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KEYWORDS

- TORCH • Toxoplasmosis • *Treponema pallidum* • Rubella • Parvovirus • HIV
- Hepatitis B • Hepatitis C

KEY POINTS

- The TORCH pneumonic typically comprises toxoplasmosis, *Treponema pallidum*, rubella, cytomegalovirus, herpesvirus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus and other viruses, including varicella, parvovirus B19.
- These infections are well-described causes of stillbirth and may account for up to half of all perinatal deaths globally.
- The burden is especially great in developing countries.
- Stigmata of disease may be seen at birth, in the early neonatal period, or later.
- Treatment strategies are available for many of the TORCH infections.
- Early recognition, including maternal prenatal screening and treatment when available, are key aspects in management of TORCH infections.

INTRODUCTION

Congenital infection is a well-described cause of stillbirths, as well as perinatal morbidity. TORCH infections classically comprise toxoplasmosis, *Treponema pallidum*, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis viruses, human immunodeficiency virus (HIV), and other infections, such as varicella and parvovirus B19. The epidemiology of these infections varies, and in low-income and middle-income countries, where the burden of disease is greatest, TORCH infections are major contributors to prenatal and infant morbidity and mortality (**Table 1**).^{1–14} Transmission of the pathogens may occur prenatally, perinatally, and postnatally, through, respectively, transplacental passage of organisms, from contact with blood and vaginal secretions, or from exposure to breast milk for CMV, HIV, and HSV. Evidence of infection may be seen at birth, in infancy, or not even until years later,

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	Worldwide Prevalence	US Prevalence of Congenitally Acquired Disease in the United States	Seropositivity in Women of Childbearing Age ^a	
			Low Prevalence (%)	High Prevalence (%)
Toxoplasmosis	201,000 ^b	10–33/100,000 live births	11 (Europe)	77 (South America)
<i>Treponema pallidum</i>	36.4 million	7.8/100,000 live births	0.67 (North America)	10 (Central Africa)
CMV	Unavailable	800/1000,000 live births	30–50 (United States)	>90 (South America)
Hepatitis B	240 million	<0.1/1000,000 US population	1.3 (North America)	8.7 (west sub-Saharan Africa)
Hepatitis C	130–150 million	<0.1/100,000 US population	1.2 (North America)	>10 (Middle East, Eastern Asia)
HIV	35.3 million	162 infants/y, 2010	0.1 (North America, Western Europe)	12 (Southern Africa)

^a Women aged 15–49 y.

^b Congenital toxoplasmosis.

because the fetal origins of adult disease are now increasingly recognized. The infected newborn infant may show abnormal growth, developmental anomalies, or multiple clinical and laboratory abnormalities. Many of the clinical syndromes for those viruses that present in the immediate neonatal period overlap, as shown in [Table 2](#).¹⁵ Some have classic physical stigmata, as shown in [Figs. 1](#) and [2](#).^{16,17} For many of these pathogens, treatment or prevention strategies are available; early recognition, including prenatal screening, is key, and recognized national and international standards and protocols are available to the provider. This article covers toxoplasmosis, parvovirus B19, syphilis, rubella, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV; other sections are dedicated to HSV, CMV, and varicella zoster virus.

TOXOPLASMOSIS

Disease Description

The protozoa *Toxoplasma gondii* is an obligate intracellular parasite, which is ubiquitous in the environment, and whose only definitive hosts are members of the feline family. The forms of the parasite are oocysts, which contain sporozoites; these sporozoites divide and become tachyzoites; tachyzoites localize in neural and muscle tissue and develop under the pressure of the host immune system into bradyzoites, which congregate into tissue cysts. These cysts remain in skeletal and heart muscle, brain and retinal tissue, and lymph nodes. Cats acquire the infection either by consuming tissue cysts from their prey or ingesting oocysts in soil. Replication occurs in the intestine of the cat, and oocysts are formed, excreted, and sporulate to become infectious in as little as 24 hours.^{18–21}

Transmission/Pathogenesis

Both animals in the wild and animals bred for human consumption may become infected from oocysts in the environment. Human infection (other than congenital) occurs by ingestion of the tissue cysts from undercooked or raw meat or oocysts from contact with cat feces or contaminated food or soil, or from transfusion of blood products or organ transplantation. Three genotypes (I, II, III) of *T gondii* have been isolated.

Table 2
Clinical findings associated with selected TORCH infections

	Hepatosplenomegaly	Cardiac Lesions	Skin Lesions	Hydrocephalus	Microcephaly	Intracranial Calcifications	Ocular Disease	Hearing Deficits
Toxoplasmosis	+	(-)	Petechiae/purpura, maculopapular rash	++	+	Diffuse intracranial calcifications	Chorioretinitis	(-)
<i>Treponema pallidum</i>	+	(-)	Petechiae/purpura, maculopapular rash	(-)	(-)	(-)	Chorioretinitis, glaucoma	(-)
Rubella	+	Patent ductus arteriosus, pulmonary artery stenosis, myocarditis	Petechiae/purpura	+	(-)	(-)	Chorioretinitis, cataracts, microphthalmia	++
CMV	+	+	Petechiae/purpura	(-)	++	Periventricular calcifications	Chorioretinitis	++
HSV	+	Myocarditis	Petechiae/purpura, vesicles	+	+	(-)	Chorioretinitis, cataracts	+
Parvovirus B19	+	Myocarditis	Subcutaneous edema, petechiae	(-)	(-)	(-)	Microphthalmia, retinal and corneal abnormalities	(-)

Adapted from Remington J, Klein J, Wilson C, et al, editors. Infectious diseases of the fetus and newborn infant. 7th edition. Philadelphia: Elsevier Saunders, 2011; with permission.

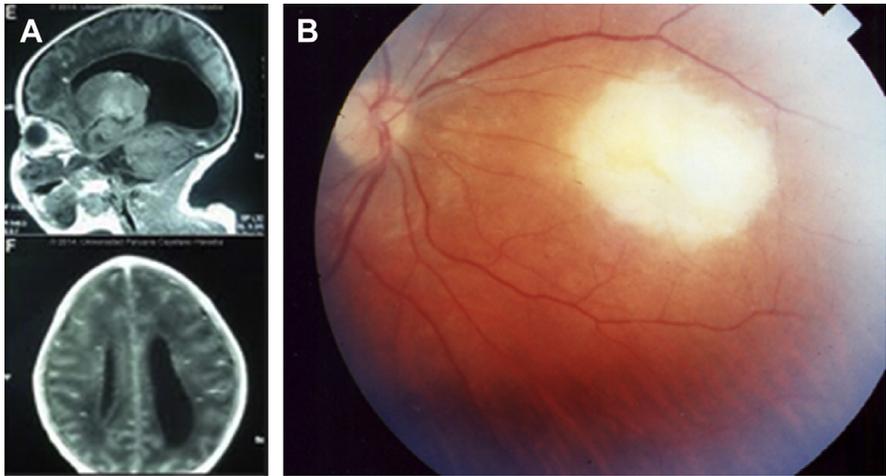


Fig. 1. Ophthalmologic and cerebral findings of congenital toxoplasmosis. (A) Diffuse intracerebral calcifications and hydrocephalus. (B) Acute retinitis.

Type II is the predominate lineage responsible for up to 80% of congenital infections in Europe and in the United States. During active parasitemia, the tachyzoite replicates rapidly and destroys infected cells, causing necrosis, which may then transform into tissue calcification.^{18,22,23}

Congenital infection results most commonly from the transplacental transmission of *T gondii* after maternal primary infection during pregnancy, during a time of high parasite burden with tachyzoites. However, women infected shortly (≤ 3 months) before conception may also transmit *T gondii* as a result of persistent parasitemia, which continues into the pregnancy. In addition, reactivation of toxoplasmosis in immunocompromised women (ie, women with HIV) may also lead to congenital toxoplasmosis. Infection with *T gondii* leads to lifelong immunity; however, it has also been posited that women may be infected with a different genotype of *T gondii* during pregnancy.^{18,20,22–24}

As shown in **Fig. 3**,²⁵ the risk of transmission increases with the date of maternal infection, from less than 15% at 13 weeks of gestation to greater than 70% at 36 weeks.

Epidemiology

Seroprevalence in pregnant women varies greatly among countries; the highest prevalence is noted in regions with tropical climates, where the oocysts can survive



Fig. 2. Cutaneous and ophthalmologic findings of congenital rubella. (A) Purpuric "blueberry muffin" rash and (B) Cataracts. (Courtesy of CDC Public Health Image Library.)

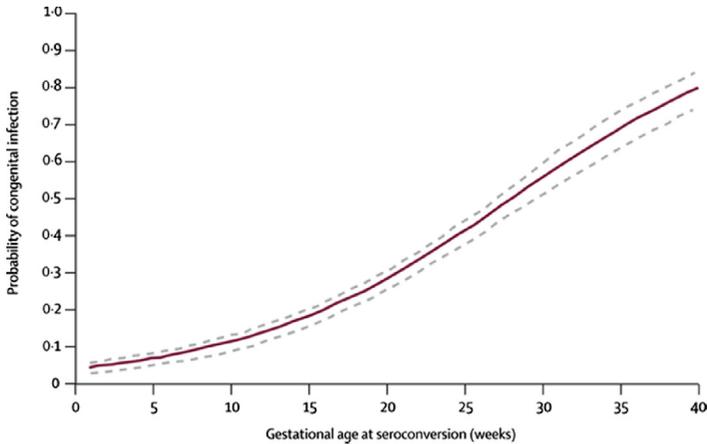


Fig. 3. Risk of MTCT of *T gondii* by gestational age at maternal seroconversion (n = 1721). Dotted lines are bounds of 95% confidence interval. (From SYROCOT (Systematic Review on Congenital Toxoplasmosis) study group, Thiébaud R, Leproust S, et al. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. Lancet 2007;369(9556):118; with permission.)

in soil, as well as countries with dietary customs of raw meat consumption. Seroprevalence among Brazilian, French women, and women in the United States at child-bearing age is approximately 77%, 44%, and 11%, respectively. Prevalence of congenital infection ranges from 0.1 to 0.01 per 1000 live births, with concomitant decrease in both maternal prevalence and congenital infection as a result of aggressive screening approaches in certain countries.^{8,18,23,26,27}

Clinical Correlation

Most (70%–90%) infants infected with *T gondii* are asymptomatic at birth; the classic diagnostic triad of symptoms (chorioretinitis, hydrocephalus, and intracranial calcifications) is rare but still remains highly suggestive. More common manifestations include^{18,22}:

- Anemia
- Seizures
- Jaundice
- Splenomegaly
- Hepatomegaly
- Thrombocytopenia

The signs and symptoms of *T gondii* overlap other TORCH infections; more severe manifestations usually indicate infection earlier in gestation, whereas fetal infections occurring in the third trimester are usually subclinical at birth. Newborns who show mild or no signs and symptoms are still at high risk for development of late manifestations and sequelae of the disease.^{28,29} These manifestations and sequelae include:

- Chorioretinitis
 - Approximately 20% of infants are noted to have retinal lesions at birth, but up to 90% of untreated congenitally infected infants develop chorioretinitis, into and including early adulthood³⁰
- Motor and cerebellar dysfunction

- Microcephaly
- Seizures
- Intellectual disability (mental retardation)
- Sensorineural hearing loss

Discussion

Diagnosis and treatment

Prenatal There is no 1 universally endorsed screening protocol for *T gondii* in pregnant women: most providers take a risk factor–based approach,^{8,25} and screen based on suspicious findings (ie, hydrocephalus, cerebral, hepatic, or splenic calcifications) on ultrasonography. Maternal screening comprises^{31,32}:

- *T gondii* IgM
 - This test has a high false-positive rate and may persist for up to 2 years after acute infection
- *T gondii* IgG
 - More sensitive techniques such as IgG avidity testing allow for more accurate timing of maternal infection
- Polymerase chain reaction (PCR)
 - Amniotic fluid PCR at 18 weeks' gestation can determine fetal infection and guide medical therapy

Maternal treatment

- For maternal infection diagnosed before 18 weeks' gestation, treatment begins with spiramycin until PCR and ultrasonography results are available^{25,28}
- If fetal infection is confirmed, treatment switches to pyrimethamine sulfadiazine and folic acid, and spiramycin
- No trial data exist on the efficacy of either of these therapies to reduce transmission to the fetus or reduce disease burden in congenitally infected infants; however, observational data²⁹ do suggest both decreased fetal infection and incidence of serious neurologic sequelae

Postnatal Infant with stigmata of congenital toxoplasmosis:

- IgG, IgM, and IgA, which is more sensitive than IgM, as well as serum (and cerebrospinal fluid [CSF], if indicated); PCR should be obtained.
 - Testing should be performed at experienced reference laboratories.
- Ophthalmologic, auditory, and neurologic examinations
- Computed tomography of the head is the preferred method of visualization of intracranial calcifications.

For infants diagnosed prenatally with toxoplasmosis, either symptomatic or asymptomatic, as well as infants diagnosed postnatally, treatment of 12 months with pyrimethamine and sulfadiazine is indicated. Folic acid is also given to minimize pyrimethamine-associated hematologic toxicity.^{8,18,28–32} Repeat testing is recommended 1 month after discontinuation of therapy. Close and sequential follow-up with serial ophthalmologic as well as auditory and neurologic examinations is the key to recognizing sequelae from this disease.

TREPONEMA PALLIDUM

Disease Description

Syphilis is a sexually transmitted infection caused by the spirochete *Treponema pallidum*. Unlike many other congenital infections, syphilis is treatable, and thus,

preventing infection of the infant is possible. Infection may occur in the newborn as a result of transmission of spirochetes across the placenta during pregnancy.

Transmission/Pathogenesis

Characteristic features of congenital infection are detectable after 18 to 22 weeks' gestation, when the fetal immune response occurs. It has been postulated^{33,34} that congestion of the placenta as a result of infection may cause constricted blood flow and result in severe adverse pregnancy outcomes, such as miscarriage and stillbirth. Diagnosis and treatment of syphilis in the mother during antepartum visits is critical for prevention of maternal to child transmission (MTCT) of syphilis. Recognizing the stages of maternal infection is important. The primary stage (3–6 weeks) presents as a painless, spontaneously resolving papule. The secondary stage occurs 6 to 8 weeks later, with diffuse inflammation and a disseminated rash (often on the palms and soles). The latent stage then occurs, in which women are characteristically asymptomatic. If untreated, maternal syphilis may then progress to the final or tertiary stage of the disease, which is characterized by granulomas affecting the bones and joints as well as the cardiovascular and neurologic systems. Infection of the neonate occurs when maternal infection is active, inadequately treated, or untreated.

Risk for congenital syphilis is dependent on the stage of maternal infection and the stage of infection at the time of exposure during pregnancy. One of the most important risk factors for neonatal infection is lack of maternal prenatal care, including antenatal clinic visits, screening, and treatment of syphilis.³⁵ Other factors that increase the risk of transmission of congenital syphilis include high nontreponemal test titers, early stages of syphilis during pregnancy, late treatment of infection (eg, short time between treatment and delivery), and lack of complete treatment.³⁶

Epidemiology

MTCT of syphilis is declining but is still prevalent in the United States. The US Centers for Disease Control and Prevention (CDC) estimates that the annual rate of primary or secondary syphilis among women was 0.9 cases per 100,000, representing approximately 1500 cases in 2012.³⁷ The incidence of congenital syphilis was 7.8 cases per 100,000 live births for a total of 322 congenital cases reported in 2012.³⁸ Southern states in the United States have the highest incidence of MTCT of syphilis.³⁹ Global estimates of pregnant women with syphilis indicate that approximately 2 million women were infected in 2003 and 1.4 million cases in 2008.^{35,40} World Health Organization (WHO) data are based on voluntary reporting by countries, which is incomplete and variable. However, from reported data, it can be concluded that maternal syphilis is a significant problem in African countries as well as countries in the Americas.

In addition, recent increases in seroprevalence have also been documented in China.³⁷ In 2007, WHO launched a program for the global elimination of syphilis with the goal of 50 or fewer cases of congenital syphilis per 100,000 live births. These goals were to be achieved by structured service delivery interventions, including increasing the number of women having at least 1 antenatal care visit ($\geq 95\%$ compliance), increased testing of pregnant women ($\geq 95\%$ compliance), and early treatment of syphilis in pregnancy ($\geq 95\%$ compliance).^{40,41}

Clinical Correlation

A recent literature review and meta-analysis on adverse outcomes of maternal syphilis infection from 1917 to 2000⁴² showed that the range of adverse pregnancy outcomes ranged from 53% to 82% in untreated women versus 10% to 20% in women without syphilis. A study to estimate global impact of adverse outcomes in pregnancy based on antenatal

surveillance found that 520,905 adverse outcomes occurred because of maternal syphilis. These estimates included 212,327 stillbirths, 92,764 neonatal deaths, 65,267 preterm or low birth weight infants, and 151,547 infected newborns.³⁵ Approximately 66% of the adverse outcomes occurred in antenatal clinic attendees who were not screened or treated.

Clinical evidence of congenital syphilis may be characterized as early manifestations (within 2 years) and late. Early findings may include hepatosplenomegaly, snuffles (nasal secretions), lymphadenopathy, mucous membrane lesions, pneumonia, osteochondritis and pseudoparalysis, maculopapular rash, edema, Coombs negative hemolytic anemia, and thrombocytopenia. Untreated infants, even those without early evidence of infection, may present with manifestations involving the central nervous system, bone and joint, teeth, eyes, and skin. **Table 3** shows both early and late sequelae of congenital syphilis.⁴³

Discussion

Diagnosis and treatment

Prenatal Maternal screening

- All pregnant women should be screened for syphilis at the first prenatal visit; many advocate repeat screening at the time of delivery⁴⁴

Maternal treatment comprises:

- Intramuscular (IM) benzathine penicillin; pregnant women with syphilis who are allergic to penicillin should be desensitized

Postnatal

- Diagnosis of congenital syphilis may be made by examination of the placenta (dark field microscopy to detect spirochetes, which is clinically and practically not available in most settings)

Table 3 Selected early and late sequelae of congenital syphilis		
Organ System	Signs and Symptoms	Percent of Cases and Approximate Time of Presentation
Reticuloendothelial	Lymphadenopathy	4–8 wk
	Anemia	
	Leukopenia or leukocytosis	
	Thrombocytopenia	30%
	Hepatosplenomegaly	50%–90%
Mucocutaneous	Rhinitis	<5%; within first week of life
	Maculopapular rash on palms and soles	1–2 wk of life and lasts ≤3 mo of age
	Mucous patches	
Skeletal	Symmetric long bone lesions (upper extremity>lower extremity)	50%–95%; 6 wk–6 mo (resolve spontaneously)
	Metaphyseal and osteochondritis	
	Ostitis and dactylitis	
Neurologic	Meningitis	40%–60% abnormal CSF parameters
	Infarction and hydrocephalus	10–40 y
	Cranial nerve deafness	
Ocular	Chorioretinitis	5–20 y
	Glaucoma	

Adapted from Follett T, Clarke D. Resurgence of congenital syphilis: diagnosis and treatment. *Neonatal Netw* 2011;30(5):320–8.

- After evaluation of maternal testing, the infant should be tested using standard nontreponemal serologic tests, including:
 - The Venereal Disease Research Laboratory test or
 - The rapid plasma regain test
- Nontreponemal tests detect antibodies to the cardiolipin
- False-negative results may occur in congenital syphilis as a result of high titers (called the prozone effect), and thus, diluting the sample before testing is recommended
- Reactive nontreponemal tests should be confirmed with a *Treponema*-specific test, such as:
 - Fluorescent antibody absorption, microhemagglutination tests for antibodies to *T pallidum*, *T pallidum* enzyme immunoassay, or *T pallidum* particle agglutination tests.

Guidance on interpretation of maternal and infant testing, as well as the treatment guidelines endorsed by the American Academy of Pediatrics (AAP) are provided on page 695 of the AAP 2012 *Report of the Committee on Infectious Diseases*.⁴⁵

RUBELLA

Disease Description

Congenital rubella is infection with a single-stranded positive-sense RNA virus. Transmission and infection of the mother occurs by inhalation of aerosolized particles from an infected individual.

Transmission/Pathogenesis

Congenital rubella occurs primarily after maternal infection in the first trimester (80%–100%), with decreasing risk to the fetus of congenital infection in the second trimester (10%–20%), but higher risk again at term (up to 60%). Infection with the rubella virus causes cellular damage as well as having an effect on dividing cells. The pathologic effects result in progressive necrotizing vasculitis and focal inflammatory response.⁴⁶ Infection may also result in miscarriage, stillbirth, or congenital rubella syndrome (CRS). There is a higher risk of vertical transmission (80%–90%) from a nonimmune mother with primary rubella infection in the first trimester of pregnancy, and infection during this period is associated with the most severe manifestations at birth.

Epidemiology

Indigenous rubella transmission and CRS were declared eliminated in the United States in 2004.⁴⁷ However, worldwide, it is estimated that around 110,000 infants are born with CRS every year, and WHO has targeted regional elimination of CRS by 2015.⁴⁸

Clinical Correlation

The classic picture of CRS is a small for age infant with a constellation of anomalies, including:

- Sensorineural deafness (66%)
- Cataracts (78%)
- Cardiac defects (58%)⁴⁹:
 - Patent ductus arteriosus
 - Pulmonary artery stenosis
 - Coarctation of aorta

- Other ocular findings:
 - Microphthalmia
 - Corneal opacity
 - Glaucoma

Features common to other perinatal infections such as the blueberry muffin rash, hepatosplenomegaly, and thrombocytopenia may also be present.

Delayed manifestations include a higher incidence of:

- Diabetes mellitus
- Hypertension
- Panencephalitis
- Behavioral disorders

Discussion

Diagnosis, prevention, and treatment

Prenatal Prevention of congenital rubella is achieved by providing rubella vaccination to all children and adolescents. Women who are of childbearing age should have evidence of immunity to rubella. If they are found to be nonimmune, the Advisory Committee on Immunization Practices (ACIP) recommendation is for vaccination with 1 dose of measles-mumps-rubella (MMR) vaccine. Pregnant women should have serologic screening with rubella IgG if they lack evidence of rubella immunity; those who are not immune should be vaccinated with 1 dose of the MMR vaccine on completion of their pregnancies and be counseled to avoid becoming pregnant for 28 days after administration of MMR vaccine.⁵⁰

Postnatal Case definitions and testing recommendations for suspected and probable CRS were published by the CDC in 2009.⁴⁸ Diagnosis can be based on:

- Isolation of the virus by PCR or culture
- Rubella-specific IgM, which is usually positive at birth to 3 months for congenital infection
 - This diagnosis is confirmed by stable or increasing serum concentrations of rubella-specific IgG over the first 7 to 11 months of life
 - False-positive IgM can occur
 - Avidity testing of IgG can help diagnose recent infection
- Rubella virus RNA can be also be detected by reverse transcriptase PCR in nasopharyngeal swabs, urine, CSF, and blood at birth⁴⁸

Specific treatment of infected children is not available. All suspected cases of CRS should be reported to the CDC. All infants with CRS are considered contagious until at least 1 year of age, unless 2 cultures of clinical specimens obtained 1 month apart are negative for rubella virus after 3 months of age.⁵¹

PARVOVIRUS B19

Disease Description

Human parvovirus B19 is a single-stranded DNA virus in the family Parvoviridae. Parvovirus B19 is primarily transmitted by respiratory droplets, but infection from blood products as well as prenatal vertical transmission can occur.

Transmission/Pathogenesis

Approximately 35% to 55% women of childbearing age are not immune to parvovirus. The incidence of parvovirus infection in pregnancy is approximately 1% to 2%, with

differential incidence occurring seasonally or during outbreak conditions. The vertical transmission rate is approximately 35%. Fetal parvovirus infection takes place via transplacental transmission 1 to 3 weeks after maternal infection, during peak maternal viremia.^{52–55} Occupational exposures (ie, health care workers, childcare workers, or teachers) have historically been described as having increased risk of parvovirus seroconversion between early pregnancy and birth. However, the CDC does not recommend that pregnant women refrain from employment in these areas.⁵⁶

Clinical Correlation

Infection with parvovirus B19 is characterized by a distinctive facial rash, described as slapped cheek, with a pruritic, laticiform macular rash on the trunk, which spreads to the extremities and may be accompanied by a polyarthritis. The rash is often preceded by a mild, nonspecific illness consisting of fever, malaise, myalgia, and headache 1 week before the exanthem. However, many women are asymptomatic during primary infection. Fetal infection may resolve spontaneously or lead to severe consequences such as nonimmune hydrops fetalis and miscarriage.

Parvovirus shows a high affinity toward erythroid progenitor cells. Cellular receptors, including the receptor of blood group P antigen are present in erythroid precursor cells. In addition, some antigenic receptors are present in endothelial cells and myocardial cells and may therefore be infected with parvovirus. Both direct toxic cell injury by the viral proteins and the induction of apoptosis contribute to cell death and the manifestations as fetal anemia and myocarditis. The risk of fetal complications is believed to be highest when infection occurs before the end of the first trimester of pregnancy. Fetal anomalies are typically evident on prenatal sonograms at 1 to 33 weeks of gestation, regardless of the gestational age at time of maternal infection.^{52,53,57–59}

Fetal parvovirus infection may lead to:

- Fetal demise
- Severe anemia
- Nonimmune hydrops fetalis caused by fetal heart failure
 - High-output cardiac failure from anemia
 - Myocardial failure attributable directly to parvovirus infection
- Thrombocytopenia
- Maternal mirror syndrome
- Meningoencephalitis is rare but described⁶⁰

Many of these conditions necessitate premature delivery. In the infant, persistent viremia with anemia caused by red cell aplasia after perinatal infection with parvovirus has been well described.^{59,61,62}

Discussion

Diagnosis and treatment

Prenatal There is no endorsed routine screening protocol for parvovirus in pregnant women. Diagnosis of infection is made whether caused by maternal symptoms with the classic clinical presentation, suspicious finding (ie, hydrops fetalis) on screening ultrasonography, or known maternal exposure.^{52,55,58,59}

Diagnosis of maternal infection⁵⁷:

- Parvovirus IgM
 - Becomes detectable in serum 7 to 10 days after infection, peaks at 10 to 14 days
 - The sensitivity of IgM antibody detection between 8 and 12 weeks after maternal infection is reported as 60% to 70%

- Parvovirus B19 DNA PCR
 - Sensitivity reported up to 96%
 - B19V DNA levels may persist for longer periods after acute infection

Fetal infection

- Amniotic fluid PCR can determine fetal infection
- Monitoring for fetal hydrops and anemia is recommended for at least 12 and up to 20 weeks after exposure

Treatment

- There is no treatment of maternal infection
- Fetal treatment is targeted toward anemia and subsequent fetal hydrops, with a goal of reduction in fetal demise
 - In utero fetal transfusion has become the mainstay of treatment

Postnatal Treatment of the hydropic neonate is primarily supportive.

Persistent congenital infection manifested as red cell aplasia has increasingly been reported, because supportive care has improved and prenatal transfusion therapy is now widely used. The use of intravenous γ globulin has been extrapolated from its use in persistent symptomatic parvovirus infection in immunocompromised hosts. Case studies in infants have shown that this therapy may be adventitious in improving the need for red blood cell transfusion but that repeated infusions are often required for weeks to months after birth.^{61,62}

Case series only are available to evaluate the long-term outcomes of infants with congenital parvovirus infection; it has been posited that survivors of the neonatal period may have an increased risk of neurodevelopmental impairment when compared with healthy population standards, but these finding may be confounded⁶³; in general, survivors of the neonatal period have a good prognosis and neurologic outcomes.^{64,65}

PERINATAL HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Disease Description

HIV-1 and HIV-2 are lentiviruses that belong to the family Retroviridae. There are 3 distinct groups of the virus worldwide: M (major), O (outlier), and N (new). HIV infection is transmitted by exposure to infected body fluids, including through sexual contact, percutaneous blood exposure, mucous membrane exposure, and MTCT during pregnancy, labor, and delivery, or through breastfeeding. The pathogenesis of infection is complex and not completely understood. HIV infects dendritic cells; active replication occurs at the lymphoid tissues, with resultant primary viremia. This stage is followed by a massive loss of gut-associated lymphoid tissues, downregulation of CD8 cells, and the production of neutralizing antibodies. There are usually no clinical manifestations of HIV infection at birth.

Epidemiology

Perinatally acquired HIV-1 infection is less common in the United States as a result of earlier identification of maternal HIV infection, access to comprehensive HIV treatment programs, including combination antiretroviral therapy (cART) for pregnant women, and the avoidance of breastfeeding. The perinatal transmission rate has been reduced from 18% to 32% in the preantiretroviral era to 1% to 2% in the United States as a result of these interventions.⁶⁶ In 2011, it was estimated that there were 192 children younger than 13 years who were diagnosed with HIV in the United States.⁶⁷ Globally, WHO estimates that there are 3.2 million children younger than 15 years living with HIV. Most (>90%) of these children live in sub-Saharan Africa. Interventions instituted in resource-limited settings have reduced the estimated number of children newly

infected with HIV from greater than 400,000 in 2009 to approximately 200,000 in 2013.⁶⁸ HIV-2 is endemic in some West African countries but rare in the United States and is not discussed further in this article. **Table 4**, from the *Global Update on Health Sector Response to HIV*, describes the impact of efforts to prevent MTCT of HIV.

Transmission/Pathogenesis

There are several factors that increase the risk of perinatal HIV transmission. These factors include maternal plasma viral load, maternal CD4 count, more advanced WHO clinical disease stage, breastfeeding and mastitis, and acute maternal infection.^{69,70} A recent meta-analysis⁷¹ reported that incident HIV during pregnancy and postpartum was associated with a significantly higher risk of MTCT of HIV. **Table 5** shows the timing of HIV transmission and some possible mechanisms for transmission.^{72,73}

Discussion

Diagnosis and treatment

In the United States, recommendations for HIV testing in early pregnancy have been promoted by many prominent medical service groups, including the Panel on

Year	Estimated Number of Pregnant Women Living with HIV (Range)	Estimated Mother-to-Child Transmission Rate of HIV (Range) (%)	Estimated Number of Children Newly Infected with HIV (Range)	Estimated Cumulative Number of Infections Averted by Prevention of MTCT (Range) ^a
2005	1,410,000 (1,320,000–1,520,000)	33 (31–36)	470,000 (430,000–510,000)	41,000
2006	1,390,000 (1,290,000–1,490,000)	32 (30–35)	450,000 (420,000–490,000)	73,000
2007	1,370,000 (1,270,000–1,470,000)	31 (29–33)	420,000 (390,000–460,000)	130,000
2008	1,360,000 (1,260,000–1,450,000)	29 (27–31)	400,000 (360,000–430,000)	200,000
2009 ^b	1,340,000 (1,250,000–1,430,000)	26 (24–28)	350,000 (310,000–380,000)	320,000
2010	1,330,000 (1,230,000–1,420,000)	23 (21–25)	300,000 (280,000–330,000)	480,000
2011	1,310,000 (1,210,000–1,400,000)	21 (20–23)	280,000 (250,000–300,000)	660,000
2012	1,290,000 (1,190,000–1,380,000)	17 (16–19)	220,000 (200,000–250,000)	880,000
2013	1,260,000 (1,170,000–1,360,000)	16 (15–17)	200,000 (170,000–230,000)	1,120,000

^a Compared with the counterfactual scenario in which no ARVs are provided for MTCT.

^b Baseline year for the Global Plan.

From WHO. Global update on the health sector response to HIV, 2014. Geneva: World Health Organization, 2014; with permission.

Timing of Transmission	Rate (%)	Mechanism	Prevention
In utero	Approximately 30	Placental breakdown and microtransfusions; chorioamnionitis	Early maternal diagnosis Maternal cART
Intrapartum	Approximately 50	Contact with infant mucous membranes and >4 h rupture of amniotic membranes	cART Cesarean section Neonatal ART
Breastfeeding	Approximately 20	Contact with infant mucous membranes	No breastfeeding

Antiretroviral Therapy and Medical Management of HIV-Infected Children, the US Public Health Service, the AAP, the American College of Obstetricians and Gynecologists, and the US Preventive Services Task Force. These testing algorithms have made a significant impact on perinatal HIV as a result of early identification of maternal infection.^{74–80}

Prenatal: maternal testing Opportunities for testing include:

- Early in pregnancy
- Third trimester of pregnancy
- At the time of labor or delivery
- Immediately post partum

Postnatal testing of HIV-exposed infants Diagnosis of HIV infection in infants requires the use of nucleic acid tests (NATs), including HIV DNA or HIV RNA assays. For high-risk exposures, such as maternal HIV, or when maternal HIV status is unknown, testing of the infant at birth is recommended.⁷⁵ In general, testing for the HIV-exposed infant should be:

- Within 48 hours of birth
- At 2 weeks of life
- At 4 to 6 weeks of life
- At 4 to 6 months of life

Both HIV DNA PCR and qualitative HIV RNA are sensitive for the diagnosis of perinatally acquired infection, although HIV DNA PCR may be less affected by cART. Therefore, infants who receive cART at birth should be retested with an HIV NAT to 4 weeks after cessation of cART. HIV RNA testing of infants does have the advantage of being more sensitive than HIV DNA PCR for nonsubtype B viruses, which are found around the world. An HIV-exposed infant is generally considered to be HIV-1 negative if the HIV NAT is negative at up to 4 months of age. Any infant with a positive HIV NAT should have the test repeated immediately to confirm the result.⁷⁵

Treatment Early cART for HIV-infected infants is associated with reduced mortality and attainment of normal developmental milestones and gross motor skills when compared with infants who have cART delayed.^{81,82} The reported functional cure in an HIV-infected child in Mississippi led many experts to consider early cART initiation for HIV-exposed infants. This child was treated at 30 hours of life to 18 months of age and maintained HIV viral suppression for a period.⁸³ However, current data now show HIV viral rebound in this child off therapy. Therefore, empirical treatment at birth and interruption of therapy after early initiation cannot be recommended.⁸⁴

The latest guideline recommendations for infant antiretroviral (ARV) prophylaxis are shown in **Table 6** and include⁸⁵:

- Six-week zidovudine regimen or 4-week regimen if maternal cART was given with consistent viral suppression and no concerns for lack of maternal adherence
- Zidovudine regimen started as close to birth as possible and within 6 to 12 hours of delivery
- Infants born to women who did not receive cART should receive 6 weeks of zidovudine combined with 3 doses of nevirapine in the first week of life (first dose given from birth to 8 hours, second dose given 48 hours after the first dose, and third dose given 96 hours after the second dose)

Table 6		
Recommendation for prophylaxis of newborns exposed to HIV		
All HIV-Exposed Infants (Initiated as Soon After Delivery as Possible)		
ZDV	Dosing	Duration
ZDV	≥35 wk gestation at birth: 4 mg/kg/dose PO twice daily, started as soon after birth as possible and preferably within 6–12 h of delivery (or, if unable to tolerate oral agents, 3 mg/kg/dose IV, beginning within 6–12 h of delivery, then every 12 h)	Birth to 4–6 wk ^a
ZDV	≥30 to <35 wk gestation at birth: 2 mg/kg/dose PO (or 1.5 mg/kg/dose IV), started as soon after birth as possible, preferably within 6–12 h of delivery, then every 12 h, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 h at age 15 d	Birth to 6 wk
ZDV	<30 wk gestation at birth: 2 mg/kg body weight/dose PO (or 1.5 mg/kg/dose IV) started as soon after birth as possible, preferably within 6–12 h of delivery, then every 12 h, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 h after age 4 wk	Birth to 6 wk
Additional ARV Prophylaxis Agents for HIV-Exposed Infants of Women who Received No Antepartum ARV Prophylaxis (initiated as soon after delivery as possible)		
In addition to ZDV as shown above, administer NVP	Birth weight 1.5–2 kg: 8 mg/dose PO Birth weight >2 kg: 12 mg/dose PO	3 doses in the first week of life <ul style="list-style-type: none"> • First dose within 48 h of birth (birth–48 h) • Second dose 48 h after first • Third dose 96 h after second

Abbreviations: IV, intravenously; NVP, nevirapine; PO, orally; ZDV, zidovudine.

^a A 6-week course of neonatal zidovudine is generally recommended. A 4-week neonatal zidovudine chemoprophylaxis regimen may be considered when the mother has received standard ART during pregnancy with consistent viral suppression and there are no concerns related to maternal adherence.

From Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. 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. Available at: <http://aidsinfo.nih.gov/contentfiles/vguidelines/PerinatalGL.pdf>. Accessed October 29, 2014.

- Consult pediatric infectious diseases specialist about options for 3-drug ARV prophylaxis regimens for extremely high-risk infants (eg, mother with high viral load, known resistant virus) (discussions before delivery are recommended)
- Infants born to mother of unknown status
 - Expedited HIV testing of mother or infant (rapid HIV test) should be performed, followed by:
 - Immediate initiation of infant ARV prophylaxis if initial test positive
 - If confirmatory testing of the infant's mother is negative, infant ARV prophylaxis can be discontinued
- In the United States, HIV ARV drugs other than zidovudine and nevirapine cannot be recommended in premature infants, because dosing and safety data are lacking
- Free consultation is available at the National Perinatal HIV Hotline (1-888-488-8765)

HEPATITIS B

Disease Description

HBV is a partially double-stranded circular DNA enveloped hepadnavirus. It is composed of an outer lipoprotein envelope containing the hepatitis B surface antigen (HBsAg) and an inner nucleocapsid consisting of hepatitis B core antigen (HBcAg). The genome contains 4 partially overlapping open reading frames, coding for viral surface proteins, which correspond to HBsAg, the core antigen, and the soluble antigen e (HBeAg), the viral polymerase that possesses a DNA polymerase and reverse transcriptase, a regulatory X protein essential for virus replication and activating the expression of numerous cellular and viral genes.⁸⁶⁻⁸⁸

The virus itself is not directly cytotoxic to hepatocytes or other cells; instead, the cellular injury seen in the disease is related to the host immune response, most commonly with HBV directed cytotoxic T cells. After infection occurs, HBV DNA and HBsAg increase exponentially in the serum. The peak of HBV DNA and HBsAg is reached before the acute disease, and both decrease after the onset of clinical symptoms. HBsAg disappears, unless a chronic carrier state is present.⁸⁸ It is now known that HBV genome may also become integrated into hepatocytes, and produce an occult HBV infection, in which the carrier is HBsAg negative, but the integrated virus is able to reactivate and replicate under certain conditions.⁸⁹

Transmission/Pathogenesis

Most MTCT of HBV occurs at the time of delivery, with less than 2% to 4% of all transmission occurring in utero. Hypothesized prenatal modes of transmission include transplacental or inhalation or chronic ingestion of infected amniotic fluid. HBV infection caused by fetal contamination with maternal blood during procedures such as amniocentesis has been posited but not proved to occur.⁹⁰

Perinatal transmission of HBV usually occurs from exposure to blood during labor and delivery; HBV has also been isolated in vaginal secretions. The highest rate of viral transmission occurs from mothers who are HBsAg and HBeAg positive; of women who are acutely infected during pregnancy, the risk of neonatal infection is greatest when maternal infection occurs during the third trimester. Historically, of infants who do not receive appropriate prophylaxis, only 5% to 20% who are born to HBsAg-positive but HBeAg-negative mothers become infected, as opposed to up to 90% of infants born to women who are both HBsAg and HBeAg positive.^{1,86,90,91}

The biological basis for this finding is that HBeAg is produced during active viral replication and is associated with high HBV DNA levels. Maternal HBeAg can pass through the placenta because of its small size. This factor induces T-cell intolerance

in the fetus to both HBeAg and HBcAg as a result of cross-reactivity between HBeAg and HBcAg. After birth, cytotoxic T-helper cell recognition and response may be shown to HBeAg and HBcAg, but not to HBsAg; this enables both acute infection with HBV and persistent HBV infection after delivery.^{86,88,92}

Epidemiology

HBV is estimated to affect approximately 360 million people globally. The prevalence of HBV infections varies throughout different regions of the world, but up to half of the world's population live in regions where the prevalence of chronic HBV infection (CHB) is greater than 8%. Transmission during pregnancy or delivery is responsible for more than one-third of CHBs worldwide. **Table 1**, adapted for the Red Book, shows the prevalence of HBV as indicated by HBsAg positivity and the major source of new infections.^{88,93} In these regions, most new infections occurred in early childhood or perinatally. In regions of intermediate HBV endemicity, where the prevalence of HBV infection is 2% to 7%, multiple modes of transmission (ie, perinatal, household horizontal transmission, sexual transmission, injection drug use) contribute to the burden of infection. In countries of low endemicity, such as the United States, where CHB prevalence is less than 2% and immunization readily available, the peak age of new infections is among the unimmunized in older age groups.⁹³

Clinical Correlation

The risk of progressing to CHB is primarily determined by the age at the time of acute infection. Approximately 90% of infants infected perinatally or in the first year of life develop CHB. Between 25% and 50% of children infected between 1 and 5 years of age develop CHB, whereas 5% to 10% of acutely infected older children and adults develop CHB. Infants infected with HBV rarely show signs of disease at birth or in the neonatal period, and the natural history of perinatally acquired chronic HBV may be classified into the immune tolerant, immune active/clearance, inactive carrier state, and reactivation stages. Children who are infected perinatally develop mildly increased alanine aminotransferase concentrations, with detectable HBeAg and high HBV DNA concentrations ($\geq 20,000$ IU/mL), with minimal or mild liver histologic abnormalities, defining the immune-tolerant phase, starting at approximately 2 to 6 months of age. Spontaneous loss of HBeAg in this stage is low, which typically lasts for many years, and children are contagious as a result of their high viral burden.^{87–89}

A few infants develop clinical hepatitis within a few months of age and present with jaundice, poor feeding, and vomiting.

Infection of an infant with HBV caused by vertical transmission from an HBV-infected mother is most commonly diagnosed by the presence of HBsAg by 1 to 2 months of age.

Discussion

Diagnosis and treatment

Prenatal In the past, women were screened for HBsAg if they fell into a high-risk group based on such data as immunization status, history of exposure to blood products, intravenous drug use, and so forth. However, less than 60% of HBsAg carriers were captured using these screening criteria, and thus, it is recommended that all pregnant women be screened for HBsAg at the first prenatal visit. Additional screening at the time of delivery is recommended if any of the maternal risk factors outlined earlier are present.^{94,95}

Postnatal Newborns of HBsAg-positive mothers should receive:

- Hepatitis B immunoglobulin (HBIG) and
- Single-antigen hepatitis B vaccine within 12 hours of birth
- The vaccine series should then be completed according to the standard ACIP/AAP schedule^{96–99}

Follow-up:

- Testing after the hepatitis B vaccine series of infants born to HBsAg-positive mothers should then be performed at 9 to 18 months of age
- Postvaccination testing is not recommended before 9 months of age, to minimize the likelihood of detecting passively transferred anti-HBs from HBIG and to maximize the likelihood of detecting HBV disease that presents with late HBsAg positivity¹⁴
- Although breast milk is theoretically capable of transmitting HBV, the risk for transmission in HBsAg-positive mothers whose infants have received timely HBIG and hepatitis B vaccine is not increased by breastfeeding

Best Practice

- Universal screening for HBV in pregnant women (HBsAg) at first prenatal visit, regardless of risk stratification
- Repeat screening for women at high risk for HBV at delivery
 - Prophylaxis of infant
 - Maternal HBsAg positive
 - HBIG 0.5 mL IM and single-antigen hepatitis B vaccine IM within 12 hours of delivery
 - Complete vaccine series by 6 months of life
 - Follow-up testing at 9 to 18 months
 - Maternal HBsAg negative
 - Single-antigen hepatitis B vaccine IM soon after birth, before hospital discharge
 - Complete vaccine series by 6 to 18 months of life months of life⁹⁹

HEPATITIS C

Disease Description

HCV is an enveloped, single-stranded RNA with 6 main genotypes. A hypervariable region within the structural protein E2 also leads to subtypes, or quasispecies, that show varying clinical presentation and degrees of resistance to antiviral therapy. The virus infects hepatocytes or other cells, but like HBV virus, may not be directly cytotoxic to the cells. Signs and symptoms of this disease often parallel the host immune response with HCV-directed CD8+ and then CD4+ T cells.^{100–102}

Transmission/Pathogenesis

MTCT of HCV in the absence of maternal viremia is rare; however, studies of perinatal transmission of HCV have yielded conflicting results, and the timing and mechanisms of transmission from mother to infant are unclear. Infants may have positive cord or serum HCV PCR tests soon after delivery, suggesting in utero transmission. However, after 18 months of age, some of these children have negative PCR testing, recommending against using early PCR as a diagnostic tool.¹⁰¹ Hypothesized mechanisms

of transmission include prenatal or perinatal exposure to maternal peripheral blood mononuclear cells (PBMCs) infected with HCV and release of virus into fetal or infant circulation. Fetal and maternal HLA type, as well as HCV quasispecies, has been implicated in transmission.^{103–107} Research into differential predilection for PBMCs by quasispecies may help elucidate the risk of MTCT of HCV. Other risk factors described by epidemiologic studies include female gender and coinfection with HIV, mediated through viral load and immunologic status. Mode of delivery and exposure to breast milk do not seem to be associated with infection.^{103–109}

Epidemiology

HCV is one of the most common causes of chronic liver disease worldwide, with global prevalence estimated at 130 to 150 million and maternal seroprevalence at approximately 1% to 2% in developed countries. MTCT has been estimated from 4% to 8% historically, and a recent meta-analysis showed that in children born to HIV-negative women, the pooled risk of vertical HCV infection was 5.8% as opposed to a 10.8% risk of HCV vertical transmission in children born to HIV-positive women. Incidence in infants and children remains low, with a prevalence of less than 0.1 per 100,000 in the United States.^{12,108,110}

Clinical Correlation

Infants infected perinatally are generally asymptomatic; although up to 80% of infants infected perinatally develop chronic HCV, most are still asymptomatic at age 5 years.

Discussion

There are no known prenatal or perinatal interventions to prevent congenital HCV. Although observational studies have suggested that invasive instrumentation or prolonged rupture of membranes may confer a higher risk of transmission, no experimental data exist to confirm these findings. Elective cesarean section is not recommended in the case of maternal HCV infection, nor is breastfeeding prohibited, although mothers with cracked or bleeding nipples are advised to abstain.

Diagnosis and treatment

Prenatal

- Routine screening of pregnant women is not advocated. However, targeted screening in high-risk women (ie, HIV positive, history of intravenous drug abuse) is recommended.^{102,111}

Postnatal follow-up

- Anti-HCV IgG:
 - Persistence of maternal antibodies can be as long as 18 months, and therefore, testing is after the age of 18 months
- HCV Nucleic acid amplification test (RNA PCR):
 - May be performed at 1 to 2 months of life
 - Should be repeated after 12 months of age, because up to 30% of infants may clear their infection

Although interferon-based therapy combined with ribavirin is approved for children aged 3 years and older, neither this nor therapy with intravenous γ globulin is indicated in infancy.^{102,110,111} There now exist direct acting antiviral agents, both first and second generation, which have proved efficacious in the treatment of chronic HCV in adults. Therapy in pregnant women is not indicated to prevent perinatal transmission, but this may change as these drugs become more widely used.^{102,112}

SUMMARY

Infants with a suspected congenital infection should undergo a judicious review of both the maternal and perinatal history to appropriately guide the next steps in evaluation and therapy. As sensitive and specific diagnostic tools become widely available, prevalence estimates of maternal, fetal, and perinatal infection will likely increase as the burden and spectrum of these diseases become more apparent. We hope that this situation will allow for the development of more sophisticated pre-natal therapeutic and preventive strategies, targeted at key moments in the disease process, with the intent of mitigating sequelae of these diseases.

Best practices
<p>What is the current practice?</p> <ul style="list-style-type: none"> • Toxoplasmosis • <i>Treponema pallidum</i> • Rubella • Parvovirus B19 • HIV • Hepatitis B • Hepatitis C <p>Best practice/guideline/care path objective(s)</p> <p>What changes in current practice are likely to improve outcomes?</p> <ul style="list-style-type: none"> • Universal screening for <i>T pallidum</i>, HIV, and HBV, as well as for immunity to rubella in pregnant women at first prenatal visit, regardless of risk stratification • Targeted screening for toxoplasmosis, parvovirus B19, and HCV in pregnant women <p><i>Major Recommendations</i></p> <p>Toxoplasmosis: CDC recommendations for prevention of toxoplasmosis in pregnant women can be found at: http://www.cdc.gov/parasites/toxoplasmosis/prevent.html.¹¹³</p> <p>HBV: Recommendations for screening for HBV infection in pregnancy can be found at: US Preventive Services Task Force reaffirmation recommendation statement⁹⁵</p> <p>HCV: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition practice guidelines for the diagnosis and management of hepatitis C infection in infants, children, and adolescents can be found at <i>J Pediatr Gastroenterol Nutr</i> 2012; 54:838–55¹¹¹</p> <p><i>Clinical Algorithm(s)</i></p> <p><i>T pallidum</i>: Testing and treatment algorithm endorsed by the AAP are provided on page 695 of the AAP 2012 <i>Report of the Committee on Infectious Diseases</i>.⁴⁵</p> <p>HIV: Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. <i>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</i>. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed October 31 2014⁸⁵</p> <p>HBV: American Academy of Pediatrics. Hepatitis B. In: <i>Red Book: 2012 Report of the Committee on Infectious Disease</i> (29th edition), Pickering, LK. (Ed), American Academy of Pediatrics, Elk Grove Village, IL 2012. p. 384, Table 3.2.</p>

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