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Congenital Infections, Part I: Cytomegalovirus, *Toxoplasma*, Rubella, and Herpes Simplex

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Abstract

The clinical importance of early diagnosis of congenital neonatal infections and initiation of early therapy was recognized more than half a century ago. As a result, a serology screening panel was established for *Toxoplasma gondii*, rubella virus, cytomegalovirus, and herpes simplex virus ("TORCH") that is still widely used in many institutions. Although it no longer is possible to diagnose all recognized congenital infections with one panel, the original TORCH diseases continue to be of clinical importance, and advances in medicine and new findings in epidemiology, preventive medicine, developmental biology, and immunology have brought optimistic changes and intriguing insights to the field. We summarize information from recent studies to provide updates about the diagnostic and therapeutic strategies to combat this complex group of pathogens.

Objectives

After completing this article, readers should be able to:

1. List the epidemiology and typical clinical signs of common congenital infections.
2. Describe the recent developments in prevention of congenital human cytomegalovirus (CMV) infection.
3. Describe the pros and cons of universal screening for congenital human CMV and *Toxoplasma* infection.
4. Discuss the short- and long-term sequelae of common congenital infections.

Introduction

Congenital neonatal infection occurs during pregnancy or the peripartum period and often causes devastating long-term consequences. Intrauterine infections of bacterial and non-bacterial causes were well described about half a century ago. Rubella embryopathy was the first documented neonatal congenital infection, discovered by the Australian ophthalmologist Sir Norman Gregg in 1941. (1)(2) The acronym "TORCH" was introduced by Nahmias in 1971 to highlight a group of pathogens that cause congenital and perinatal infections: *Toxoplasma gondii*, rubella virus, human cytomegalovirus (HCMV), and herpes simplex virus (HSV). (3)(4) Nahmias recognized the clinical importance of early diagnosis because prevention and treatment can be effective and improve prognosis and called for the development of new diagnostic tests to identify all known causes of TORCH. The resulting TORCH serology panel remains in wide use. Although it no longer is possible to diagnose all recognized congenital infections with one panel, the original TORCH diseases continue to be of clinical importance. This article reviews recent studies addressing diagnostic and therapeutic challenges of these infections.

Abbreviations

CMV:	cytomegalovirus
CNS:	central nervous system
CSF:	cerebrospinal fluid
HCMV:	human cytomegalovirus
HIG:	hyperimmune globulin
HSV:	herpes simplex virus
Ig:	immunoglobulin
MMR:	measles-mumps-rubella
PCR:	polymerase chain reaction

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Human Cytomegalovirus

Epidemiology

HCMV is a ubiquitous herpesvirus that usually causes only mild disease. It is commonly acquired in infancy and childhood through "saliva sharing," particularly in less developed countries where more than 90% of infants are infected in childhood compared with approximately 60% in developed countries. HCMV is the most common congenital viral infection in the United States; approximately 40,000 infants are born with HCMV infection every year, making this infection a more widespread cause of birth defects than other relatively frequent conditions such as Down syndrome or fetal alcohol syndrome. (5) HCMV is the most common cause of nonhereditary sensorineural hearing loss in children. (6)(7)

Young children at child care centers and infected sexual partners are the most likely sources of infection for pregnant women in the United States. Viral shedding persists for years after primary infection. The relative immunocompromised state of pregnancy can result in virus reactivation and asymptomatic viral excretion. Recurrent infections with different HCMV strains are possible. Transmission can be prenatal (congenital, placental), natal (50% of exposed infants become infected), or postnatal (human milk in preterm infants, blood transfusion, transplant).

Higher rates of congenital HCMV infection are associated with young maternal age, single marital status, nonwhite race, and women who have occupations associated with increased exposure to young children. Seronegative women who have contact with young children are most likely to be infected. Approximately 50% of the women of middle and higher socioeconomic status in the United States are seronegative for HCMV. Half of seronegative women acquire a HCMV infection within 1 year if they are exposed frequently to infected young children. Serology studies have shown that neutralizing titers and immunoglobulin (Ig)G avidity to HCMV antigens are inversely correlated with transmission. (8) Transmission of HCMV is more common in a primary maternal infection, which results in fetal infection in 30% to 40% of cases. The risk of fetal infection correlates with the viral load in the fetal amniotic fluid or in the newborn's plasma. Preexisting maternal immunity reduces the incidence of maternal-to-fetal transmission to about 1%. (9) On the other hand, similar severity of the disease following primary or nonprimary maternal infections suggests a protective but incomplete immunity against HCMV in previously infected pregnant women.

Clinical Manifestations

Symptomatic HCMV-infected infants can be affected differently, displaying symptoms such as hepatosplenomegaly, conjugated hyperbilirubinemia, thrombocytopenia with petechiae/purpura ("blueberry muffin" spots) (Fig. 1), small size for gestational age, microcephaly (Fig. 2), intracranial calcifications (Fig. 3), and chorioretinitis. In severe cases, migrational central nervous system (CNS) defects, such as cortical dysplasia, encephalitis resulting in *ex vacuo* ventriculomegaly, or even lissencephaly (Fig. 3) can be found. More unusual findings include inguinal hernia and defective enamelization of deciduous teeth (Table).

Diagnosis

Debate surrounds whether pregnant women should be tested routinely for HCMV immunity. In view of the diagnostic achievements and newly developed prevention options, more investigators have called for the introduction of routine antenatal screening for HCMV. (10)(11)(12) Interventional programs were suggested to target both pregnant women who had primary HCMV infections and newborns identified with congenital HCMV infection during newborn screening. However, diagnosis of asymptomatic maternal primary infection using serologic methods to document seroconversion rarely is achieved because universal serial serologic screening during pregnancy is not standard in the United States. In addition, IgM antibodies in maternal sera can be detected in both primary HCMV infections and reactivation or reinfection of HCMV, making it a nonspecific

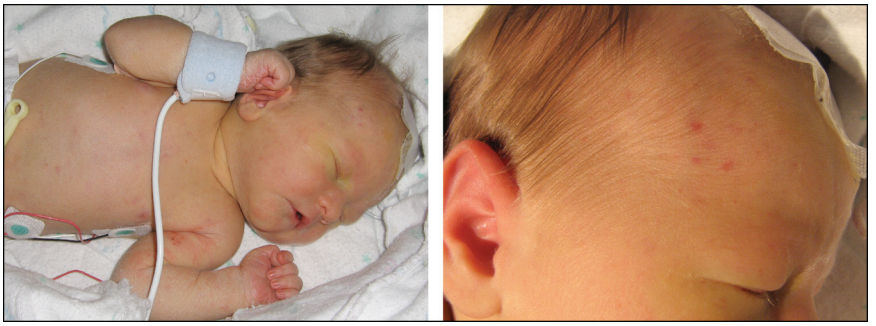

Figure 1. One-day-old term infant who exhibits cholestatic jaundice and "blueberry muffin" spots consistent with extramedullary (dermal) hematopoiesis after congenital human cytomegalovirus infection.

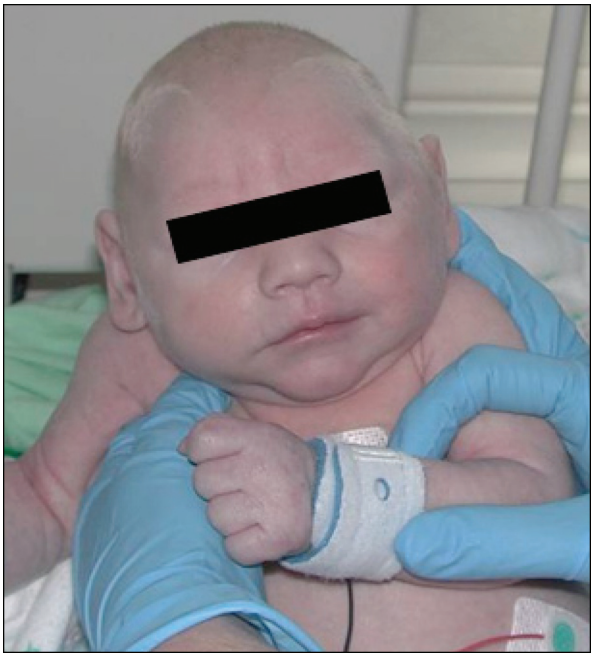

Figure 2. Newborn who has microcephaly associated with congenital human cytomegalovirus infection.

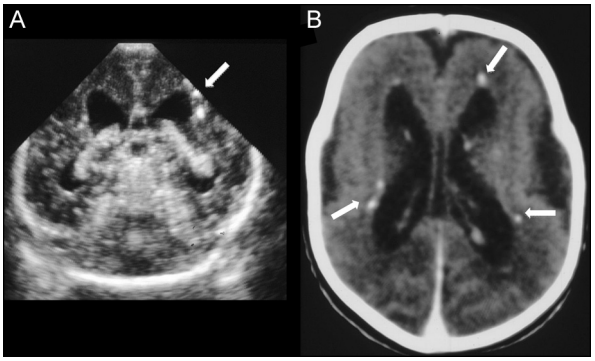

Figure 3. A. Posterior angled coronal sonogram presenting echogenic foci adjacent to the left lateral ventricle (arrow), consistent with periventricular calcifications. B. Axial computed tomography scan of the same patient, illustrating multiple periventricular calcifications (arrows) and ventriculomegaly. The cerebral mantle is agyric, which, in this term infant, is consistent with lissencephaly. Pictures courtesy of Marta Hernanz-Schulman, MD.

test for primary infection. Studies suggest that the combination of anti-HCMV IgM and low-avidity anti-HCMV IgG is the best approach to diagnosing a primary maternal infection, based on the observation that antibody avidity increases in the first weeks and months after a primary infection. (8)(13)

Viral culture of the amniotic fluid is 100% specific for prenatal diagnosis of HCMV fetal infection but has considerable false-negative results. Polymerase chain reaction (PCR) of amniotic fluid is both specific and sensitive for prenatal diagnosis after 21 weeks' gestation. In addition to antigen detection, fetal abnormalities or placental enlargement detected by ultrasonography are sensitive predictive factors of HCMV infection and long-term sequelae for the infected neonates. Because HCMV viremia identified in neonates by PCR may indicate a high risk of developing systemic infection and long-term neurologic complications, screening of newborns for congenital HCMV infection may be beneficial when safe and effective therapeutic options become available. Theiler and associates (14) evaluated the feasibility and yield of screening umbilical blood for HCMV DNA using quantitative PCR. Using discarded cord blood specimens, two infants among 433 tested (0.5%) were diagnosed with congenital HCMV. The authors concluded that incorporation of neonatal HCMV screening into routine care is both feasible and beneficial. Isolation of HCMV from urine or saliva before 3 weeks of age helps to differentiate prenatal HCMV infection from natal or postnatal infection. Viremia during early infancy is associated with long-term sequelae. (15)(16)

Prevention

Studies for possible preventive strategies have focused on evaluation of hygienic behavior changes, administration of HCMV hyperimmune globulin (HIG), and vaccine development. Interestingly, hygienic interventions have proven to be effective for pregnant women but not for those who are attempting conception. (17) Whether the failure of protection before pregnancy is associated with exposure during the early gestational age or there is less strict adherence to hygienic behavior needs further investigation. Prevention of fetal infection by HIG has been studied recently. Adler and Nigro (18) reported a significant reduction of fetal infection in the HIG treatment group in a nonrandomized study of the Congenital Cytomegalovirus Collaborating Group. Pregnant women whose amniotic fluid contained either HCMV or HCMV DNA were treated with intravenous HIG at a dose of 200 units/kg of weight. Only one of 31 mothers gave birth to an infant who had HCMV disease compared with seven of 14 women who did not receive treatment. A different group of pregnant women who had recent primary infection before 21 weeks' gestation or who declined amniocentesis were studied using monthly HIG at 100 units/kg of weight. Six of 37 women in the prevention group had infants who had congenital

Table. **Clinical Manifestations of Common Congenital Infections**

Sign	Cytomegalovirus	*Toxoplasma*	Rubella	Herpes Simplex Virus
Hepatosplenomegaly	++	+	+	+
Jaundice	+	+	+	+
Exanthem	−	+	−	++
Petechiae/purpura	++	+	+	−
Hydrocephalus	+	++	−	+
Microcephalus	++	+	−	+
Intracerebral calcifications	++	++	−	+
Heart defects	−	−	++	−
Bone lesions	−	−	++	−
Glaucoma	−	−	+	−
Intrauterine growth restriction	+	+	+	+
Chorioretinitis	++	++	−	+
Cataracts	−	−	++	+
Adenopathy	−	+	+	+
Dental defects	+	−	−	−

−=never or rare, +=occurs, ++=diagnostic importance
Modified after C.J. Baker, MD, personal communication.

HCMV infection compared with 19 of 47 women who did not receive prevention. Although encouraging, this study had considerable methodologic limitations, and results must be duplicated in randomized, controlled trials before passive immunization can be recommended for all cases.

Development of experimental vaccine against HCMV has been making slow but steady progress. Recently, the results of a phase 2 trial of a vaccine containing recombinant CMV glycoprotein B subunit antigen combined with MF59 adjuvant for the prevention of CMV infection in seronegative women of childbearing age were published. (19) The investigators reported 50% vaccine efficacy, with time to maternal CMV infection being the primary endpoint. Breakthrough infection was observed in 19 women receiving the CMV vaccine, and one vaccinated mother delivered an infant who had congenital CMV. Although this report is a step forward for CMV vaccine development, a future trial to test efficacy on the basis of fetal infection will require enrollment of more than 50,000 women. Because of reports suggesting that nonprimary maternal HCMV infection can be as severe as primary infection, (20) the efficacy of preconception immunization never may approach 100%.

Treatment

Recent studies evaluating pre- and postnatal treatment of congenital HCMV infection have shown encouraging clinical results for ganciclovir administration. (21)(22)(23)(24) In several case reports, both intravenous and oral valganciclovir have been shown to be effective and safe to use in mothers of HCMV-infected fetuses in the early stages of pregnancy without teratogenicity. (25)(26) However, the safety and efficacy of ganciclovir in prenatal therapy needs to be evaluated further in controlled trials.

A randomized, controlled trial showed that 6 weeks of intravenous ganciclovir therapy at 12 mg/kg per day begun in the neonatal period in HCMV-infected infants who had CNS involvement may preserve hearing. (21) The study was limited by only 43 of 100 enrolled patients having hearing tested at both baseline and at 1 year of age or beyond. However, a statistically significant reduction in hearing deterioration was noted in this group. In the same study, 63% of treated infants developed significant neutropenia during therapy compared with 21% in the control group. Other potential adverse effects of ganciclovir in neonates include nephrotoxicity and increased liver enzymes. In animal studies, short-term high doses of ganciclovir inhibited spermatogenesis and induced possible carcinogenic effects. (27) Valganciclovir and foscarnet have been investigated for treatment of congenital HCMV infections in case studies. (28)(29)(30) Although information is still limited, both treatments have shown promising positive benefits without adverse effects. Recently, an Israeli group described treatment of 23 infants who had culture-proven congenital HCMV infection with intravenous ganciclovir for 6 weeks, followed by oral valganciclovir to age 12 months. (31) The authors concluded that this prolonged treatment regi-

men was safe and led to improved auditory outcome. A phase III, randomized, placebo-controlled, blinded investigation for safety and efficacy comparing a 6-week course to a 6-month course of oral valganciclovir is in progress (ClinicalTrials.gov: NCT00466817).

Congenital Toxoplasmosis

Epidemiology

Congenital toxoplasmosis is the most common congenital parasitic infection in the United States, with an estimated incidence of 0.1 to 1 in 1,000 live births, resulting in 400 to 4,000 cases each year. (32)(33) Approximately 85% of woman of childbearing age in the United States are susceptible to acute infection with *T gondii*. The domestic cat is the primary host of *T gondii*. Infection during pregnancy can be contracted by ingesting oocysts present in fecal material of infected hosts contaminating soil, cat litter, garden vegetables, or water or by ingestion of pseudocysts present in undercooked meat. *Toxoplasma* oocysts have been found in the feces of up to 12% of domestic cats in the United States. The rate in other countries varies from 1% to 55%. Kittens are more likely to excrete the oocysts than adult animals. Although fetal infection is more likely after acute *T gondii* infection in a pregnant woman, it can occur after reactivation of latent infection. (34) Most infected women have no symptoms, but 15% report acute flulike illness with lymphadenopathy. The incidence of transmission is less than 2% with maternal infection in the first 10 weeks of gestation and rises to near 80% when it occurs close to term. However, the later the infection occurs in the gestation, the less severe is the disease. The highest risk for severe congenital toxoplasmosis with serious sequelae (approximately 50%) is after infection in the first trimester, followed by 25% in the second and less than 3% in the third trimester.

Clinical Manifestations

Most cases of congenital toxoplasmosis (70% to 90%) are asymptomatic at birth, but up to 80% of affected infants develop learning or visual disabilities later in life. In contrast to infected term infants, who typically have milder symptoms such as hepatosplenomegaly and lymphadenopathy, preterm infants often develop CNS and ocular disease in the first 3 months after birth. In many cases, reduction of visual acuity or new eye lesions does not occur until the third decade of life or later. Of the 10% to 30% symptomatic newborns, some present with a systemic form of the disease characterized by a maculopapular rash, lymphadenopathy, hepatosplenomegaly, thrombocytopenia, and jaundice; others have predominant CNS manifestations of meningoencephalitis, intracranial calcifications, hydrocephalus, microcephaly, chorioretinitis, seizure disorder, or deafness. The more severe forms of congenital toxoplasmosis can be fatal before or shortly after birth.

Diagnosis

Antenatal diagnosis can be performed using PCR for parasite DNA detection in amniotic fluid or fetal blood or by isolating the organism from the placenta or fetal blood by mouse or tissue culture inoculation. (34)(35)(36) For postnatal investigations, typically serologic tests of cord or infant blood conducted in the Palo Alto reference laboratory (www.pamf.org/serology/) are recommended. *T gondii*-specific IgG antibodies are detectable indefinitely 1 to 2 months postinfection. *T gondii*-specific IgM testing often yields false-positive or false-negative results, and IgM antibodies can persist for 6 to 24 months. *T gondii*-specific IgA and IgE testing is preferred to IgM testing because IgA and IgE concentrations drop sooner than those of IgM. Serology should be repeated after 10 days because placental leak can cause false-positive results. (37)(38) The Palo Alto infant panel includes a differential agglutination test that uses two antigen preparations: one found early following acute infection (AC antigen) and one found at later stage of infection (HS). In addition, increased IgG avidity indicates that infection occurred more than 12 to 16 weeks ago.

In a recent study, Lago and associates (39) used neonatal screening for *T gondii*-specific IgM antibodies to help identify neonates who had congenital toxoplasmosis. A fluorometric assay was used to analyze *T gondii*-specific IgM in filter paper specimens obtained from newborns for routine screening for metabolic diseases. When *T gondii*-specific IgM screening was positive, serum samples from both the infant and the mother were requested for confirmatory serologic testing, and the infant underwent clinical examination. Among 10,000 infants screened, seven were found to be positive for *T gondii*-specific IgM. Six of the seven patients were confirmed to have congenital toxoplasmosis. Two of the patients were identified solely through neonatal screening with the *T gondii*-specific IgM test. This finding suggests that neonatal screening can be helpful in identifying cases of congenital toxoplasmosis that are not detected by prenatal maternal serology testing, primarily when infection is acquired in late pregnancy or when the mother does not receive regular prenatal serologic testing or prenatal care.

To investigate the utility of *T gondii*-specific T-cell

immunity for early and accurate diagnosis of congenital toxoplasmosis infection, Ciardelli and colleagues (40) examined T-cell proliferation, interferon-gamma production, and lymphocyte activation antigens expression in 23 infected and 65 uninfected neonates in the first year after birth. Evaluation of the specific T-cell response allowed identification of all infected infants plus two additional cases at 3 months of age or younger. Once infection is confirmed using PCR or serologic or cultural tests, additional postnatal investigations are recommended, including blood testing for anemia and thrombocytopenia, liver function tests, cranial ultrasonography and head computed tomography scan for hydrocephalus and calcification, and repeated ophthalmologic examinations.

Prevention

Education and serologic screening of pregnant women are currently available strategies for the prevention of congenital toxoplasmosis. Pregnant women should be warned to avoid foods/products that may be contaminated with *T gondii* oocytes by cooking food at safe temperatures; peeling or thoroughly washing fruits and vegetables; washing kitchen utensils and hands with hot soapy water; and wearing gloves when touching soil, sand, or cat litter. Studies demonstrated that educational approaches may help reduce the risk of congenital toxoplasmosis.

Treatment during pregnancy may reduce mother-child transmission within 3 weeks of seroconversion. (41) Valentini and associates (42) reported 76 infants born to mothers who had acquired toxoplasmosis during pregnancy and were treated with spiramycin, cotrimoxazole, and folinic acid. Only two infants were found to be infected, and none showed signs of congenital infection. A large randomized, controlled clinical trial is needed to provide valid evidence for the potential benefit of prenatal treatment.

Universal antenatal screening is currently not performed in the United States because of the costs and risks involved (amniocentesis), the lack of conclusive evidence for effective prenatal treatment, and concerns about treatment-associated adverse effects (neutropenia). Vaccine development to date has relied on using attenuated parasites to allow correct processing and presentation of antigen to the host immune system to stimulate proper cell-mediated immune responses. Live vaccines have problems with safety, short shelf life, and large-scale production. Therefore, devising novel vaccines using defined recombinant antigens is the current focus.

Treatment

There are no randomized clinical trials for the treatment of toxoplasmosis, and the regimens vary among countries and centers. Many experts recommend termination of pregnancy if there is documented fetal infection in the first 10 weeks of gestation complicated with hydrocephalus on ultrasonography. For infants born with congenital toxoplasmosis, a combination treatment with pyrimethamine-sulfadiazine and folinic acid for about 1 year is recommended. Because bone marrow suppression and hepatotoxicity can develop during treatment, fortnightly blood tests often are suggested. For patients who experience serious adverse effects, an alternative regime of four 21-day cycles of pyrimethamine-sulfadiazine and folinic acid, interrupted with 30 days of spiramycin, offers less toxicity. Prednisone 1 mg/kg should be considered when cerebrospinal fluid (CSF) protein is greater than 1 g/dL and chorioretinitis threatens vision. Ongoing ophthalmologic and developmental follow-up is warranted for infants diagnosed with congenital toxoplasmosis.

Congenital Rubella Syndrome

Epidemiology

Congenital rubella syndrome results from rubella infection in the mother during pregnancy. In the United States, before licensure of vaccine in 1969, there were an estimated 57,686 cases of congenital rubella syndrome. Currently, with immunization rates greater than 90% in the United States, fewer than 10 cases of congenital rubella syndrome occur per year, all of which are imported cases. (43) However, with only a few countries routinely providing immunization, rubella remains a common disease worldwide. In nonimmunized populations, 10% to 20% of women of childbearing age are susceptible. Reinfection occurs in approximately 2% of people but is generally subclinical. However, cases of congenital infection were described with maternal reinfection. (44)(45)(46) Congenital defects can occur in as many as 75% of infants if infection occurs during the first 8 weeks of gestation, 50% during weeks 9 to 12, 20% during weeks 13 to 20, and 0 to 10% after 20 weeks. (47)

Clinical Manifestations

Congenital rubella syndrome is a severe, disabling condition featuring adenopathy, radiolucencies of long bones, encephalitis, cardiac defects (pulmonary arterial hypoplasia and patent ductus arteriosus), cataracts, salt-

and-pepper chorioretinitis, microphthalmia, growth restriction, hepatosplenomegaly, thrombocytopenia, and purpura. Affected infants can be asymptomatic at birth but develop clinical sequelae during the first postnatal year.

Diagnosis

The diagnosis of congenital rubella syndrome usually is suggested by a typical clinical rubella infection in the mother, which is characterized by a 1- to 5-day prodrome of low-grade fever, headache, malaise, mild coryza, and conjunctivitis. Arthralgia or arthritis may occur in up to 70% of affected adult women. When maternal infection is suspected, maternal seroconversion, demonstrated by the presence of rubella-specific IgM for primary infection or more than a fourfold increase of rubella-specific IgG titer for reinfection, is diagnostic. These occur about 10 days after contact. The IgM assay is particularly useful when the exact "contact time" is unknown. IgM persists for about 2 months after primary infection. When maternal infection is confirmed, fetal or postnatal tests for congenital rubella syndrome are used to detect congenital infection. Cord blood rubella-specific IgM and PCR of amniotic fluid are valuable fetal diagnostic methods. The postnatal diagnosis can be confirmed through rubella-specific IgM testing in serum or isolation of rubella virus from many body sites, including pharyngeal secretions, eye, throat, CSF, stool, and urine.

Once congenital rubella infection is confirmed, additional tests are necessary to evaluate disease severity and to monitor development of infection. These include blood tests for anemia and thrombocytopenia, liver function tests, renal function tests, electrolyte assessment, cranial and renal ultrasonography, echocardiography, lumbar puncture, chest and long bone radiographs, and serial hearing and ophthalmologic assessments over the first few postnatal years. Screening for endocrine complications such as diabetes mellitus and hypothyroidism are indicated for long-term management.

Prevention

After the first rubella vaccine was licensed for use in 1969, a dramatic decrease of rubella and congenital rubella cases was documented in the United States. Before vaccination became available, the 1964 to 1965 United States epidemic of rubella led to an estimated 11,250 fetal deaths, 2,100 newborn deaths, 11,600 infants born deaf, 3,580 infants born blind, and 1,800 infants born mentally handicapped. In the past decade, the number of cases of congenital rubella syndrome in the United States has been less than 10 cases per year. Hispanic immigrant infants have an increased risk of congenital rubella syndrome compared with infants from other ethnic backgrounds. (48)

The controversy over the measles-mumps-rubella (MMR) vaccine and its possible cause of autism has been put to rest. Panels convened by the Institute of Medicine, Medical Research Council, and World Health Organization have all agreed that studies do not support the hypothesis that MMR vaccination is a cause of autism. (49)(50)(51) It is worth noting that the original publication describing the association between MMR and autism recently was retracted by the journal *Lancet*. (52)

Treatment

There is no specific treatment for congenital rubella infection. Care involves supportive treatment. The outcome for a child who has congenital rubella depends on the severity of problems present. Heart defects often can be corrected surgically, but damage to the nervous system is permanent.

Herpes Simplex Virus

Epidemiology

Neonatal herpes is usually the result of HSV-2 infection, which is the primary type of HSV associated with genital infection. The prevalence of genital HSV infection varies from country to country and among different ethnic backgrounds. Many genital herpes cases remain asymptomatic for long periods, with no history of infection despite shedding virus. The chance of a woman who has a past history of genital herpes shedding virus at the time of delivery is approximately 1%. However, in most cases of neonatal infection, mothers do not give a history of active genital herpes at the time of delivery. Infants born to mothers who have primary first-episode genital herpes infections at the time of delivery have a 50% risk of developing infection compared with a 25% risk when mothers have antibodies to HSV-1 only (nonprimary first episode) and less than 2% in cases of recurrent infections in seropositive mothers. (53). In the United States, the prevalence of neonatal herpes is 0.05 to 0.3 per 1,000 live births, with 1,500 cases occurring every year. The transmission rate for intrapartum infection is about 88% to 93%, which is much higher than for infections acquired from other routes, such as only 5% to 10% for postpartum infection and less than 2% for intrauterine infection.

Clinical Manifestations

Neonatal HSV infection typically presents within 1 to 3 weeks of birth but should be considered up to 46 weeks postmenstrual age. Localized disease presents as vesicles or zoster-like eruptions on skin, eyes, or mouth. If left untreated, more than 70% of cases progress to disseminated disease. Nonspecific presentations with disseminated disease include poor feeding, fever, lethargy, apnea, convulsion, respiratory distress, hepatomegaly, jaundice, and disseminated intravascular coagulation. Despite systemic treatment, disseminated disease is associated with mortality rates between 50% (HSV-2) and 70% (HSV-1). (54) Hemorrhagic pneumonitis, severe coagulopathy, liver failure, and meningoencephalitis are associated with a poor prognosis. It is noteworthy that up to 40% of patients who have disseminated disease do not develop skin lesions.

Approximately 30% of neonates present with CNS disease, in one third of cases without skin findings. Clinical signs include seizures, lethargy, irritability, tremors, poor feeding, temperature instability, and a bulging fontanelle. At least 50% of patients suffer long-term sequelae, despite high-dose acyclovir treatment. Seizures at or before initiation of antiviral therapy are associated with an increased risk for morbidity.

Although less than 2% of neonatal herpes cases are caused by intrauterine infection, these cases present with a broad spectrum of findings involving the skin (scarring, active lesions) and the CNS (microphthalmia, retinal dysplasia, chorioretinitis, microcephaly, hydranencephaly, calcifications).

Diagnosis

Because most affected newborns are born to mothers who do not have current active genital HSV lesions, a high level of vigilance is necessary to screen acutely ill infants for HSV infection. All infants should be examined for vesicles. Viral cultures after 48 hours of age are collected from various sites, including mouth, nasopharynx, conjunctivae, rectum, skin vesicles, urine, stool, blood, and CSF. Although histology and viral culture of brain tissue by biopsy confirms the diagnosis of HSV encephalitis, the method of choice for the clinical diagnosis of HSV encephalitis is HSV-PCR testing from CSF in experienced laboratories. However, one negative HSV-PCR test result does not completely rule out HSV infection, and the clinical picture of herpes encephalopathy may warrant continued treatment. (55) Electroencephalography and brain imaging are useful adjuncts in cases where CNS infection is suspected despite negative HSV-PCR results. Liver function and coagulation tests are helpful to evaluate disseminated disease.

Prevention

Although knowledge of the serologic status of a couple can help guide clinical management, (56) routine HSV screening among previously undiagnosed women during pregnancy is not currently recommended by the American College of Obstetricians and Gynecologists. A meta-analysis of five studies has shown that antiviral suppression therapy during pregnancy reduces the rate of HSV outbreaks and the resultant need for cesarean section. (57) However, given the low risk of neonatal infection, antiviral suppressive therapy late in gestation for all HSV-2 positive patients is controversial. (58) In the absence of lesions during the third trimester, routine serial cultures for HSV are not indicated for women who have a history of recurrent genital herpes because viral shedding is brief and intermittent. Prophylactic cesarean section typically is performed immediately if ruptured membranes and active genital lesions or a prodromal syndrome are present at term. In the absence of active genital lesions at the time of delivery, maternal history alone or asymptomatic shedding of genital HSV are not indications for cesarean delivery. Importantly, cesarean section even before rupture of membranes does not prevent infection in all cases. In a national surveillance study of 184 cases of neonatal HSV infections, (59) 15 cases occurred despite cesarean delivery performed before membrane rupture.

Treatment

For skin-eye-mouth disease, intravenous acyclovir 20 mg/kg per dose three times daily for 14 days is recommended. For disseminated disease and encephalitis, treatment for at least 21 days is required. For HSV encephalitis, acyclovir should be continued until CSF PCR test results become negative. The neutrophil counts should be monitored at least twice weekly during treatment to avoid severe neutropenia. Topical ophthalmic drugs are helpful for eye lesions, and ophthalmologic referral is essential. Newer antiviral agents with better bioavailability (eg, valacyclovir) should be evaluated in randomized trials for the treatment of localized neonatal disease or for infants who have recurrences after the neonatal period.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the epidemiology, prevention, and pathogenesis of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with herpes 1, herpes 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster.
- Know the epidemiology, pathogenesis, and prevention of congenital infections with measles, mumps, and rubella.
- Know the clinical manifestations, diagnostic criteria, treatment, and complications of congenital infections with measles, mumps, or rubella.
- Know the epidemiology, pathogenesis, and prevention of perinatal infections with toxoplasmosis.
- Know the clinical manifestations, diagnostic features, management, and complications of perinatal infections with toxoplasmosis.

References

1. Hertzberg R. Congenital cataract following German measles in the mother. Abstracts from the publications of the late Sir Norman McAlister Gregg. *Aust N Z J Ophthalmol.* 1985;13:303–309

2. Gregg NM. Congenital cataract following German measles in the mother. 1941. *Aust N Z J Ophthalmol.* 1991;19:267–276

3. Nahmias AJ, Walls KW, Stewart JA, Herrmann KL, Flynt WJ. The TORCH complex. Perinatal infections associated with *Toxoplasma*, rubella, cytomegalovirus and herpes [abstract]. *Pediatr Res.* 1971;5:405–406

4. Nahmias AJ. The TORCH complex. *Hosp Pract.* 1974;9:65–66

5. Alford CA, Stagno S, Pass RF, Britt WJ. Congenital and perinatal cytomegalovirus infections. *Rev Infect Dis.* 1990;7(suppl): S745–S753

6. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol.* 2006;35:226–231

7. Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. *J Clin Virol.* 2008;41:57–62

8. Gutierrez J, Piedrola G, Maroto MC. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection. *J Infect Dis.* 1998;178:599–600

9. Fowler KB, Stagno S, Pass RF. Maternal immunity and prevention of congenital cytomegalovirus infection. *JAMA.* 2003;289: 1008–1011

10. Duff P. A thoughtful algorithm for the accurate diagnosis of primary CMV infection in pregnancy. *Am J Obstet Gynecol.* 2007; 196:196–197

11. Abdel-Fattah SA, Bhat A, Illanes S, Bartha JL, Carrington D. TORCH test for fetal medicine indications: only CMV is necessary in the United Kingdom. *Prenat Diagn.* 2005;25:1028–1031

12. Collinet P, Subtil D, Houfflin-Debarge V, Kacet N, Dewilde A, Puech F. Routine CMV screening during pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2004;114:3–11

13. Grangeot-Keros L, Mayaux MJ, Lebon P, et al. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection in pregnant women. *J Infect Dis.* 1997;175: 944–946

14. Theiler RN, Caliendo AM, Pargman S, et al. Umbilical cord blood screening for cytomegalovirus DNA by quantitative PCR. *J Clin Virol.* 2006;37:313–316

15. Bradford RD, Cloud G, Lakeman AD, et al. Detection of cytomegalovirus (CMV) DNA by polymerase chain reaction is associated with hearing loss in newborns with symptomatic congenital CMV infection involving the central nervous system. *J Infect Dis.* 2005;191:227–233

16. Lanari M, Lazzarotto T, Venturi V, et al. Neonatal cytomegalovirus blood load and risk of sequelae in symptomatic and asymptomatic congenitally infected newborns. *Pediatrics.* 2006;117: e76–e83

17. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus among pregnant women. *J Pediatr.* 2004;145:485–491

18. Adler SP, Nigro G. Findings and conclusions from CMV hyperimmune globulin treatment trials. *J Clin Virol.* 2009;4(suppl 4):S54–S57

19. Pass RF. Development and evidence for efficacy of CMV glycoprotein B vaccine with MF59 adjuvant. *J Clin Virol.* 2009; 4(suppl 4):S73–S76

20. Boppana SB, Rivera LB, Fowler KB, Mach PHM, Britt WJ. Intrauterine transmission of cytomegalovirus to infants of women with preconceptional immunity. *N Engl J Med.* 2001;344: 1366–1371

21. Kimberlin DW, Lin CY, Sánchez PJ, et al; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr.* 2003;143:16–25

22. Lackner A, Acham A, Alborno T, et al. Effect on hearing of ganciclovir therapy for asymptomatic congenital cytomegalovirus infection: four to 10 year follow up. *J Laryngol Otol.* 2009;123: 391–396

23. Oliver SE, Cloud GA, Sanchez PJ, et al; National Institute of Allergy, Infectious Diseases Collaborative Antiviral Study Group. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol.* 2009;46(suppl 4):S22–S26

24. Michaels MG, Greenberg DP, Sabo DL, Wald ER. Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J.* 2003;22:504–509

25. Schleiss MR, McVoy MA. Overview of congenitally and perinatally acquired cytomegalovirus infections: recent advances in antiviral therapy. *Expert Rev Anti Infect Ther.* 2004;2:389–403

26. Puliyanda DP, Silverman NS, Lehman D, et al. Successful use of oral ganciclovir for the treatment of intrauterine cytomegalovirus infection in a renal allograft recipient. *Transpl Infect Dis.* 2005;7: 71–74

27. Fan-Havard P, Nahata MC, Brady MT. Ganciclovir–a review of pharmacology, therapeutic efficacy and potential use for treatment of congenital cytomegalovirus infections. *J Clin Pharm Ther.* 1989;14:329–340

28. Nigro G, Sali E, Anceschi MM, et al. Foscarnet therapy for congenital cytomegalovirus liver fibrosis following prenatal ascites. *J Matern Fetal Neonatal Med.* 2004;15:325–329

29. Muller A, Eis-Hubinger AM, Brandhorst G, Heep A, Bartmann P, Franz AR. Oral valganciclovir for symptomatic congenital

cytomegalovirus infection in an extremely low birth weight infant. *J Perinatol*. 2008;28:74–76
30. Galli L, Novelli A, Chiappini E, et al. Valganciclovir for congenital CMV infection: a pilot study on plasma concentration in newborns and infants. *Pediatr Infect Dis J*. 2007;26:451–453
31. Amir J, Wolf DG, Levy I. Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir. *Eur J Pediatr*. 2010. Epub ahead of print
32. Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. *Int J Parasitol*. 2009; 39:1385–1394
33. Elsheikha HM. Congenital toxoplasmosis: priorities for further health promotion action. *Public Health*. 2008;122:335–353
34. Remington JS, Mcleod R, Thuilliez P, Desmonts J. Toxoplasmosis. In: Remington JS, Klein JO, Wilson CB, Baker C, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 6th ed. Philadelphia, Pa: Elsevier Saunders; 2006:947–1091
35. Romand S, Wallon M, Franck J, Thulliez P, Peyron F, Dumon H. Prenatal diagnosis using polymerase chain reaction on amniotic fluid for congenital toxoplasmosis. *Obstet Gynecol*. 2001;97: 296–300
36. Hezard N, Marx-Chemla C, Foudrinier F, et al. Prenatal diagnosis of congenital toxoplasmosis in 261 pregnancies. *Prenat Diagn*. 1997;17:1047–1054
37. Foudrinier F, Villena I, Jaussaud R, Aubert D, Chemla C, Martinot F, Pinon JM. Clinical value of specific immunoglobulin E detection by enzyme-linked immunosorbent assay in cases of acquired and congenital toxoplasmosis. *J Clin Microbiol*. 2003;41: 1681–1686
38. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis*. 2002;185:S73–S82
39. Lago EG, Neto EC, Melamed J, et al. Congenital toxoplasmosis: late pregnancy infections detected by neonatal screening and maternal serological testing at delivery. *Paediatr Perinat Epidemiol*. 2007;21:525–531
40. Ciardelli L, Meroni V, Avanzini MA, et al. Early and accurate diagnosis of congenital toxoplasmosis. *Pediatr Infect Dis J*. 2008; 27:125–129
41. Desmonts G, Couvreur J. Congenital toxoplasmosis: a prospective study of the offspring of 542 women who acquired toxoplasmosis during pregnancy. In: Thalhammer O, Pollak A, Baumgarten K, eds. *Perinatal Medicine: Proceedings of the 6th European Congress, Vienna*. Stuttgart, Germany: Georg Thiema Publisher; 1979:51–60
42. Valentini P, Annunziata ML, Angelone DF, et al. Role of spiramycin/cotrimoxazole association in the mother-to-child transmission of toxoplasmosis infection in pregnancy. *Eur J Clin Microbiol Infect Dis*. 2009;28:297–300
43. Reef SE, Redd SB, Abernathy E, Zimmerman L, Icenogle JP. The epidemiological profile of rubella and congenital rubella syndrome in the United States, 1998–2004: the evidence for absence of endemic transmission. *Clin Infect Dis*. 2006;3(suppl):S126–S132
44. Aboudy Y, Fogel A, Barnea B, et al. Subclinical rubella reinfection during pregnancy followed by transmission of virus to the fetus. *J Infect*. 1997;34:273–276
45. Bullens D, Smets K, Vanhaesebrouck P. Congenital rubella syndrome after maternal reinfection. *Clin Pediatr (Phila)*. 2000; 39:113–116
46. Keith CG. Congenital rubella infection from reinfection of previously immunised mothers. *Aust N Z J Ophthalmol*. 1991;19: 291–293
47. Peckham C. Clinical and laboratory study of children exposed in utero to maternal rubella. *Arch Dis Child*. 1972;47:571–577
48. Zimmerman L, Reef SE. Incidence of congenital rubella syndrome at a hospital serving a predominantly Hispanic population, El Paso, Texas. *Pediatrics*. 2001;107:E40
49. Taylor B, Miller E, Farrington CP, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet*. 1999;353:2026–2029
50. Halsey NA, Hyman SL; Conference Writing Panel. Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12–13, 2000. *Pediatrics*. 2001; 107:E84
51. DeStefano F, Thompson WW. MMR vaccine and autism: an update of the scientific evidence. *Expert Rev Vaccines*. 2004;3: 19–22
52. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. 1998;35:637–641. Partial retraction in: Murch SH, Anthony A, Casson DH, et al. *Lancet*. 2004; 363:750. Retraction in *Lancet*. 2010. doi: 10.1016/S0140-6736(10)60175-4
53. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA*. 2003;289: 203–209
54. Kimberlin DW, Lin CY, Jacobs RF, et al; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics*. 2001;108:223–229
55. Kimberlin DW. Neonatal herpes simplex infection. *Clin Microbiol Rev*. 2004;17:1–13
56. Gardella C, Brown Z, Wald A, et al. Risk factors for herpes simplex virus transmission to pregnant women: a couples study. *Am J Obstet Gynecol*. 2005;193:1891–1899
57. Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. *Obstet Gynecol*. 2003;102:1396–1403
58. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med*. 2009;361:1376–1385
59. Stone KM, Brooks CA, Guinan ME, Alexander ER. National surveillance for neonatal herpes simplex virus infections. *Sex Transm Dis*. 1989;16:152–156

NeoReviews Quiz

12. Congenital viral infections can cause devastating long-term consequences. Of the following, the *most* common cause of nonhereditary sensorineural hearing loss in children is congenital viral infection caused by:

    A. Adenovirus.
    B. Cytomegalovirus.
    C. Herpes simplex virus.
    D. Respiratory syncytial virus.
    E. Rubella virus.

13. Human cytomegalovirus is the most common cause of congenital viral infection in the United States. Of the following, higher rates of congenital cytomegalovirus infection are seen in seronegative women of:

    A. Advanced maternal age.
    B. High socioeconomic status.
    C. Married status.
    D. Occupations with exposure to children.
    E. White race.

14. Congenital toxoplasmosis is the most common congenital parasitic infection in the United States, with an estimated incidence of 0.1 to 1.0 per 1,000 live births. Of the following, the *most* accurate statement regarding congenital toxoplasmosis is that:

    A. Adult cats are more likely than kittens to excrete *Toxoplasma* oocysts.
    B. Fetal infection is more likely from reactivation of latent infection than from primary infection.
    C. Frequency of transmission of *Toxoplasma* during pregnancy increases with advancing gestation.
    D. Most affected women manifest flulike illness with lymphadenopathy.
    E. Serious sequelae are more likely after infection in the third trimester of pregnancy.

15. Congenital rubella syndrome is a severe, disabling condition in the newborn characterized by features that include encephalitis, cataracts, chorioretinitis, cardiac defects, hepatosplenomegaly, thrombocytopenia, and growth restriction. Of the following, the *most* accurate statement regarding congenital rubella virus infection is that:

    A. Frequency of fetal congenital defects is highest when infection occurs after 20 weeks of gestation.
    B. Infants of Hispanic immigrants are more immune to congenital rubella syndrome than infants of other ethnicities.
    C. Maternal seroconversion is demonstrated by the presence of rubella-specific immunoglobulin G after primary infection.
    D. Measles-mumps-rubella vaccination is an established cause of autism in immunized children.
    E. Most women who have rubella virus infection manifest fever, coryza, conjunctivitis, and arthralgia.

16. Neonatal herpes simplex virus infection has a prevalence of 0.05 to 0.3 per 1,000 live births in the United States. Of the following, the *most* accurate statement regarding neonatal herpes simplex virus infection is that most cases:

    A. Are associated with maternal active genital herpes at the time of delivery.
    B. Are not associated with long-term sequelae following high-dose acyclovir treatment.
    C. Of disseminated disease have a mortality ranging from 10% to 20%.
    D. Result from intrauterine or postpartum infection.
    E. Typically present with localized disease involving skin, eyes, or mouth.

Congenital Infections, Part I: Cytomegalovirus, Toxoplasma, Rubella, and Herpes Simplex

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