Fetal Infections and Brain Development

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Nearly four decades ago TORCH, an acronym signifying \textit{Toxoplasma gondii}, \textit{Rubella}, \textit{Cytomegalovirus (CMV)}, and \textit{Herpesviruses}, emerged as a unifying concept that underscored the importance of intrauterine infections in humans.\textsuperscript{1} This acronym reminds clinicians that several infectious agents can produce similar and potentially devastating effects on the fetus and developing nervous system. Although rubella has since disappeared in nations with compulsory immunization against this agent and some have questioned the use of the TORCH concept, the pathogens signified by TORCH, and more recently recognized agents, including lymphocytic choriomeningitis (LCM virus), remain major causes of deafness, blindness, and permanent neurodevelopmental disabilities among children born in both developed and developing nations.

This article summarizes current knowledge regarding the clinical manifestations, pathogenesis, treatment, and prevention of congenital infections with these agents. In particular, this material updates readers regarding the encouraging results of treatment trials for congenital toxoplasmosis and CMV disease. The article concludes with a brief section describing perinatal parechovirus and herpes simplex virus (HSV) infections, additional disorders that can damage the developing nervous system during the immediate postnatal period.

EPIDEMIOLOGY

Before widespread immunization against rubella virus, epidemics of rubella (German measles), once the most common cause of congenital infection in humans, occurred worldwide at 6- to 9-year intervals. Humans represent the only reservoir of rubella virus; transmission results from contact with infected respiratory secretions. During the 1962 to 1965 pandemic, the last major outbreak of rubella in the United States,
approximately 20,000 infants were affected by congenital rubella syndrome (CRS). In addition, there were more than 10,000 fetal deaths and 2000 neonatal deaths during the pandemic. By the late 1980s, CRS had largely disappeared from the United States and other developed nations because of compulsory immunization programs. A comprehensive French study identified an incidence of 28 cases per 100,000 live births during the 1970s and 1980s and a 10-fold reduction by 2002 after aggressive immunization of young children. CRS remains a major health concern in developing nations, however, and as recently as 2006, more than 100,000 cases of CRS were estimated to occur worldwide annually. Moreover, CRS still appears sporadically in the United States and other developing nations as the result of immunization noncompliance and importation of cases from countries without immunization programs. Eliminating CRS remains a major goal of the World Health Organization.

With the near-elimination of rubella in developed nations, congenital CMV infection emerged as the most commonly recognized congenital or intrauterine viral infection in many regions. United States studies indicate that 0.25% to 1% of infants shed CMV at birth, and because 5% to 10% of these have symptomatic infections, approximately 4000 infants are born annually in the United States with congenital CMV disease. CMV resides in human populations with transmission resulting from direct human-to-human contact with infected saliva, urine, semen, or cervical secretions. Maternal risk factors for delivering a congenitally infected infant include young maternal age; multiple sexual partners; and contact with young children, a major reservoir of CMV in human populations.

Congenital toxoplasmosis currently represents the second most commonly recognized congenital infection. *T. gondii*, a ubiquitous parasite, infects birds and many mammals, especially felines, worldwide. Domestic cats, a major source of human infection, excrete vast quantities of oocysts, and the resulting sporozoites remain viable in soils for extended periods. Human infection results from ingestion of meats containing viable *T. gondii* tissue cysts or foods contaminated with oocysts. The seroprevalence rates of toxoplasmosis are highest in France; intermediate in Latin America, sub-Saharan Africa, and central Europe; and lowest in North America, South-East Asia, and Oceania. Rates of congenital infection range from less than 0.1 to approximately 1 per 1000 live births.

Each year as many as 2 million pregnant women worldwide acquire syphilis, the consequence of infection with the spirochete *Treponema pallidum*. Infection results from direct contact with infected human secretions by oral, anal, or vaginal intercourse. Fomites do not participate in the transmission of *T. pallidum*. Transmission of the spirochete to the fetus occurs in as many as 50% of the maternal infections, leading to fetal death, stillbirth, and congenital infection. Rare in most developed countries, congenital syphilis affects several hundred infants annually in the United States, especially in densely populated urban areas or in the rural South.

Congenital infections with other pathogens occur less frequently. The incidence of neonatal HSV infections ranges from 0.025 to 0.3 per 1000 live births, but only 5% to 10% of these represent congenital infections. The rates of varicella in pregnant women range from less than 1 to 3 per 1000, and very few of the infected women (< 2%) deliver infants with congenital infections. Infections with LCM virus, a rodent-borne arenavirus, have been reported from the United States and Eastern Europe, but the incidence of congenital infection, although presumed to be very low, is unknown. Humans become infected with LCM virus through contact with infected aerosols or fomites. Current data regarding the incidence of congenital Chagas disease, caused by maternal infection with the parasite *Trypanosoma cruzi*, although imprecise, suggest that as many as 10,000 infants are infected with this
agent annually in the Americas. Finally, despite considerable concern about the
public health consequences of West Nile virus infection of pregnant women, only
a single case of congenital West Nile virus infection has been reported to date. The
current annual incidence of these selected intrauterine and perinatal infections
is presented in Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Annual Incidence (Per 1000 Live Births)</th>
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<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>2.9–10 a</td>
</tr>
<tr>
<td>Herpes simplex virus (congenital)</td>
<td>&lt; 0.01–0.33</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td>Unknown, but presumed rare</td>
</tr>
<tr>
<td>Rubella virus b</td>
<td>0-&gt;1</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>&lt; 0.1–1</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>0.1</td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>0.01–0.7</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Very rare</td>
</tr>
<tr>
<td>Human parechovirus</td>
<td>Unknown</td>
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Estimated from various sources.
a Approximately 90% are asymptomatic.
b Congenital rubella syndrome.

**CLINICAL MANIFESTATIONS**

**Early**

Most of the pathogens associated with intrauterine infections can produce systemic
and neurologic features that appear in the neonatal period. Clinicians should suspect
intrauterine infections when infants display jaundice, hepatomegaly, splenomegaly,
rash, intrauterine growth retardation, microcephaly, hydrocephalus, or chorioretinitis.
Although the TORCH paradigm reminds clinicians of the manifestations potentially
shared by these agents, some pathogens have unique clinical characteristics. Rubella
virus, as an example, is the only agent causing congenital heart lesions, characteristic-
ly patent ductus arteriosus, and varicella zoster virus (VZV) is the only agent
causing a unique pattern of skin scarring known as a “cicatrix.” Prominent osteopathy
suggests congenital syphilis or CRS, whereas isolated chorioretinitis is compatible
with either congenital toxoplasmosis or LCM virus infection. LCM virus affects only
the brain and eye of congenitally infected infants, causing microcephaly, hydroceph-
alus, and chorioretinitis.

Jaundice, hepatomegaly, and splenomegaly are the most frequently encountered
systemic manifestations of intrauterine infections. Of symptomatic infants with
congenital CMV infection, jaundice and hepatosplenomegaly are each exhibited in
approximately 70% or more, and more than 75% of the infants with congenital
toxoplasmosis also have jaundice and hepatosplenomegaly. Approximately 50% of
the infants with congenital Chagas disease or congenital syphilis have these
abnormalities. By contrast, infants with CRS have relatively low rates of jaundice or
hepatosplenomegaly, on the order of 20%, and such features are distinctly unusual
in congenital infections with varicella and LCM virus.

Purpuric or petechial rash should suggest congenital CMV disease, toxoplasmosis,
syphilis, or CRS, whereas vesicular rash can suggest congenital varicella syndrome or
congenitally or perinatally acquired HSV infections. As many as 30% of the infants with disseminated or encephalitic perinatal HSV infections, however, lack vesicular rash. Petechiae or purpura are present in 70% of CMV-infected infants and in 20% to 25% of the infants affected by congenital toxoplasmosis or syphilis. The classic “blueberry muffin” rash, a sign indicating extramedullary hematopoiesis, can be observed in congenital rubella virus or CMV infections. Zigzag skin lesions (cicatrix) conforming to a dermatomal distribution suggest congenital varicella syndrome; rarely, bullous lesions can be observed in congenital infections with HSV or LCM virus. Infants with congenital syphilis can exhibit maculopapular or bullous rashes of the palms; mucous patches; or condyloma lata, raised wartlike lesions.

The neonatal neurologic manifestations of congenital infections consist of microcephaly, hydrocephalus, seizures, meningoencephalitis, and abnormalities of muscle tone. Microcephaly commonly accompanies infections with congenital CMV, rubella virus, HSV, and VZV, whereas macrocephaly, usually indicating hydrocephalus, commonly accompanies congenital toxoplasmosis. Microcephaly or hydrocephalus can be observed in congenital LCM virus infections, and hydrocephalus and macrocephaly can develop postnatally as a result of obstructive hydrocephalus in infants who were initially microcephalic. Seizures, focal or generalized, can be an early or late manifestation of congenital infection with several agents. Features of meningoencephalitis caused by CMV, rubella, or HSV can include lethargy, irritability, and full or bulging fontanels.

Ophthalmologic features in congenital infections include chorioretinitis, cataract, pigmentary retinopathy, optic atrophy, and microphthalmia. Chorioretinitis occurs in greater than 90% of the infants with congenital LCM virus infection, 75% of the infants with congenital toxoplasmosis, approximately 50% of the infants with congenital varicella syndrome, and 10% to 20% of the infants with congenital CMV disease. Approximately 80% or more of the infants with CRS have cataracts, and a substantial number also have pigmentary retinopathy or microphthalmia. Cataracts can be observed in congenital infections with VZV, HSV, and LCM virus, but are distinctly uncommon in congenital infections with CMV and T gondii. Cortical visual impairment, reflecting damage to the occipital cortex or optic pathway, can be a complication of virtually all of these infections.

Sensorineural hearing loss is a prominent manifestation of CRS and congenital CMV disease. During the 1962 to 1965 United States epidemic of German measles, more than 20,000 infants were born with CRS, and nearly 90% had sensorineural hearing loss. In many, deafness was the only manifestation of CRS. CMV currently represents the most common nongenetic cause of permanent hearing loss among children living in the United States. Sensorineural hearing loss affects 50% of the infants with congenital CMV disease and approximately 8% of the so-called “asymptomatically infected infants.” The latter infants lack clinical or laboratory manifestations of congenital infection at birth, but exhibit sensorineural hearing loss that can appear during childhood and fluctuate or progress. Sensorineural hearing loss in congenitally infected infants can be unilateral or bilateral and ranges from mild to profound. Approximately 10% of the infants with congenital toxoplasmosis have sensorineural hearing loss; deafness is an infrequent complication of infections with T pallidum, T cruzi, varicella, LCM virus, or HSV.

**Late**

Certain neurologic or systemic manifestations of congenital infections may not appear for months or years after intrauterine infection. Classic examples of this phenomenon are the immune-mediated endocrinologic abnormalities, diabetes mellitus, and
hypothyroidism, which appear in the teens or early 20s in patients with CRS. Late-onset sensorineural hearing loss in children with congenital CMV disease can be progressive or fluctuating, even among infants without signs of CMV infection during the neonatal period. Infants with congenital syphilis can have a constellation of late findings that includes saber shins; saddle-nose deformity; mulberry molars; frontal bossing; rhagades; and Hutchinson’s triad (sensorineural deafness, interstitial keratitis, and Hutchinson teeth [peg-shaped upper incisors]). Obstructive hydrocephalus can occur postnataally in infants with congenital LCM virus infections. Infantile spasms can appear during the first year of life in infants with congenital CMV infection, congenital toxoplasmosis, CRS, or perinatal HSV infection. Infants with CRS are a risk of postrubella panencephalitis, a rare, fatal neurodegenerative disorder that can appear years after CRS.

**LABORATORY FEATURES AND MICROBIAL DIAGNOSIS**

**Laboratory Features**

Laboratory abnormalities suggesting intrauterine infection include direct hyperbilirubinemia, hemolytic anemia, thrombocytopenia, and elevations of the serum transaminases alanine aminotransferase and aspartate aminotransferase. Approximately 70% of the infants with congenital CMV disease have mild to moderate elevations of the serum transaminases; occasional infants have severe hepatitis that leads to cirrhosis and liver failure. These features reflect viral replication in hepatocytes and virus-induced hepatic dysfunction. Transient hepatic dysfunction commonly occurs also in congenital toxoplasmosis, CRS, and congenital syphilis.

Thrombocytopenia, often in the range of 15,000 to 50,000/µL, can be seen in infections with CMV, *T. gondii*, and rubella virus. Approximately 50% or more of the infants with congenital CMV disease have thrombocytopenia, and about one third of these have platelet counts lower than 50,000/µL. Most infants with symptomatic CRS have thrombocytopenia; nearly 20% of such infants have platelet counts less than 20,000/µL. Thrombocytopenia in congenital CMV disease and other congenital infections results from a combination of virus-induced marrow dysfunction, consumption of platelets by disseminated intravascular coagulopathy or hypersplenism, and autoimmune destruction of mature platelets.

Anemia, resulting from marrow dysfunction or hemolysis, commonly accompanies congenital syphilis, toxoplasmosis, CMV disease, Chagas disease, and CRS. Hemolytic anemia is suggested by an increased reticulocyte count and peripheral smears showing polychromasia, nucleated red blood cells, and abnormalities of erythrocyte morphology. Examination of bone marrow aspirates may show an increased erythroid/myeloid ratio in cases of hemolysis or decreased erythrocyte precursors in cases of virus-induced marrow suppression. Cerebrospinal fluid features of congenital infection can consist of protein elevation and lymphocytic pleocytosis. Normal cerebrospinal fluid results, however, do not eliminate congenital infection from consideration.

**Microbial Diagnosis**

The diagnosis of congenital infections relies on serologic, molecular, or culture methods, depending on the pathogen (Table 2). Serologic methods remain the most useful strategy when infections caused by *T. gondii* or LCM virus are suspected. Because IgM and IgA do not cross the placenta, detection of *T. gondii*—specific IgM or IgA in the infant’s serum strongly suggests congenital toxoplasmosis. By contrast, absence of *T. gondii*—specific IgG or IgM in the infant’s serum and IgG in maternal
serum virtually eliminates this disorder. Congenital LCM virus infection is supported by detection of LCM virus–specific IgM in the infant’s serum using ELISA.

Although culture of CMV from an infant’s saliva or urine during the first 3 weeks of life remains the gold standard for the diagnosis of congenital CMV disease, congenital infection is established by detection of CMV-specific IgM in the infant’s serum or CMV nucleic acids in urine or saliva using the polymerase chain reaction. Because CMV is commonly acquired by nursing infants, congenital infection cannot be confirmed by culture or polymerase chain reaction detection of CMV in urine samples obtained after 4 weeks of age. Polymerase chain reaction detection of CMV in neonatal blood spots using Guthrie cards represents an important breakthrough in the ability retrospectively to establish congenital CMV infection.29,30 Virus culture or polymerase chain reaction can be used to establish the diagnosis of intrauterine or perinatally acquired HSV infections; HSV DNA can be detected in the cerebrospinal fluid of approximately 70% of the infants with perinatal HSV meningoencephalitis.10 The diagnosis of congenital varicella syndrome can be made by detection of VZV-specific DNA in tissues or fluids, detection of VZV-specific IgM in neonatal serum, or persistence of VZV-specific IgG beyond 7 months of age.31

### Table 2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Preferred Diagnostic Method</th>
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<tr>
<td>Cytomegalovirus</td>
<td>Urine PCR or culture</td>
</tr>
<tr>
<td>Herpes simplex viruses</td>
<td>CSF, serum, vesicle fluid PCR</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis virus</td>
<td>Serum lymphocytic choriomeningitis virus–specific IgM</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Serum rubella-specific IgM; RT-PCR</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>T gondii-specific IgM</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>CSF, serum VDRL</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Varicella-zoster virus–specific IgM; CSF PCR</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>CSF, serum West Nile virus–specific IgM</td>
</tr>
<tr>
<td>Human parechovirus</td>
<td>CSF PCR</td>
</tr>
</tbody>
</table>

**Abbreviations:** CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; VDRL, Venereal Disease Research Laboratories.

CT and MRI have major roles in evaluating infants with suspected or proved congenital or perinatal infections; neuroimaging features, such as intracranial calcifications, may be the initial clue to the presence of a congenital infection. Ultrasonography remains a useful imaging modality for studying unstable infants who cannot be transported to an imaging suite, but cranial ultrasound lacks the sensitivity to characterize adequately the central nervous system effects of intrauterine infections. Features common to congenital infections include periventricular hyperechogenicities, intracranial calcifications, cystic encephalomalacia, atrophic ventriculomegaly, and periventricular leukomalacia.

Approximately 50% of the infants with congenital CMV disease have intracranial calcifications (Fig. 1), usually in a periventricular distribution, and periventricular calcifications can also be observed in infants with CRS, LCM virus infections, and congenital toxoplasmosis. In the latter disease intracranial calcifications tend to be scattered diffusely throughout the brain parenchyma (Fig. 2), but some infants with
CMV or LCM virus infections can also have a parenchymal pattern of calcifications (Fig. 3).\textsuperscript{14,32} Calcifications in infants with congenital HSV infections distinctively involve the thalamus and basal ganglia.\textsuperscript{33} Infants with CRS have periventricular or parenchymal calcifications, but because CRS largely disappeared in developed
nations before major advances in neuroimaging, the neuroradiographic descriptions of CRS are quite sparse.34 Various abnormalities of the cerebral cortex, including polymicrogyria, schizencephaly, pachgyria-lissencephaly, hydranencephaly, and cleft cortical dysplasia, can be observed in infants with congenital HSV, CMV, LCM virus, and VZV infections.12,14,32–36 CMV commonly causes polymicrogyria (see Fig. 3) and can also produce lissencephaly, schizencephaly, and various patterns of cortical dysplasia (Fig. 4). Cerebellar hypoplasia can occur in infants with congenital CMV (Fig. 5) or LCM virus infections.14 These imaging features, influenced primarily by the timing of fetal infection, provide important insights into the pathogenesis of intrauterine infections.

THE PATHOGENESIS OF BRAIN ABNORMALITIES ASSOCIATED WITH CONGENITAL INFECTION

The neurodevelopmental consequences of congenital infection reflect several factors, including maternal immunity, the infectious agent, the cellular tropism of the infectious agent, and the timing of maternal infection. Less well understood are the genetically regulated factors that may determine susceptibility to infection or the severity of maternal or fetal infection. Because congenital infections must begin with maternal infection, maternal immune status is an important factor. The fetuses of rubella-immune women, as indicated by the presence of rubella-virus specific IgG in mothers preconceptually, are protected from CRS,2,28 and women who are seropositive for CMV preconceptually are less likely than seronegative women to give birth to infants with congenital CMV disease.37

The timing of maternal infection has a major influence on the outcome of fetal infection and the pathogenesis of the central nervous system abnormalities associated with congenital infection. This paradigm is illustrated best by the pathogenesis of CRS.
following maternal rubella virus infection. Maternal rubella during the initial 8 to 12 weeks of pregnancy in nonimmune women can lead to ophthalmologic abnormalities and congenital heart disease, and infection during the initial 16 weeks can cause sensorineural hearing loss. Intracranial abnormalities, particularly periventricular or

Fig. 4. T2-weighted, coronal MRI of an infant with congenital CMV infection showing dysplastic cortex (arrow).

Fig. 5. Unenhanced head CT of another child with congenital CMV infection shows marked hypoplasia of the cerebellum (arrow) and cerebellar and cerebral calcifications.
parenchymal calcifications, can appear during this time. By contrast, infections after the twentieth week, although producing sensorineural hearing loss in some infants, are usually silent and unassociated with permanent neurodevelopmental disabilities. Overall, 20% to 50% of first-trimester rubella virus infections result in CRS.\textsuperscript{27}

Although the relationship between the timing of maternal infection and outcome in congenital CMV infections is less clearly established than in CRS, CMV-induced defects of neuronal migration, such as lissencephaly, schizencephaly, polymicrogyria, and cortical dysplasia (Fig. 6), suggest that infections before the twentieth week of gestation produce more severe neurodevelopmental abnormalities. Early infections with the parasite \textit{T gondii} also seem to be associated with more severe outcome.\textsuperscript{22}

The outcome of LCM virus infections is tightly linked to the timing of maternal infection, a conclusion supported by studies of LCM virus infection of experimental animals.\textsuperscript{38} Finally, congenital varicella syndrome rarely, if ever, happens when maternal infection occurs before the fifth week or after the twenty-fourth week of gestation.\textsuperscript{31}

The pathogenesis of CRS begins with maternal infection and viremia and continues when the placenta becomes infected.\textsuperscript{27} The virus replicates in placental tissues, causing villitis, capillary endothelial necrosis, and cellular viral inclusions, pathologic features indicating active viral replication.\textsuperscript{27} The virus then enters the fetal circulation and disseminates hematogenously to target organs, particularly the liver, spleen, heart, brain, cochlea, and eye, where virus replication and cell death lead to tissue damage and congenital defects. Pathologic studies of neural tissues demonstrate leptomeningitis and ischemic necrosis of cerebral parenchyma.\textsuperscript{39} The latter leads to dystrophic cerebral calcifications, a feature common in CRS and several other viral or parasitic intrauterine infections, and atrophic ventriculomegaly. Unlike infections with CMV and LCM virus, cortical malformations are unusual features of CRS.

For the most part, other congenital infections, whether viral, spirochetal, or parasitic, begin with maternal and placental infections and culminate in dissemination

![Fig. 6. Unenhanced head CT of a child with pseudo-TORCH syndrome shows scattered calcifications, especially frontally (circle), and cortical dysplasia reminiscent of cytomegalovirus or LCM virus infection (arrow).](image)
of the infectious pathogen to the fetus, replication in target organs, and damage to fetal tissues, including the brain. Although dystrophic calcifications can be attributed to virus-induced necrosis of neuronal tissues, the pathogenesis of other neuropathologic abnormalities, such as CMV-induced lissencephaly, schizencephaly, or cerebellar hypoplasia, is not readily explained by direct viral replication in neural tissues. Placental inflammation can lead to vasculitis and placental insufficiency, causing fetal death, miscarriage, stillbirth, intrauterine growth retardation, and impaired brain growth and development.

Studies of murine CMV infection suggest that virus-induced inflammatory responses participate in the pathogenesis of CMV-induced cerebellar hypoplasia (see Fig. 5). Whether this or other mechanisms, such as virus-induced vasculitis or inactivation of genes critical to brain development, cause cortical dysplasia, schizencephaly, or polymicrogyria in congenital infections, is unknown. Schizencephaly, for example, can result from mutations in EMX2, and perisylvian polymicrogyria is associated with mutations in several genes, including SRPX2, PAX6, TBR2, KIAA1279, RAB3GAP1, and COL18A1. The intriguing similarities between the imaging and the neuropathologic features of congenital viral infections, especially CMV and LCM virus, and rare familial disorders, such as pseudo-TORCH syndrome (see Fig. 6), suggest that much remains to be learned about the interplay of virus infections and the genes that determine the complex patterns of neural development.

PREVENTION AND TREATMENT OF CONGENITAL INFECTIONS

As illustrated by the remarkable success in eradicating CRS from developed nations, immunization of susceptible women before conception remains the most effective means to eliminate the neurologic morbidity associated with many congenital infections. By September 2008, 65% of the world’s countries incorporated rubella vaccine into their national immunization schedule; eliminating CRS remains a major goal of the World Health Organization. Widespread use of VZV vaccine will likely have comparable effects in eliminating the congenital varicella syndrome. Despite the obvious success of the rubella vaccine campaign and the potential benefits of VZV immunization, progress in eliminating congenital CMV disease by vaccine has been remarkably slow.

Public health measures can have a beneficial impact by diminishing the burden of disease caused by several congenital infections. Congenital syphilis, for example, can be prevented by identifying women infected with *T pallidum* and treating them with penicillin. Cases of congenital toxoplasmosis can be prevented by recommending that pregnant women not clean cat litter boxes and avoid undercooked meats, and some cases of congenital LCM virus infection could theoretically be prevented by recommending that women avoid contact with mice, hamsters, or their excreta during pregnancy. Transmission of *T cruzi*, the cause of Chagas disease, can be interrupted by screening blood products and controlling triatominae insects, the principal vectors for human infection in endemic areas of Latin America. Prevention of congenital or perinatal HSV infections remains problematic, however, given that most infected women are unaware of their HSV infections.

Postnatal treatment of certain congenital infections can substantially improve the neurodevelopmental prognosis for infants with congenital toxoplasmosis and the hearing outcomes in infants with congenital CMV disease. Shunting of obstructive hydrocephalus and extended courses of antitoxoplasma therapy using pyrimethamine and sulfadiazine have a remarkably beneficial effect on the outcome of infants with congenital toxoplasmosis. Resolution or improvement in intracranial calcifications
has been reported in treated children. Postnatal therapy with ganciclovir for 6 weeks is associated with improved hearing outcomes in congenitally infected infants.

Infants who survive congenital infections are at high risk of permanent neurodevelopmental disabilities consisting of cerebral palsy, deafness, visual dysfunction, epilepsy, and developmental delay or mental retardation. Longitudinal studies performed in infants with symptomatic congenital CMV infections before the availability of ganciclovir suggested that approximately 80% had permanent disability attributable to CMV infection. Infants with intracranial calcifications are more likely to have adverse neurodevelopmental sequelae. At least 50% of the infants with congenital CMV disease had sensorineural hearing loss; fewer ganciclovir-treated infants likely have permanent deafness. The potential effect of ganciclovir on other neurodevelopmental outcomes is uncertain at this time. Among infants with congenital toxoplasmosis treated with pyrimethamine-sulfadiazine, most have normal outcomes and very few have sensorineural hearing loss or new eye lesions caused by T gondii recrudescence. This contrasts with greater than 50% morbidity associated with symptomatic congenital toxoplasmosis in the pretreatment era.

The long-term morbidity associated with congenital syphilis can be prevented by perinatal penicillin therapy. Although the benefit of antiparasitic therapy in infants with congenital Chagas disease has not been established by controlled trials, consensus statements from the Southern Cone of America and the World Health Organization recommend 30 to 60 days of antiparasitic therapy, using benznidazole or nifurtimox. Currently, no effective antiviral therapy exists for infants with CRS, and although postnatal therapy with acyclovir seems logical in infants with suspected congenital HSV or VZV infections, there are no studies suggesting that acyclovir improves the outcome of such infants.

PERINATAL VIRAL INFECTIONS

Neonatal infections with HSV, either type 1 or type 2, affect 500 to 2000 infants annually in the United States, and most occur perinatally. Approximately 2% of women in the United States acquire HSV-2 annually and approximately 80% of these occur without symptoms. Neonatal HSV infections have historically been considered mucocutaneous (skin, eye, mouth, without central nervous system involvement); disseminated (with or without central nervous system involvement); and encephalitic. The latter infants become symptomatic somewhat later than those with mucocutaneous or disseminated infants and present subtly with fussiness, lethargy, or poor feeding or overtly with seizures and coma. Because one third of the infants with perinatal HSV encephalitis lack cutaneous signs of HSV and more than two thirds of the mothers of such infants have no known history of HSV infection, clinicians must maintain a high index of suspicion for this disorder. Management consists of high-dose (60 mg/kg/d) acyclovir for 21 to 28 days. Infants who survive perinatal HSV infections are at high risk for cerebral palsy, epilepsy, and developmental delay despite aggressive acyclovir therapy.

Neonatal infections with parechovirus, a picornavirus with at least 14 types, can be associated with encephalitis and central nervous system injury. Verboon-Maciolek and colleagues recently described 10 infants with this disorder and indicated that 50% had neurodevelopmental sequelae consisting of epilepsy, cerebral palsy, or developmental delays. MRIs showed white matter injury in most of the infants. This disorder should be suspected in infants with fever, rash, and seizures, features that mimic neonatal enterovirus infection; diagnosis can be established by polymerase
chain reaction studies of cerebrospinal fluid. At present, no specific antiviral therapy exists for this disorder.

REFERENCES