Congenital Cytomegalovirus Infection: Epidemiology, Timely Diagnosis, and Management

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PRACTICE GAPS

1. Congenital cytomegalovirus (cCMV) has a spectrum of presentations from asymptomatic to severely symptomatic at birth and can present as isolated sensorineural hearing loss. Late-onset sequelae can occur in infants who are asymptomatic or symptomatic at birth. There is a critical window for timely, definitive diagnosis of cCMV within the first 3 weeks after birth.
2. Antiviral therapy with oral valganciclovir for 6 months has been shown to improve end hearing and neurodevelopmental outcomes in symptomatic infants with cCMV. All infants with cCMV require prospective audiologic monitoring for the development or progression of hearing loss.

OBJECTIVES *After reading this article, readers should be able to:*

1. Describe key manifestations of congenital cytomegalovirus (cCMV) infection, especially signs and symptoms that would prompt targeted screening for cCMV in a newborn.
2. Explain screening approaches for cCMV and the recommended diagnostic testing sample and timeframe.
3. Describe the evaluation and treatment of infants with cCMV, including which symptomatic infants currently qualify for antiviral therapies.

ABSTRACT

Congenital cytomegalovirus (cCMV) infection is common because of the ubiquitous nature of the virus and the lack of an effective prevention strategy during pregnancy. Most infants with cCMV are asymptomatic, although a notable subset can have sequelae including, most commonly, sensorineural hearing loss and neurodevelopmental disability, which may not be present at birth. Timely screening for cytomegalovirus in the first weeks after birth is critical to appropriately diagnose congenital infection, evaluate affected infants, and determine the treatment course. Antiviral therapy with valganciclovir can optimize end hearing and neurodevelopmental outcomes in symptomatic infants. This review discusses the epidemiology and clinical manifestations of cCMV, targeted and universal screening approaches, and treatment and monitoring of infants with cCMV.

AUTHOR DISCLOSURES Drs Jenks, Hoff, and Mithal have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

cCMV	congenital cytomegalovirus
CMV	cytomegalovirus
IUGR	intrauterine growth restriction
PCR	polymerase chain reaction
SNHL	sensorineural hearing loss

EPIDEMIOLOGY

Cytomegalovirus (CMV) is a member of the herpesvirus family and is highly prevalent, infecting a majority of people worldwide by childhood or early adulthood. (1) Prevalence among women of reproductive age is estimated to be 58% to 79% in North America and 86% globally. (2)(3) As a result, congenital CMV (cCMV) is the most common intrauterine infection seen, (4) with an incidence of approximately 0.5% to 1.3% in the United States (5)(6) and higher in developing countries, resulting in about 20,000 to 30,000 infants infected with cCMV in the United States each year.

Intrauterine CMV transmission occurs during a primary maternal infection or nonprimary infection in seropositive pregnant women that results from either reactivation of latent virus or infection with a different strain; the type of maternal infection has a different impact on affected infants (Table 1). Primary maternal infection confers a 40% risk of transmission to the fetus, whereas nonprimary infection carries a 0.5% to 2% risk. Given the high rate of maternal seropositivity, the majority of cCMV infections results from maternal nonprimary infections. (7) Studies suggest that severe manifestations in infants, including neurologic deficits, are more likely to result from congenital infection following primary maternal infection, but manifestations can also occur following nonprimary infection. (8)(9) Previous studies have demonstrated that approximately 10% to 15% of infants with cCMV resulting from maternal primary infection are symptomatic at birth and 25% exhibit sequelae by age 2 years. Following maternal nonprimary infection, less than 1% of infants with cCMV are expected to be symptomatic at birth and 8% have sequelae by 2 years of age. However, a recent meta-analysis found no differences in the rate of symptomatic manifestations in maternal primary and nonprimary infections (pooled odds ratio of symptomatic cCMV: 0.83, 95% confidence interval 0.55–1.27), suggesting that further data collection is needed. (10) Maternal infection in the first half of pregnancy is associated with decreased risk of transmission to the fetus, but the risk of severe sequelae is increased if congenital infection occurs during this period. Despite available epidemiologic data and given the limited sensitivity and positive predictive value of prenatal imaging, it is difficult to prognosticate which infants will have sequelae of cCMV. This highlights the need for further research in this area.

To prevent cCMV, preemptive measures for pregnant women can be followed, including standard precautions (hand hygiene) and limiting contact with saliva from other people. There is no universally recommended CMV screening in pregnancy, and to date, no proven intervention to decrease transmission to the fetus. Prevention efforts that are currently being studied include CMV-specific immunoglobulin (11)(12)(13)(14) (which has not shown significant reproducible prevention benefits), antivirals (15)(16) (in the case of recognized CMV infection during pregnancy), and importantly, CMV vaccine development. (17)

CLINICAL MANIFESTATIONS

Clinical manifestations of cCMV range from absence of any short- or long-term sequelae to multisystem involvement. Symptoms of cCMV in the newborn include any of the following: central nervous system abnormalities (microcephaly, cortical malformations, ventriculomegaly, periventricular calcifications, and/or germinal cysts), sensorineural hearing loss (SNHL), chorioretinitis, hepatosplenomegaly, transaminitis, direct hyperbilirubinemia, petechiae/thrombocytopenia, and intrauterine growth restriction (IUGR). Patients with SNHL identified soon after birth without any other clinical manifestations are classified as a subgroup of asymptomatic infection. An additional 5% to 15% of cCMV infants who are asymptomatic at birth without SNHL will develop late-onset sequelae, the most common of which is SNHL.

Given that SNHL is the most common sequelae of cCMV, it is not surprising that cCMV is the most common nongenetic cause of hearing loss in children, accounting for about one-quarter of cases. SNHL occurs in 20% to 65% of infants with symptomatic cCMV and 6% to 25% of infants with asymptomatic cCMV (this

Table 1. Impact on Infants with cCMV as a Result of Maternal Primary versus Nonprimary Infection (5)(6)(7)(8)(9)

Impact of Infection	Maternal Primary CMV Infection	Maternal Nonprimary CMV Infection
Risk of cCMV infected newborn (ie, congenital transmission)	30%–50% (30% first trimester; 40%–70% third trimester)	0.5%–2%
Symptomatic at birth	18%	<1%
Typical severity of infant illness	More severe (particularly with first trimester primary infection)	Less severe
Sequelae by age 2 y	25%	8%

CMV=cytomegalovirus; cCMV=congenital cytomegalovirus.

includes infants with isolated SNHL soon after birth and those patients who develop late-onset SNHL). (18)(19) Hearing loss varies from mild to profound, may be unilateral or bilateral, and can be stable, progressive, or fluctuating. For affected infants with SNHL, the loss rarely improves over time and most children with SNHL (both symptomatic and asymptomatic patients) ultimately have progression of loss. (20)(21)(22) The onset of hearing loss can be delayed and may occur during the first several years of life. (19)(20) In addition, affected patients presenting with unilateral hearing loss are at high risk of developing SNHL in the contralateral ear. Among symptomatic cases of cCMV, IUGR, petechiae, microcephaly, and abnormal neuroimaging findings are associated with SNHL. (23)(24)(25)(26) Among asymptomatic infants with cCMV, prematurity and low birthweight are associated with SNHL. (18)(27)(28) There is no reliable method to predict which children with cCMV will develop SNHL.

Long-term morbidity in patients with cCMV results from neurologic disability and includes cerebral palsy, motor/cognitive impairments, and seizure disorders. In addition, visual impairment, both from ocular manifestations and cortical blindness can occur in patients with cCMV. Mortality among infants with symptomatic cCMV in the United States is estimated to be less than 5%. (29)(30)

SCREENING AND DIAGNOSIS

Testing for cCMV should be done within the first 3 weeks after birth to distinguish congenital infection from postnatally acquired infection (acquisition through saliva or breastmilk). Postnatal CMV infection does not have the same constellation of symptoms or risk for hearing loss as cCMV, (31) though postnatal CMV can cause significant clinical illness, particularly in preterm infants. (32) Thus, diagnostic and treatment dilemmas can be avoided with early neonatal testing for CMV. Screening programs could be targeted (ie, only testing newborns with signs or symptoms suspicious for cCMV infection) or universal (ie, testing all newborns).

Targeted Screening

At this time, targeted screening for cCMV is increasingly common in the United States. In this approach, neonates with abnormalities suspicious for cCMV are tested for CMV. Although some neonates diagnosed via targeted screening will not meet the criteria for antiviral treatment, routine targeted testing allows neonates who are diagnosed with cCMV to undergo a complete evaluation (brain imaging, laboratory testing, and ophthalmologic examination). After a complete evaluation, the clinician can assess whether treatment is indicated and if so, initiate therapy within the appropriate timeframe. Furthermore, infants with cCMV who do not qualify for antiviral treatment soon after birth can be appropriately monitored (ie, repeated audiology testing) and may have the opportunity to enroll in clinical trials. The ethical implications of this targeted approach have been reviewed previously. (33)

Hearing-targeted screening for cCMV focuses on infants who have an abnormal newborn hearing screen during the newborn hospitalization. (34) Many states have legislation requiring hospitals to provide parents of infants who fail their hearing screen with information about cCMV and an opportunity to test for cCMV. Some health care systems have policies for reflexive cCMV testing in newborns with a failed hearing screen before discharge from the hospital. Some states have legislation mandating cCMV testing of neonates with suspected hearing impairment as a result of routine newborn hearing screening. In general, surveyed parents seem to be supportive of routine newborn screening for CMV. (35) Targeted screening for cCMV in infants with a failed hearing screen is particularly helpful because the absence of other abnormalities found in patients with symptomatic cCMV does not rule out cCMV as a possible cause of the hearing loss.

Some experts advocate for clinicians to investigate for additional causes of hearing loss among patients with a failed hearing screen and a diagnosis of cCMV to identify overlapping causes of hearing loss. Genetic causes of hearing loss have been reported in a small percentage of this population. (36)(37) Discovery of an additional plausible cause of hearing loss may affect the analysis of potential risks and benefits of antiviral treatment for cCMV, particularly if the infant does not have other manifestations of cCMV.

Expanded targeted screening is another approach whereby testing for cCMV is performed on infants who have findings consistent with cCMV (other than SNHL) including thrombocytopenia/petechiae, conjugated hyperbilirubinemia, hepatosplenomegaly, hepatitis, IUGR, small for gestational age, microcephaly, rash consistent with cCMV, abnormal head ultrasound scan with unexplained ventriculomegaly or periventricular calcifications.

Targeted screening has 2 key aspects that can optimize timely diagnosis of cCMV:

1. Screening before newborn hospital discharge, if possible (recognizing that, in the case of hearing-targeted screening, a subset of failed newborn hearing screens

is false and repeat screening weeks after birth could be normal).
2. Consideration of cCMV and screening early in the NICU, before 3 weeks of age, even in preterm infants.

Universal Screening

Congenital CMV is a major cause of childhood disability and has a notably higher incidence than disorders that are currently included in newborn screening programs. (38) However, CMV is not currently included in any state newborn screening program. Universal newborn hearing screening has improved early detection of SNHL and increased early identification of infants with cCMV; however, a significant proportion of infants with cCMV are missed because the hearing loss presents beyond the newborn period. (39) This provides a rationale for universal newborn CMV screening, (38)(40)(41)(42) which would lead to prompt diagnosis and a complete evaluation of all infants with cCMV. This universal approach would identify children in need of prospective audiologic and developmental monitoring to detect later-onset manifestations. In addition to health outcomes and quality-of-life benefit, a cost-analysis study concluded that universal screening for cCMV would be cost-effective and result in net health care savings. (43) Although the focus should remain on symptomatic infants who have been shown to benefit from treatment, universal screening would also allow families with affected infants to make informed decisions about available treatment options. Options for a universal screening approach include hospital-based screening of all newborns during their birth hospitalization or public health department–based newborn screening programs; specific testing modalities are discussed herein.

Diagnostic Testing

The historic gold standard of CMV detection via culture has been replaced with testing for CMV DNA polymerase chain reaction (PCR) in samples of urine, saliva, or blood. Compared with a viral culture, PCR provides more rapid results, is more sensitive, and requires only 1 sample. Urine CMV PCR is the most highly sensitive and specific test. Saliva (buccal swab) may be a more convenient sample to collect in newborns and has a high sensitivity but a slightly lower specificity. (44)(45)(46) False-positive results are possible with saliva samples because of viral shedding in seropositive mothers with previous CMV infection; thus, saliva samples should be collected 1 to 2 hours after breastfeeding to minimize this likelihood. (47) Saliva PCR testing is commonly used as a screening test in nurseries because samples are easy to obtain. Rapid detection platforms are currently being validated using pooled saliva samples that can help facilitate an expeditious diagnosis. (48)(49) A positive saliva PCR result should be confirmed with a repeat test (preferably urine PCR). In infants with cCMV, urine PCR will remain positive for months, but the window for definitive diagnosis of congenital infection is a positive urine PCR result within the first 3 weeks after birth; a positive urine PCR result beyond this period could also be consistent with postnatally acquired CMV infection There is no clear role for CMV IgG/IgM (antibody) testing of the infant because the presence of maternal IgG antibodies will confound the results, and CMV IgM testing has limited predictive value.

If assessment for cCMV occurs beyond the first 3 weeks after birth, testing for CMV using a dried blood spot that had been obtained during the first 3 weeks of age and stored by newborn screening programs can be helpful. Previous studies have reported lower sensitivity of blood spot testing, but more recent studies show improved sensitivity, and it is appropriate for retrospective diagnosis in infants and children with a suspicion for cCMV infection. (50)(51) Dried blood spot cards are currently saved by health departments for varied lengths of time before they are discarded and must be requested and retrieved with permission of the family.

MANAGEMENT

The mainstay of antiviral treatment for cCMV disease includes intravenous ganciclovir and its oral prodrug valganciclovir. Treatment benefit has been demonstrated in clinical trials of symptomatic infants with cCMV (defined as having at least 1 symptom of end-organ disease related to cCMV) with antiviral initiation in the first month after birth. In 1997, a phase II clinical trial reported improved hearing outcomes after 6 weeks of ganciclovir in symptomatic infants with cCMV. (52) Subsequently, a phase III study among symptomatic infants with CMV with neurologic involvement reported improved hearing outcomes (assessed at 6 months to 1 year) (53) and neurodevelopmental sequelae. (54) Subsequently, the pharmacokinetics of oral valganciclovir was found to be equivalent to intravenous ganciclovir. (55)(56) In 2015, a phase III randomized controlled trial compared symptomatic infants with cCMV who received 6 weeks versus 6 months of valganciclovir. (57) The longer treatment resulted in improved hearing outcomes and neurodevelopmental scores at 24 months of age. (57) The most significant adverse effect of ganciclovir and valganciclovir is neutropenia, which is dose-dependent

and reversible. Additional side effects can include thrombocytopenia, anemia, renal insufficiency, and transaminitis. Theoretically, this treatment could carry the risks of teratogenesis, carcinogenesis, and male infertility, which have been observed in animal studies. (58)

Based on clinical trial data, antiviral treatment is recommended for infants with symptomatic cCMV (infants with at least 1 symptom of end-organ disease related to cCMV). Of note, these trials include a low number of infants with mildly symptomatic disease. In 2017, consensus recommendations were published, which recommended treatment of infants with moderate to severe symptomatic cCMV disease excluding patients with isolated SNHL or mild symptomatic disease. (59) Moderate to severe cCMV is defined as infants having multiple manifestations of disease including thrombocytopenia/petechiae, IUGR, hepatitis, hepatosplenomegaly *or* central nervous system involvement (microcephaly, classic radiographic abnormalities, chorioretinitis). SNHL is considered as evidence of central nervous system involvement if there are other abnormalities to suggest cCMV disease. An infant who has SNHL without other apparent cCMV manifestations is categorized as having "asymptomatic infection with isolated SNHL." Mildly symptomatic cCMV infection includes infants with manifestations such as an isolated low platelet count that resolves quickly or a mild transaminitis. Ideally, the diagnosis of cCMV and eligibility for treatment should occur in the first month after birth. If indicated, treatment should be initiated by 1 month of age with antiviral duration of 6 months. A summary of this treatment approach is provided in Table 2.

Some clinical scenarios require expert opinion and discussion with families to determine whether antiviral treatment should be initiated. Factors influencing treatment include the spectrum/severity of SNHL; findings associated with, but not pathognomonic for cCMV (such as periventricular cystic lesions); and confidence in cCMV diagnosis when the testing timeframe is beyond 3 weeks of age. Consultation with an infectious disease specialist can be important and helpful in interpretation of data, determining a treatment decision, and counseling of families. During shared decision-making discussions with families about initiating valganciclovir, clinicians must be transparent about the level of evidence, applicability to the patient's individual scenario, and potential adverse effects of treatment. The scientific community must also be committed to generating high-quality data to guide evidence-based treatment of infants with cCMV. Delayed initiation of therapy, treatment beyond 6 months' duration for very severe disease, treatment of isolated or late-onset SNHL, and treatment of mild or asymptomatic disease are being actively studied and could be beneficial. (60)(61)(62) Results of these studies (ClinicalTrials.gov identifier: NCT01649869, NCT03107871, NCT03301415, and others) may eventually support expanded indications and windows for treatment.

Before treatment initiation, a complete evaluation of infants with cCMV should include a physical examination, blood counts, bilirubin and transaminase levels, assessment of renal function, brain imaging (ultrasonography, computed tomography, or magnetic resonance imaging, with ultrasonography considered first line for infants without neurologic symptoms or microcephaly), an ophthalmologic evaluation, and a complete diagnostic audiology assessment. Infants who are receiving antiviral medication, should be closely monitored with frequent complete blood cell counts with differential including absolute neutrophil counts (typically weekly to biweekly for the first month[s] of treatment, then monthly for the duration of therapy) as well as routine monitoring of transaminases and renal function.

AUDIOLOGIC MONITORING AND THERAPIES FOR SNHL

The incidence of delayed onset and progressive and fluctuating hearing loss necessitates ongoing audiologic surveillance for all patients with cCMV. Despite attempts to identify risk factors for hearing loss, it is not possible to predict which patients with cCMV will develop delayed-onset hearing loss or which patients with hearing loss are at risk for further progression. Audiologic evaluation should be completed every 6 to 12 months with consideration of more frequent testing during the first year. (22)(63) Routine audiologic monitoring until age 4 to 6 years is recommended for patients with cCMV, after which routine hearing surveillance (typically performed in school) may be resumed for patients without hearing loss. (19) Children with SNHL should undergo hearing rehabilitation, including amplification and early intervention speech therapy, to optimize hearing outcomes and prevent speech and language delays.

Cochlear implantation is an effective treatment for patients with severe to profound SNHL and deafness. The benefits of cochlear implantation are well-established and include improvement in auditory thresholds, speech perception, and speech expression. (64)(65)(66)(67) For patients with cCMV and unilateral SNHL, early cochlear implantation in the ear with SNHL is encouraged because of the high risk of progression of SNHL in the contralateral ear. This also helps to prevent a prolonged period of auditory deprivation

Table 2. Antiviral (Valganciclovir) Treatment Recommendations (59)

Indication for treatment
- Infants with moderate to severe symptomatic cCMV
- Not routinely recommended for mild symptomatic cCMV infection or isolated SNHL. *May consider on case-by-case basis.*
- Therapy *not* recommended for asymptomatic cCMV infection

Treatment regimen
- Oral valganciclovir therapy for 6 mo duration
- Initiation of treatment ideally within the first month after birth
- Monitoring blood counts including neutrophil count and platelets, transaminases, and kidney function during therapy

Neonatal cCMV disease categorization

Moderate to severe symptomatic cCMV
- Multiple abnormalities consistent with cCMV that may include thrombocytopenia/petechiae, IUGR, hepatitis (elevated transaminase levels or direct bilirubin), hepatosplenomegaly
- Central nervous system involvement that may include microcephaly, imaging abnormalities consistent with cCMV (ventriculomegaly, calcifications, cortical malformations), chorioretinitis, SNHL (along with other findings)

Mild symptomatic cCMV
- Isolated mild and transient manifestations such as low platelet count, elevated alanine aminotransferase level, or isolated IUGR

Asymptomatic cCMV with isolated SNHL
- No manifestations that could be related to cCMV but with presence of SNHL

Asymptomatic cCMV
- No apparent abnormalities to suggest cCMV disease and with normal hearing in the neonatal period

cCMV=congenital cytomegalovirus; IUGR=intrauterine growth restriction; SNHL=sensorineural hearing loss.

and further developmental delay. Children with additional disabilities, including neurologic impairment, can also benefit from cochlear implantation. (68)

Summary

CMV infection is a common congenital infection with a spectrum of manifestations and significant morbidities in a subset of affected infants. Late-onset sequelae, especially SNHL, can occur in infants with cCMV who are asymptomatic or symptomatic at birth. A broad and prompt screening approach is critical to identify newborns affected by cCMV to ensure that a complete evaluation is performed and when appropriate, treatment with antiviral medication is initiated. The critical window for timely, definitive diagnosis is within the first 3 weeks after birth using saliva or urine CMV PCR, with a confirmatory urine PCR recommended in the case of a positive saliva PCR. A complete evaluation of infants with cCMV includes a complete physical examination, blood counts, liver and kidney function tests, neuroimaging, ophthalmologic examination, and audiologic testing. Antiviral treatment can improve end hearing and neurodevelopmental outcomes for symptomatic infants with moderate to severe cCMV manifestations, and active studies are currently being performed to understand whether other infants with cCMV may benefit from valganciclovir. Infants who are not treated with antivirals require audiologic surveillance for new-onset hearing loss and/or progression of SNHL. For patients with hearing loss, prompt initiation of interventional therapies, hearing augmentation, and in the case of severe to profound loss, cochlear implantation, can improve outcomes.

American Board of Pediatrics Neonatal-Perinatal 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.

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