimens are based on congenital syphilis category.**
- **The CDC Advisory Committee on Immunization Practices provides guidance on strategies to prevent vertical transmission of HBV, which includes the universal administration of HBV vaccine and HBIG, when indicated. Determination for timing of HBV vaccine and HBIG is based on patient birth weight as well as maternal HBV status.**
- **The NIH continuously updates its recommendations for treating HIV and opportunistic infections. All HIV-exposed newborns should receive prophylaxis with either zidovudine monotherapy or a zidovudine-containing combination regimen, depending on risk factors. High-risk patients include those born to mothers who were not receiving ART, mothers with a detectable viral load at the time of delivery regardless of treatment, and mothers with acute or primary HIV infection during pregnancy or breastfeeding.**
- **The International Congenital Cytomegalovirus Recommendations Group has published guidance on treating neonates with CMV. This includes recommendations for enteral valganciclovir for 6 months in patients with moderate to severe symptoms. Intravenous ganciclovir may be used when the enteral route is not possible. Treatment is not recommended in asymptomatic patients. Treatment benefit in mildly symptomatic patients is still unclear, but treatment is not currently recommended.**
- **The AAP has a published guideline for treating asymptomatic newborns born to mothers with active genital HSV lesions. Determination for treatment with intravenous acyclovir is based on maternal findings to delineate first compared with recurrent and primary compared with nonprimary infections, neonatal virologic and PCR testing, and clinical findings to differentiate between SEM, localized CNS, and disseminated HSV disease. After a full course of intravenous acyclovir for neonatal HSV disease, enteral acyclovir should be given for 6 months for suppressive therapy.**

Enteral acyclovir is recommended for suppressive therapy after treatment with intravenous acyclovir for neonatal HSV disease because it improves neurodevelopmental outcomes and recurrence of skin lesions. The recommended dosage is acyclovir 300 mg/m^2/dose enterally every 8 hours, and the therapy duration is 6 months. Adverse events associated with acyclovir include vomiting, diarrhea, malaise, rash, increased liver function tests, acute renal failure, and injection-site inflammation for the intravenous formulation. Routine monitoring should include an absolute neutrophil count at 2 and 4 weeks after suppressive therapy initiation and then monthly thereafter. Additional monitoring values include BUN, SCr, liver enzymes, and urinary output.

CONCLUSION

In summary, many congenital infections can lead to significant morbidity and mortality in newborns. A thorough maternal and neonatal history will help determine the likely infectious pathogens and guide providers toward appropriate management. Recommendations for managing various congenital infections, including syphilis, HBV, HIV, CMV, and HSV, are continually being reviewed by national and international organizations and updated according to the most recent literature available. Clinical pharmacists should always be aware of the resources available and the most up-to-date guidelines for various congenital infections in order to help diagnose, treat, and monitor patients with congenital infections.

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Self-Assessment Questions

1. A newborn girl (weight 1.5 kg) is born at 33 weeks' gestation. Her mother received intermittent prenatal care at an outside hospital. The maternal rapid plasma reagin (RPR) test on admission is 1:8, and the mother reports knowledge of her history of syphilis. She states her previous RPR after getting treated "a long time ago" was 1:2. An RPR obtained on the infant after birth returns as 1:2. The physician reports a normal infant examination, and all laboratory evaluations (CBC, Plt, liver function tests) so far have been normal. Which one of the following best classifies this patient's congenital syphilis risk category?

   A. Congenital syphilis unlikely
   B. Congenital syphilis less likely
   C. Possible congenital syphilis
   D. Proven or highly probable congenital syphilis

2. A 4-day-old, 38 weeks' gestation boy is receiving aqueous penicillin G for proven or highly probably congenital syphilis. Treatment was initiated within a few hours after birth. Over the weekend on day of life 2, the patient has signs of abdominal distention and respiratory distress, and laboratory results show an elevated WBC. The team discontinues penicillin and initiates ampicillin and gentamicin for presumed sepsis. It has been 48 hours, and the team plans to discontinue ampicillin and gentamicin and resume penicillin therapy. Which one of the following is best to recommend for this patient?

   A. Initiate aqueous penicillin G for 6 more days to complete a 10-day course. Count ampicillin therapy toward treatment of congenital syphilis.
   B. Initiate procaine penicillin G for 6 more days to complete a 10-day course. Count ampicillin therapy toward treatment of congenital syphilis.
   C. Initiate aqueous penicillin G for 8 more days to complete a 10-day course so that the central line may be removed and to reduce the risk of future infections. Ampicillin therapy does not count toward treatment of congenital syphilis; however, treatment need not be reinitiated if penicillin therapy was discontinued for less than 72 hours.
   D. Initiate aqueous penicillin G for 10 days. Ampicillin therapy does not count toward treatment of congenital syphilis, and treatment must be reinitiated from the beginning.

3. A girl is born at 41 weeks' gestation to a mother with adequate prenatal care. The mother was given a diagnosis of syphilis on her initial prenatal visit and received adequate treatment with penicillin. Her venereal disease research laboratory (VDRL) test decreased from 1:64 at diagnosis to 1:2 at the time of delivery. Examination of the newborn is normal. Treponemal tests ordered overnight are positive for syphilis in the neonate. Neonatal serum VDRL is 1:2. Which one of the following is best to recommend for this patient?

   A. Obtain a CSF cell count, chemistry, and quantitative VDRL.
   B. No interventions are needed; ensure adequate follow-up at discharge.
   C. Initiate aqueous penicillin G 50,000 units/kg intravenously every 12 hours and order additional testing.
   D. Administer benzathine penicillin G 50,000 units/kg intramuscularly x 1.

4. Your neonatal ICU receives an outside hospital transfer of an infant (weight 2.1 kg) of unknown gestational age. The infant's mother received scant prenatal care. Maternal infectious workup revealed a negative RPR, negative HIV rapid test, rubella immunity, and group B *Streptococcus* positive. Hepatitis B virus (HBV) testing was not obtained. The mother has left against medical advice, and the medical team has been unable to contact her. Which one of the following is best to recommend for preventing HBV transmission to this infant?

   A. Administer the HBV vaccine as soon as possible. Obtain HBV testing on the newborn.
   B. Administer the HBV vaccine as soon as possible. Do not give hepatitis B immune globulin (HBIG) because maternal HBV-positive status cannot be confirmed.
   C. Administer the HBV vaccine and HBIG 0.5 mL as soon as possible.
   D. Defer the HBV vaccine because the mother cannot receive the Vaccine Information Statement.

5. A 23 weeks' gestation newborn (weight 600 g) was just admitted to your neonatal ICU. Maternal laboratory test results show that the mother is positive for antibody to hepatitis B surface antigen (anti-HBs) at 15 mIU/mL and is negative for hepatitis B surface antigen (HBsAg). Which one of the following is best to recommend for preventing HBV in this patient?

   A. Administer the HBV vaccine and HBIG 0.5 mL as soon as possible. The HBV vaccine does not count toward the primary vaccination series.
   B. Administer the HBV vaccine and HBIG 0.5 mL as soon as possible. The HBV vaccine does count toward the primary vaccination series.
   C. Administer the HBV vaccine as soon as possible and defer HBIG until further testing can be completed. The HBV vaccine does not count towards the primary vaccination series.
   D. Administer the HBV vaccine at 30 days of life. The HBV vaccine does count toward the primary vaccination series.

Questions 6 and 7 pertain to the following case.

T.R. is a 47-year-old woman with HIV infection who presents to your family birth center in labor at 39 weeks' gestation. She was not receiving antiretroviral therapy (ART) before becoming pregnant and did not initiate ART until her second trimester because of significant nausea and vomiting. T.R. has mostly adhered to her regimen. Laboratory test results during her last prenatal visit (1 week ago) show an HIV RNA of 500 copies/mL.

6. Which one of the following intrapartum management strategies is best to recommend to prevent HIV transmission to T.R.'s newborn?

A. Discontinue home ART regimen and administer intravenous zidovudine. Schedule cesarean delivery.

B. Continue home ART regimen and consider administering intravenous zidovudine. Continue with vaginal delivery as planned.

C. Continue home ART regimen. Do not administer intravenous zidovudine. Schedule cesarean delivery.

D. Continue home ART regimen and administer intravenous zidovudine. Schedule cesarean delivery.

7. Which one of the following is best to recommend as initial postnatal treatment for T.R.'s child?

A. Zidovudine 4 mg/kg/dose enterally every 12 hours

B. Zidovudine 4 mg/kg/dose enterally every 12 hours plus lamivudine 2 mg/kg/dose enterally every 12 hours plus nevirapine 12 mg enterally for three doses

C. Zidovudine 4 mg/kg/dose enterally every 12 hours plus nevirapine 12 mg enterally for three doses plus sulfamethoxazole/trimethoprim 5 mg/kg/day three times per week

D. Zidovudine 4 mg/kg/dose enterally every 12 hours plus lamivudine 2 mg/kg/dose enterally every 12 hours plus nevirapine 6 mg/kg/dose enterally every 12 hours

8. After a 1-week hospital stay, a mother and her infant are discharged home with a supply of zidovudine for infant HIV prophylaxis to complete a 6-week course. The infant also received 3 doses of nevirapine while in the hospital. Four weeks later, the mother has failed to bring her child in for routine visits because of transportation issues. However, the mother states that she was "really good" about ensuring the infant takes the medication. The infant's laboratory tests at 3 weeks of age were negative on HIV virologic testing. Which one of the following is best to recommend for the infant?

A. Continue current HIV prophylaxis to complete a 6-week course. No repeat virologic testing is needed.

B. Continue current HIV prophylaxis to complete a 6-week course. Repeat virologic testing today. Initiate sulfamethoxazole/trimethoprim.

C. Discontinue current HIV prophylaxis. Repeat virologic testing at 4–6 months of age.

D. Expand current HIV prophylaxis to a three-drug regimen. Repeat virologic testing today. Initiate sulfamethoxazole/trimethoprim.

9. Your institution is writing a guideline for managing congenital cytomegalovirus (CMV). The pediatric infectious diseases attending physician is more comfortable using intravenous ganciclovir from his previous experiences. Which one of the following would be the best evidence-based argument for supporting enteral valganciclovir as the first-line agent for managing congenital CMV?

A. Decreased neutropenia rates with valganciclovir compared with ganciclovir

B. Increased parent satisfaction with the oral route over the intravenous route

C. Shorter treatment duration needed to prevent hearing loss with enteral valganciclovir than with intravenous ganciclovir

D. Proven benefit in patients with mild disease with enteral valganciclovir but not intravenous ganciclovir

10. A 4-day-old, ex-31 weeks' gestation neonate received testing for congenital CMV because of noted microcephaly and thrombocytopenia. The infant now has signs of respiratory distress, conjugated hyperbilirubinemia, and neutropenia. The team would like to initiate treatment. Which one of the following is best to recommend for this patient?

A. Valganciclovir 16 mg/kg/dose enterally every 12 hours for 6 months

B. Valganciclovir 16 mg/kg/dose enterally every 12 hours for 6 weeks

C. Ganciclovir 6 mg/kg/dose intravenously every 12 hours for 2 weeks; then reassess response to therapy

D. No treatment

11. Which one of the following patients has the highest risk of neonatal herpes simplex virus (HSV) transmission?

A. Vaginal delivery by mother with a known history of HSV who is receiving suppressive therapy for an active herpes lesion 1 week before delivery which is now resolved.

B. Vaginal delivery by mother with a known history of HSV contracted during the first trimester of pregnancy. Active lesions were noted in first trimester but are now resolved at delivery.

C. C-section delivery by mother with no known history of HSV who is given a diagnosis of active herpes lesions at the time of delivery.

D. C-section delivery by mother with no known history of HSV who is given a diagnosis of active herpes lesions 3 weeks after delivery. She has been exclusively breastfeeding.

Questions 12–14 pertain to the following case.

Y.D., a 17-year-old adolescent, presents to your hospital in labor at 34 weeks' gestation after receiving adequate prenatal care. Her medical history includes chlamydia (treated 3 months ago) and trichomonas (treated 2 weeks ago). Y.D. is noted to have genital lesions before delivery. Swabs from the lesions were taken for HSV culture in addition to maternal serum for HSV IgG antibody testing. Culture results from Y.D. are positive for HSV-2, and her HSV IgG antibodies are positive for HSV-1 only.

12. Which one of the following best assesses the type of HSV infection Y.D. has?

    A. Documented first-episode primary infection
    B. Documented first-episode nonprimary infection
    C. Assumed first-episode nonprimary infection
    D. Recurrent infection

13. In addition to routine care and clinical examination, which one of the following is best to recommend for treating HSV exposure in Y.D.'s infant?

    A. Obtain HSV surface cultures and CSF HSV PCR immediately after birth.
    B. Obtain HSV surface cultures, HSV blood PCR, CSF cell count and chemistries, CSF HSV PCR, and serum ALT at 24 hours after birth.
    C. Obtain HSV surface cultures and HSV blood PCR at 24 hours after birth.
    D. Initiate acyclovir 20 mg/kg/dose intravenously every 8 hours before obtaining any laboratory tests.

14. Y.D.'s child remains asymptomatic and laboratory findings are all normal. Which one of the following is best to recommend for Y.D.'s newborn?

    A. Acyclovir 20 mg/kg/dose intravenously every 8 hours for 10 days
    B. Acyclovir 20 mg/kg/dose intravenously every 8 hours for 14 days followed by enteral acyclovir suppressive therapy for 6 months
    C. No treatment
    D. Acyclovir 20 mg/kg/dose intravenously every 8 hours for 21 days followed by enteral acyclovir suppressive therapy for 6 months

15. A full-term boy is born in the ambulance en route to the hospital. His mother's medical history includes syphilis (treated more than 5 years ago) and chronic HBV/HIV coinfection (for which she is not being treated). Infectious laboratory values obtained before delivery include the following: group B *Streptococcus* negative, chlamydia negative, gonorrhea negative, RPR 1:128, HBsAg positive, and rapid HIV positive. The HIV RNA is pending. Which one of the following is best to recommend for this newborn?

    A. HBV vaccine, zidovudine 4 mg/kg/dose enterally every 12 hours, lamivudine 2 mg/kg/dose enterally every 12 hours, nevirapine 6 mg/kg/dose enterally every 12 hours, aqueous penicillin G 50,000 units/kg/dose every 12 hours
    B. HBV vaccine, HBIG 0.5 mL, zidovudine 4 mg/kg/dose enterally every 12 hours, lamivudine 2 mg/kg/dose enterally every 12 hours, nevirapine 12 mg for three doses in the first week of life, aqueous penicillin G 50,000 units/kg/dose every 12 hours
    C. HBV vaccine, HBIG 0.5 mL, zidovudine 4 mg/kg/dose enterally every 12 hours, aqueous penicillin G 50,000 units/kg/dose every 12 hours
    D. HBV vaccine, HBIG 0.5 mL, zidovudine 4 mg/kg/dose enterally every 12 hours, lamivudine 2 mg/kg/dose enterally every 12 hours, nevirapine 6 mg/kg/dose enterally every 12 hours, aqueous penicillin G 50,000 units/kg/dose every 12 hours