

Current Controversies in Diagnosis, Management, and Prevention of Congenital Cytomegalovirus: Updates for the Pediatric Practitioner

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Abstract

Congenital cytomegalovirus (CMV) infection has been called “the elephant in our living room” because it is a major public health problem that for decades has been unrecognized and unaddressed. Congenital CMV infection is a common cause of sensorineural hearing loss, vision loss, neurodevelopment disabilities, liver disease, and growth failure. Diagnostic tests are now widely available to identify newborns with congenital CMV infection, congenitally infected newborns now can be easily assessed for evidence of organ involvement, and there are now antiviral treatments and other interventions available to improve the outcome in children with congenital CMV disease. A licensed vaccine to prevent CMV infection is not yet available; however, a “CMV knowledge vaccine,” composed of “an ounce of CMV awareness and three simple precautions” and that is endorsed by the Centers for Disease Control and Prevention is available for pregnant women who wish to reduce their contact with potentially CMV-infected secretions and therefore reduce their risk of acquiring CMV during pregnancy. Medical experts in the field of congenital CMV have been called upon for a consensus statement for diagnosis and treatment, and nonprofit organizations of families affected by congenital CMV from around the world have formed a collaborative coalition to facilitate the spread of CMV knowledge and awareness. [*Pediatr Ann.* 2015;44(5):e115-e125.]

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Congenital cytomegalovirus (CMV) is a common congenital infection, infecting up to 40,000 newborns each year in the United States, causing death in approximately 400 children each year, and permanent disabilities in more than 8,000 children every year.¹⁻⁶ Many newborns have few or no symptoms at birth, with most also not experiencing long-term sequelae. However, for those newborns with congenital CMV infection who do exhibit symptoms, there are often lifelong disabilities and challenges for them, their families, their educators, their health care providers, and society. Furthermore, newborns without overt symptoms of CMV at birth may have congenital or late-onset hearing loss.^{7,8} Discerning which role congenital CMV is playing in a patient is challenging, but modern diagnostics and new knowledge about interventions for treatment and prevention are now available to the pediatric practitioner.

WHAT ARE THE CLINICAL MANIFESTATIONS OF CONGENITAL CMV INFECTION IN THE FETUS AND NEWBORN?

Infants with congenital CMV infection may be classified according to the presence or absence of symptoms at birth, and whether or not those symptoms involve the central nervous system (CNS) or sensory organs (**Table 1**). Symptomatic newborns congenitally infected with CMV represent only 10% of these infants (the “tip of the iceberg” of congenitally infected newborns), and they may have one or more symptoms at birth commonly associated with congenital CMV. These classic symptoms include being small for gestational age, petechiae or purpura with thrombocytopenia, jaundice at birth with hepatitis and direct hyperbilirubinemia, and hepatosplenomegaly⁹⁻¹² (**Figure 1**). Common CNS findings include microcephaly, hypotonia, seizures, and abnormal imaging such as enlarged ventricles and

linear or punctate intracranial calcifications in the periventricular region of the brain.¹³⁻¹⁷ (**Figure 2 and Figure 3**). Classic sensory findings include unilateral or bilateral sensorineural hearing loss and chorioretinitis, optic atrophy, or central vision blindness.¹⁸⁻²⁰ Some newborns with symptoms from congenital CMV infection will not have the classic signs and symptoms of symptomatic congenital CMV disease, yet still may experience long-term sequelae. Examples of newborn characteristics that are associated with congenital CMV disease but less commonly appreciated include hydrops, CMV giant cell hepatitis, hemolytic anemia, myocarditis, colitis, neurologic findings of lethargy, poor tone or seizures, cortical migration abnormalities of the brain such as polymicrogyria (PMG), and vasculitis of cerebral vessels (**Figure 4**).

Severe or unusual signs and symptoms of congenital CMV disease may also manifest in newborns with primary immune disorders of T cells, such as severe combined immune deficiency syndrome, or congenital disorders of natural killer (NK) cells. In addition, infants who are born premature (less than 32 weeks of gestation) and congenitally infected with CMV are less likely to have microcephaly, intracranial calcifications, and chorioretinitis and more likely to manifest pneumonitis and thrombocytopenia and other signs of viral sepsis syndrome, and experience neonatal death from congenital CMV than are newborns of greater than 32 weeks of gestation.⁵

Signs of congenital CMV infection may also be apparent in the fetus and may be recognized during routine prenatal care on routine fetal anatomy scans at 20 weeks of gestation or at any time during gestation.²¹⁻²⁵ Echogenic bowel may be an early sign of congenital CMV infection in the fetus, as well as intrauterine growth restriction, oligohydramnios or polyhydramnios, placental inflammation, fetal ascites, fetal hydrops, hepatic

TABLE 1.

Clinical Manifestations and Laboratory Findings Associated with Congenital CMV Infection in the Fetus and Newborn

Fetus

Symptomatic

- Hyperechogenic bowel
- In-utero growth restriction
- Ascites or hydrops
- Oligohydramnios or polyhydramnios
- Placenta enlargement
- Hepatosplenomegaly or hepatic calcifications
- Abnormalities of brain development, enlarged ventricles, calcifications
- Fetal thrombocytopenia
- Fetal demise
- Positive amniotic fluid for CMV by culture or PCR
- Fetal blood sample positive for CMV IgM antibody

Asymptomatic

- No abnormal findings on fetal ultrasound
- Placenta enlargement
- Positive amniotic fluid for CMV by culture or PCR

Newborn

Symptomatic

- Small size for gestational age
- Petechiae or purpura
- Hepatosplenomegaly
- Jaundice at birth
- Lethargy, hypotonia, poor feeding
- Microcephaly^a
- Ascites
- Myocarditis
- Enterocolitis
- Pneumonitis^b
- Chorioretinitis, retinal scars, optic atrophy, central vision loss^a
- Sensorineural hearing loss^a
- Abnormalities of brain development, ventriculomegaly, intracranial calcifications^a
- Viral sepsis^b
- Thrombocytopenia, neutropenia, lymphopenia, lymphocytosis, hemolytic anemia
- Elevated liver enzymes
- Direct hyperbilirubinemia
- Seizures^a
- Neonatal death^b
- Positive urine, saliva, and/or blood for CMV by culture or PCR at birth

TABLE 1. (continued)

Clinical Manifestations and Laboratory Findings Associated with Congenital CMV Infection in the Fetus and Newborn

Newborn

Asymptomatic

- No abnormalities at birth
- May exhibit small growth parameters and early gestational age compared to un-infected newborns
- Positive urine, saliva, and/or blood for CMV by culture or PCR at birth
- Asymptomatic with failed newborn hearing screen
- No abnormalities at birth
- Failed newborn hearing screen suggesting congenital sensorineural hearing loss
- Positive urine, saliva, and/or blood for CMV by culture of PCR at birth

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; PCR, polymerase chain reaction.

^aIndicates central nervous system involvement and/or involvement of sensory organs, with anticipated risk of long-term sequelae.

^bMore common in premature neonates with congenital CMV infection.

calcifications, and fetal abnormalities of brain growth and development. Fetal demise in-utero may also occur.

Hearing loss is the most common finding in newborns with symptomatic congenital CMV disease and is detected in over half of infants with symptomatic congenital CMV infection.²⁰ It is often bilateral and almost always progressive in nature. Chorioretinitis is the most common ocular disorder associated with congenital CMV disease, affecting between 10% and 15% of symptomatic newborns, but these infants may also experience optic atrophy, strabismus, or if the brain is severely involved, central cortical blindness.^{18,19} Some infants with congenital CMV disease will experience prolonged dysfunction of their liver or prolonged thrombocytopenia, requiring transfusions.



Figure 1. Newborn with symptomatic congenital cytomegalovirus (CMV) disease with jaundice at birth, hepatosplenomegaly, skin lesions of petechiae and purpura, small for gestational age, and microcephaly. Eye examination showed bilateral retinal hemorrhages and inflammation, consistent with acute inflammatory retinitis caused by CMV. Computed tomography imaging of brain showed periventricular calcifications. Newborn hearing test showed bilateral severe sensorineural hearing loss. Infant was treated with intravenous ganciclovir for 6 weeks. He is now currently ambulatory with some motor dysfunction, with moderate cognitive delays, and bilateral hearing loss improved with hearing aids.

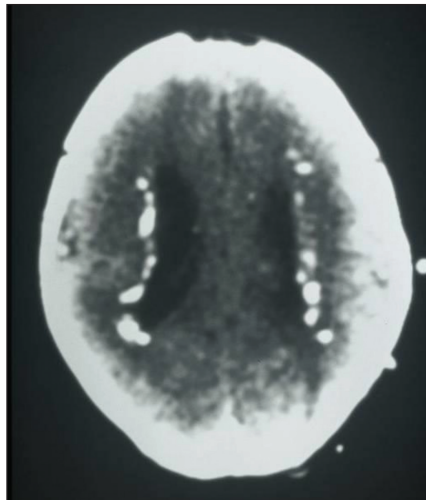


Figure 2. Computed tomography scan of brain from an infant born with congenital cytomegalovirus disease involving the central nervous system. Imaging shows typical enlarged ventricles, periventricular leukomalacia, and linear, beaded periventricular calcifications. This child was also born with microcephaly and sensorineural hearing loss. This child was treated with intravenous ganciclovir and now has hearing loss, uses hearing aids, and has moderate developmental delays.

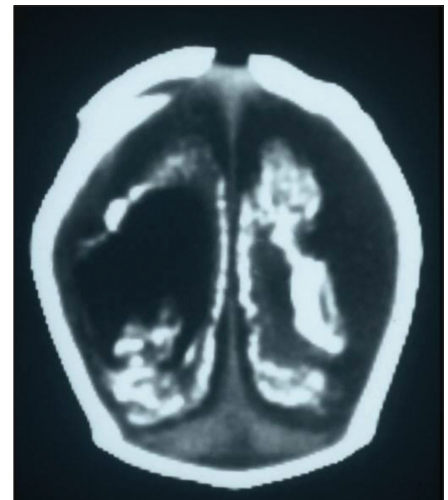


Figure 3. Computed tomography scan of brain from an infant born with congenital cytomegalovirus infection with severe microcephaly, over-riding sutures, enlarged ventricular system, prominent periventricular linear calcifications, and hydranencephaly. Only a portion of posterior fossa remained at birth. Examination was also remarkable for small size for gestation and bilateral chorioretinitis. This infant was treated with intravenous ganciclovir. This infant died at age 2 years from complications associated with a seasonal viral respiratory disease.

Approximately 8% of newborns with congenital CMV disease will die by age 3 months, despite all supportive measures available, from fulminant multi-organ disease or viral-associated hemophagocytic syndrome.^{4,5}

WHAT ARE THE IMPLICATIONS OF ASYMPTOMATIC CONGENITAL CMV INFECTION?

The vast majority of newborns with congenital CMV infection are asymptomatic or minimally symptomatic, with subtle differences such as lower birth

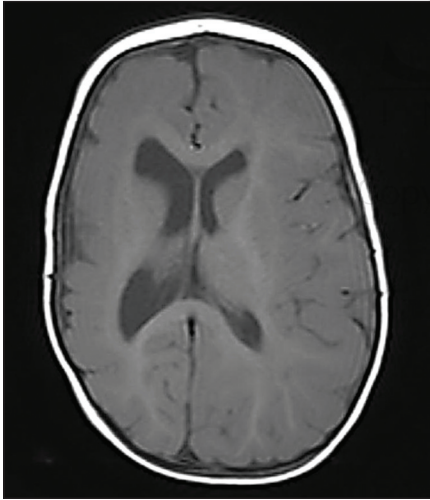


Figure 4. Magnetic resonance imaging scan of brain of an infant born with congenital cytomegalovirus (CMV) disease involving the central nervous system. This infant had microcephaly, hemiparesis, mild to moderate developmental delays, seizures, and unilateral sensorineural hearing loss. Imaging showed right-sided polymicrogyria, a cortical maldevelopment syndrome that may be associated with congenital CMV disease of the brain. This child was treated with oral valganciclovir, underwent hemispherectomy, and is now ambulatory, seizure free, and has mild to moderate developmental delays.

weight, slightly earlier gestational age, or isolated thrombocytopenia, and they likely will not have the diagnosis of congenital CMV infection considered by the pediatric practitioner. This “silent majority” of newborns with congenital CMV infection represents approximately 85% to 90% of all newborns with congenital CMV infection. Between 10% and 20% of newborns with otherwise asymptomatic congenital CMV infection will experience sensorineural hearing loss.^{7,8} Some of these newborns will have congenital hearing loss and fail their newborn hearing screen in one or both ears. In others who originally pass their newborn hearing screen, delayed onset hearing loss may occur.²⁶⁻²⁹ In all newborns with congenital CMV-associated hearing loss identified at birth or later in life, the hearing loss is progressive. Abnormal brain imaging, including periventricular leukomalacia, ventriculomegaly, and punctate calcifications, also may be present in approximately 5% to 20% of

TABLE 2.

When Should Testing for Congenital CMV Infection be Performed?

Newborns with:

- Symptoms associated with congenital CMV disease
- Failed or referred hearing screen
- Microcephaly or abnormal cranial imaging seen with CMV
- Primary immune disorder, abnormal TRECS screen
- Abnormal fetal ultrasound associated with in-utero CMV disease
- Infant born to mother with known or suspected CMV infection during pregnancy

Abbreviations: CMV, cytomegalovirus; TRECS, T-cell receptor excision circles.

asymptomatic newborns with congenital CMV infection.⁷ Children with asymptomatic congenital CMV infection do not appear to differ cognitively from children without congenital CMV infection, but some studies have detected subtle differences in cognitive outcomes in these children, but detection requires in-depth testing.³⁰⁻³²

IS A NEWBORN WITH A FAILED HEARING SCREEN AND CONGENITAL CMV INFECTION CATEGORIZED AS SYMPTOMATIC OR ASYMPTOMATIC

Before universal newborn hearing screening, newborns with congenital CMV infection who also were found to have hearing loss were traditionally categorized as having asymptomatic congenital CMV infection, often because the hearing loss was detected after the newborn period. Furthermore, unless the newborns were enrolled in a research protocol that included universal newborn screening for congenital CMV infection, asymptomatic newborns with congenital CMV infection would not be detected. However, with the advent

of universal newborn hearing screening, as well as improved diagnostics for congenital CMV infection, these infants may be detected at birth and are characterized by some experts, especially those in the specialties of otolaryngology, audiology, as well as pediatric infectious diseases, as being symptomatic from their congenital CMV infection.²⁹ However, some pediatric infectious diseases experts still consider these newborns with failed newborn hearing screens who are otherwise without symptoms to be categorized as having an otherwise asymptomatic congenital CMV infection because they do not have any other manifestations of CMV disease. This area of controversy may present the practicing pediatrician with a conundrum regarding the role of antiviral treatment to reduce the risk of hearing loss progression in these otherwise normal-appearing infants, as well as other appropriate management decisions.

WHICH NEWBORNS SHOULD BE TESTED FOR CONGENITAL CMV INFECTION?

Newborns with any of the symptoms associated with congenital CMV disease, whether or not their symptoms are “classic,” should be tested for congenital CMV infection (Table 2). Newborns who have an abnormal hearing screen, whether or not they have other symptoms of congenital CMV, should also be tested for congenital CMV infection. A newborn who fails twice on the newborn hearing screen, whether in one or both ears, in addition to audiologic and otolaryngology referral, should have testing for congenital CMV infection done prior to discharge or have CMV testing arranged within the first 3 weeks of life by the child’s pediatrician. Often, the newborn with the failed newborn hearing screen embarks on a diagnostic odyssey, being first referred for formal audiologic testing to confirm the abnormal hearing screen results, then for evaluation by an

otolaryngologist for genetic testing and temporal bone imaging, without the benefit of the time-sensitive neonatal testing for congenital CMV infection. This is another contemporary controversy the practicing pediatrician may face. Therefore, because the diagnosis of congenital CMV infection is time sensitive and restricted to the first 3 weeks of life, many pediatric hospitals and birthing centers now test newborns who fail their newborn hearing screens for congenital CMV infection prior to discharge.

Newborns with abnormal cranial imaging consistent with CMV should also be tested for congenital CMV infection. In addition, newborns who had abnormal fetal ultrasound findings consistent with in-utero CMV infection should be tested at birth for congenital CMV infection. Infants born to mothers with a known or suspected primary CMV infection during pregnancy, including a proven maternal primary CMV infection with CMV immunoglobulin G (IgG) seroconversion during pregnancy, or a presumptive maternal primary CMV infection with positive CMV IgG and CMV IgM antibody results during pregnancy, or a mononucleosis-like syndrome during pregnancy, should be tested for congenital CMV infection. A pregnant woman with primary CMV infection during pregnancy may, approximately 40% of the time, transmit CMV to her fetus and give birth to a congenitally infected newborn. Testing the newborn for CMV will provide reassurance if the testing is negative, and provide opportunity for further management decisions if positive.

One additional category of newborns in whom testing for congenital CMV is recommended are those newborns who have an abnormal T-cell receptor excision circles (TRECS) result on newborn screening, especially if they are term infants, who are less likely to have a false-positive TRECS results. A newborn with a T cell or NK cell deficiency will likely

not be able to handle a congenital CMV infection very well, whether it is asymptomatic or symptomatic, and early diagnosis and appropriate treatment of an active CMV infection prior to bone marrow transplantation to reconstitute their immune system may be critical to their survival.

WHAT ARE THE LABORATORY TESTS AVAILABLE TO CONFIRM THE DIAGNOSIS OF CONGENITAL CMV INFECTION?

The diagnosis of in-utero congenital CMV infection can be made by viral culture or CMV DNA polymerase chain reaction (PCR) detection in amniotic fluid obtained by amniocentesis.³³ With prenatal diagnosis of fetal abnormalities becoming more commonplace because of better prenatal monitoring, routine 20-week gestation fetal ultrasound evaluations, and growing CMV awareness with mothers requesting CMV antibody prenatal screening, the practicing pediatrician may be presented with a newborn whose diagnosis of congenital CMV infection was determined before birth. The diagnosis of congenital CMV infection is most often determined within the first 3 weeks of life by detection of CMV in the urine or saliva using viral culture, rapid shell vial antigen detection, or CMV DNA PCR detection techniques (Table 3). If CMV is detected in saliva or urine, then further evaluation of the newborn is recommended to determine if any end-organ disease is present.

After age 3 weeks, the detection of CMV in urine or saliva of an infant may indicate either congenital or postnatal CMV infection.¹ Postnatal CMV infection may be acquired from breast-feeding or from cervicovaginal secretions aspirated during the vaginal delivery birth process. In an infant older than age 1 month, the diagnosis of congenital CMV infection may be established retrospectively by CMV DNA PCR detection of dried blood spot samples (Guthrie cards)

TABLE 3.

Diagnostic Tests for Congenital CMV Infection

Urine or saliva specimen collected within first 21 days of life: preferred
CMV viral culture
CMV shell vial assay
CMV DNA PCR
Blood or plasma or serum: insensitive or nonspecific
CMV DNA PCR
CMV IgM antibody
CMV IgG antibody
Dried blood spot from newborn screen (Guthrie card): retrieved retrospectively
CMV DNA PCR

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

obtained for newborn screening. In most states with written parental permission, stored newborn dried blood spots may be retrieved from the state newborn screening laboratory and sent to reference laboratories for DNA elution and CMV DNA PCR testing. If positive, the diagnosis is confirmed. However, because a false-negative results may occur, a negative test on newborn dried blood spots does not exclude the diagnosis of congenital CMV infection.³³⁻³⁶

HOW IS THE DIAGNOSIS OF CONGENITAL CMV INFECTION EXCLUDED IN A NEWBORN?

A negative CMV urine or saliva culture, especially if repeat samples are collected so that at least two samples are submitted, or a negative CMV DNA PCR on the urine from one sample well collected, excludes the diagnosis of congenital CMV infection. Most reference laboratories do not have CMV DNA PCR assays validated for saliva swabs at this time; therefore, the pediatrician should order urine for CMV DNA PCR testing if at all possible. Because newborns with congenital CMV infection al-

most always shed large quantities of the virus in their saliva and urine, the CMV DNA testing should be strongly positive in high titer. If the pediatrician encounters a low or equivocal DNA CMV test result, then the test should be repeated, because this may be a false-positive result for some reason. Exclusion of congenital CMV infection can also be confirmed if the maternal CMV IgG serology is negative, indicating the mother was never infected with CMV and therefore not able to transmit CMV to her baby, or if the newborn or infant's CMV IgG serology is negative, indicating he or she was never infected with CMV.

SHOULD NEWBORNS BE SCREENED FOR CONGENITAL CMV INFECTION?

Congenital CMV infection has a substantial public health impact, but early diagnosis provides options for management that will improve outcome. Therefore, most CMV experts and public health officials support either targeted or universal newborn screening for congenital CMV infection.

Targeted newborn screening, also known as targeted newborn diagnostic testing, for congenital CMV infection is indicated for newborns who fail their newborn hearing screen.^{37,38} Many hospitals and birthing centers are adopting targeted CMV screening programs to identify CMV-infected newborns so that appropriate evaluation and treatment may be provided and appropriate audiologic follow-up arranged. Currently, one state, Utah, has passed legislation, and at least five other states (Connecticut, Hawaii, Tennessee, Illinois, and Texas) have filed bills to support targeted testing for congenital CMV infection and to provide information on available treatment and management options to pediatric practitioners and families of newborns identified with congenital CMV infection.^{38,39}

However, targeted newborn screening is not sufficient to detect all infants

with congenital CMV who would develop late-onset hearing loss or who may have unusual manifestations of congenital CMV infection.⁴⁰⁻⁴³ Therefore, universal newborn screening for congenital CMV infection has been proposed. Reliable and cost-effective methods for universal newborn screening for congenital CMV infection are available and include detection of CMV in urine

Reliable and cost-effective methods for universal newborn screening for congenital CMV infection are available.

or saliva collected at birth and tested in a local or central reference laboratory for CMV DNA by PCR. CMV culture has also been used successfully in many large-scale newborn screening studies. Detection of CMV DNA in dried blood spot samples (Guthrie cards) collected for the Recommended Uniform Screening Panel (RUSP) also may be adapted for universal screening of newborns for congenital CMV. However, not all newborns have CMV DNA in their blood at birth at levels detectable by current PCR methodology, so this approach has not been universally adopted. Also, research and development for a simple point-of-care detection method, such as a dip stick immunochromatographic assay in urine, should be encouraged, so that newborns may be tested for CMV and the results available prior to discharge home from the hospital or birthing center.⁴⁰

However, universal newborn screening for congenital CMV infection will likely be adopted at the local, regional, or state levels only if it is recommended to be included as one of the tests nationally recommended to be included on the national RUSP.⁴⁴ The RUSP

contains a list of disorders that are screened for at birth and recommended by the Secretary of the Department of Health and Human Services for states in their newborn screening programs. Based on criteria that include evidence that supports potential of net benefit to screen newborns for the disorder, the ability of each state to screen for the condition, and the availability of effective treatments or interventions, these diseases or disorders are chosen by a Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC). Historically the committee has focused on genetic disorders. Recently, however, interest in nongenetic disorders has arisen, including screening for congenital infections such as congenital CMV. The process to explore the inclusion of universal newborn screening for congenital CMV on the RUSP recently has been initiated by an advocacy group of concerned families of children born with congenital CMV and interested CMV experts.³⁹

WHAT EVALUATIONS ARE RECOMMENDED FOR THE NEWBORN DIAGNOSED WITH CONGENITAL CMV INFECTION?

An infant with virologically confirmed congenital CMV infection should be evaluated for evidence of organ involvement.¹ This evaluation includes measurements of weight and length to detect low birth weight or small for gestational age size, and head circumference (to detect microcephaly), a thorough physical examination to detect skin lesions, and screening for hepatosplenomegaly, and neurological abnormalities. Laboratory testing usually should include a complete blood count with differential and platelet count (to detect neutropenia, lymphopenia, hemolytic anemia, or thrombocytopenia) and liver function tests (to detect hepatitis, direct hyperbilirubinemia, or cholestasis).

Hearing evaluation by newborn screening should be performed to detect congenital hearing loss, and if abnormal further evaluated by auditory brain stem-evoked response testing. Because late-onset hearing loss occurs with CMV, periodic hearing evaluations should be performed every 6 months for 3 years and then annually until at least age 18 years. Ophthalmology evaluation is recommended to assess for chorioretinitis, optic atrophy, or central vision loss.

Neuroimaging is also recommended. Head ultrasonography, which is safe and easy to perform, should probably be performed in all newborns with congenital CMV infection. Infants with abnormal neurologic examination, seizures, or microcephaly should undergo additional neuroimaging by computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. CT scans are more useful to detect ventriculomegaly or calcifications and may be done quickly and often without sedation, but they do carry the risk of a radiation exposure. On the other hand, MRI is more useful to detect vasculitis and polymicrogyria, but it usually requires sedation or anesthesia to perform. The type of neuroimaging performed should also be coordinated with an ears, nose, and throat (ENT) specialist if the infant also has sensorineural hearing loss, because they will also request evaluation of the temporal bones and cochlea for atresia or structural abnormalities.

If antiviral treatment is being considered, baseline renal function tests, such as blood urea nitrogen and creatinine, should be performed. In addition, many CMV experts recommend CMV DNA quantitative PCR of whole blood or plasma to assess for level of CMV viremia.

WHAT ARE THE ANTIVIRAL TREATMENT OPTIONS AVAILABLE TO CONGENITALLY INFECTED NEWBORNS?

Intravenous (IV) ganciclovir and its orally available prodrug, valganciclovir,

are the recommended antiviral agents for treatment of congenital CMV disease (Table 4). The benefit of these antiviral medications, especially if treatment is initiated within the first month of life, has been demonstrated in multicenter, randomized clinical trials as well as in case reports and case series.⁴⁵⁻⁵⁷ Treatment is associated with improved head circumference growth and improved long-term audiologic and neurodevelopmental outcomes.⁴⁶ Antiviral treatment should be administered to infants with virologically confirmed congenital CMV infection who have at least one organ system involvement, especially if they have CNS involvement. Also, antiviral treatment for congenital CMV infection should be started if the newborn has a documented life-threatening primary immunodeficiency involving T cell or NK cell function, such as severe combined immune deficiency, even if there is no symptom of disease.

Antiviral treatment with ganciclovir or valganciclovir currently is not recommended for asymptomatic newborns who pass their newborn hearing screen or for treatment in pregnant women for treatment of in-utero CMV infection of the fetus because there is insufficient evidence of benefit to outweigh the potential risks of treatment.

The choice of antiviral agent (IV ganciclovir versus oral valganciclovir) should depend on the severity of the congenital CMV disease and the ability of the infant to tolerate oral feedings and oral medications. IV ganciclovir at a dose of 6 mg/kg every 12 hours should probably be used, at least initially, for treatment of severe disease, especially if the infant is seriously ill and receiving mechanical ventilation.^{45,50} IV treatment is administered for a total of 6 weeks. Infants with nonsevere symptoms of congenital CMV disease, especially if they are stable and taking oral feedings or well enough to be discharged home, may be successfully treated with oral valganciclovir at a dose of 16 mg/kg every 12 hours for

TABLE 4.

Antiviral Treatment Options for Congenital CMV Disease

Ganciclovir

Intravenous solution

6-mg/kg dose every 12 hours

Severe congenital CMV disease, including CNS and sensory involvement

6 weeks in duration

Neutropenia may occur in 60% of treated infants

Valganciclovir

Oral solution 50 mg/mL concentration

16-mg/kg dose every 12 hours

Mild to moderate congenital CMV disease, including CNS and sensory involvement

6 months in duration

Neutropenia may occur in 20% of treated infants

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system.

a duration of 6 months.⁵¹⁻⁵⁷ In at least one study, treatment up to 12 months with oral valganciclovir was well tolerated and associated with improved audiologic outcomes.

Monitoring for medication side effects should be done while the infant is receiving IV ganciclovir or oral valganciclovir. Complete blood count with differential and platelet count should be tested at least weekly while receiving IV ganciclovir, and at least monthly while receiving oral valganciclovir. Baseline liver function tests and kidney function tests also should be performed and be monitored if abnormal. The most common adverse effect associated with ganciclovir treatment is neutropenia (absolute neutrophil count $<500/\text{mm}^3$), which occurs in 25% to 60% of neonates treated with IV ganciclovir and 20% of infants treated with oral valganciclovir.⁵⁷ The neutropenia reverses when the medication is discontinued. Theoret-

TABLE 5.

Prevention Strategies for Congenital CMV Infection Available to Pregnant Women

CMV vaccine: not available

CMV precautions: available

Do not share food or drink or utensils with toddlers or young children

Avoid “one for mommy and one for baby” feeding practices

Avoid kissing on lips and avoid contact with saliva when kissing a child or infant

Kiss infants and toddlers on top of head, give hugs

Wash hands often after changing diapers and wiping runny noses or drool

Abbreviation: CMV, cytomegalovirus.

ical long-term effects based on previous animal studies include infertility and increased risk of cancer and tumors. However, there is no indication or evidence at this time that neonatal treatment with ganciclovir or valganciclovir will result in any long-term effects in the infant or child.⁵⁶

WHAT OPTIONS ARE AVAILABLE TO PREVENT CONGENITAL CMV INFECTION AND DISEASE?

A vaccine to prevent CMV infection was included as one of the highest priorities in the Institutes of Medicine Vaccine Priorities for the 21st Century.⁵⁸ Research and development efforts for a safe and effective CMV vaccine have been conducted by the National Institutes of Health and pharmaceutical companies for many decades. Currently, many CMV vaccine candidates are under preclinical investigation or are being evaluated in clinical trials. However, at this time, no licensed CMV vaccine exists.¹

Therefore, in the absence of a licensed CMV vaccine, other measures to reduce the public health impact of

congenital CMV infection and disease are recommended (Table 5). These measures include providing education on congenital CMV to women who are pregnant or who may become pregnant about three simple hygienic precautions that have been shown in randomized, clinical trials to significantly reduce the transmission of CMV from young children likely to be actively infected and shedding CMV in saliva and urine to CMV-seronegative pregnant women.⁵⁸⁻⁶² These CMV precautions, also known as “the CMV knowledge vaccine,” recommended for pregnant women include the following: (1) do not kiss young children on or around the mouth or cheek, rather give them a big hug or kiss the top of their head; (2) do not share food or drink or utensils with young children; and (3) wash hands carefully after changing diapers and wiping runny noses or mouth drool. The pediatric practitioner, as well as obstetricians, are in good position to discuss these CMV precautions (“the CMV knowledge vaccine” for the pregnant mom) with families at routine preventive health visits. However, published knowledge awareness surveys have documented that most women of childbearing age, as well as most medical professionals, are not knowledgeable about CMV and are not aware these precautions are now recommended.⁶³⁻⁶⁶

CMV AWARENESS: IT’S THE LAW!

Because CMV knowledge and awareness gaps exist, one approach has been to encourage CMV education of practitioners about recommendations for testing and treatment for newborns with congenital CMV, and education of pregnant women and their health care professionals about available interventions, through legislation. This legislative approach is embraced by many but also considered controversial by some experts and agencies. The pediatric practitioner may provide positive influ-

ence to lawmakers and their constituents who wish to encourage their legislatures to pass laws relating to testing for and education about congenital CMV in pregnant women and infants. Most pediatricians are not knowledgeable about how to bring research or medical practice into public policy, but this knowledge can be very effective in influencing the health and welfare of many children in their state.

The following text describes the usual steps necessary for a bill to become a law in a state. First, a state senator or representative must agree to author and sponsor the proposed bill in the house or senate of the state legislature. This first step is often the most challenging, but it can be facilitated by personal stories, physician and other content experts, one-page fact sheets, and personal visits along with emails to the senator’s or representative’s office. Often the interested constituent will meet with staff members first, who will brief the senator or representative on the issue. Once a bill is filed, it is receives a committee assignment, usually in a health-related committee. The committee assigned to the bill will then hold a hearing on the bill, and it is at the hearing that testimony from health care professionals, as well as personal testimony from families, may be given in person or via email.^{67,68} After the committee hearing, the bill goes to a vote in the legislative body where it originated (either the house or the senate). After the bill passes both the house and senate of the state legislature, then the governor of the state signs the bill and it becomes a law. Coordination of efforts from families and physicians who are constituents, as well as with the department of state health services, local health care agencies, and nonprofit advocacy groups will enhance the chance of success.

At this time only one state Utah, has successfully enacted a health law providing guidance for testing of new-

borns for CMV who fail their newborn hearing screen, and education of pregnant women, families, and health care professionals about available treatment and prevention measure.³⁹ Currently five other states (Connecticut, Hawaii, Illinois, Tennessee, and Texas), through the individual efforts of families directly affected by CMV and their physicians who care for these families, now have bills similar to the Utah law filed in their state legislatures.⁶⁹⁻⁷³

Individual state laws to provide guidance for CMV education and CMV testing is an important first step, and the addition of CMV newborn screening to the RUSP is an important next step.⁷⁴ Also, improved education about CMV diagnosis and prevention, commensurate with the high prevalence and public health importance of congenital CMV, should be encouraged in medical schools, as well as nursing school and schools for ancillary services such as audiologists and therapists, as well as daycare center workers.⁶³⁻⁶⁶

CONCLUSION

Congenital CMV infection has been called “the elephant in our living room” because it is a major public health problem that for decades has continued to go unrecognized and unaddressed. However, the tide appears to be turning and the practicing pediatrician, as well as the obstetrician who cares for pregnant women, both may play an important role in this process of change. We now have widely available diagnostic methods to identify CMV-infected pregnant women and their newborns, we can assess congenitally infected newborns for evidence of CMV organ disease, and we can provide treatments and interventions to improve outcomes. As research and development continues for a safe and effective CMV vaccine, global CMV awareness and education efforts continue so that pregnant women and their health care professionals are bet-

ter aware of CMV, are knowledgeable about how it is detected and transmitted, and offered information on the recommended hygienic precautions that will reduce their risk of CMV during pregnancy. Recently, a congenital CMV non-profit collaborative group was formed to promote CMV awareness globally.⁷² In addition, an international committee of congenital CMV experts should be convened and should publish a consensus report to provide medical expert opinion and guidance to practitioners and policy makers on how to diagnose, treat, and prevent congenital CMV infection and its sequelae.⁷³ Through all of these collective efforts we can continue to reduce the public health burden, the economic impact, and the individual suffering associated with congenital CMV infection and disease around the world.

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