Congenital Cytomegalovirus Infection: Update on Management Strategies

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Opinion statement

Congenital cytomegalovirus (CMV) infections are underrecognized as a cause of serious morbidity in newborn infants. The era of therapeutic nihilism regarding these infections has come to an end, however, as useful therapies are now available that may modify the outcome. The infected fetus can be treated in utero, or the newborn infant can be treated when CMV is recognized in the neonatal period. Expanded screening of newborns for congenital CMV infection will make it even more important for clinicians to be aware of current therapeutic options. The most effective option for the treatment of life-threatening or sight-threatening CMV disease at any age is the nucleoside analog ganciclovir. For the newborn with congenital CMV infection, the value of ganciclovir appears to relate to its ability to preserve hearing; other improvements in overall neurodevelopmental status are inferred but remain to be proven. In the pregnant woman with primary CMV infection, the use of CMV-specific immune globulin, though still investigational, is garnering attention and may prove to be a valuable therapy.

Introduction

Cytomegalovirus (CMV) infection is ubiquitous in the general population and rarely produces symptoms in the immunocompetent infant, child, or adult. CMV-induced illness may be serious in individuals with impaired immune systems, however, including those who are HIV-infected, patients who have received solid-organ or hematopoietic transplants, and infants infected in utero. In the developed world, congenital CMV infection is the most common congenital viral infection, present in about 1% (0.5%–2%) of all live births [1]. This corresponds to approximately 40,000 infants born with CMV infection every year in the United States, making this infection a more common cause of birth defects in newborns than other, better-known childhood conditions such as Down syndrome, fetal alcohol syndrome, or spina bifida [2••]. Rates of congenital CMV infection tend to parallel those of maternal seropositivity. It is estimated that in the United States every year, about 27,000 women acquire primary CMV infection during pregnancy [3••]. Young maternal age, single marital status, and nonwhite race are associated with higher rates of congenital CMV infection. Women with occupations associated with increased exposure to young children, such as teachers and day-care providers, may be at increased risk of acquiring primary CMV infections [4].

Transmission of CMV appears to be more common in the setting of a primary maternal infection. Primary maternal infection during pregnancy results in intrauterine infection of the fetus in 30% to 40% of cases, compared with a risk of about 1% in women with preconception immunity who are reinfected during pregnancy (nonprimary infection) [5,6]. Although preexisting maternal immunity reduces the incidence of maternal-fetal transmission, recent evidence seems to suggest that the severity of congenital CMV disease in the infected newborn is similar following primary or nonprimary maternal infections [7–10]. Thus, intervention programs could be targeted both to the woman with a primary CMV infection identified during pregnancy and to the newborn infant identified with congenital CMV infection during newborn

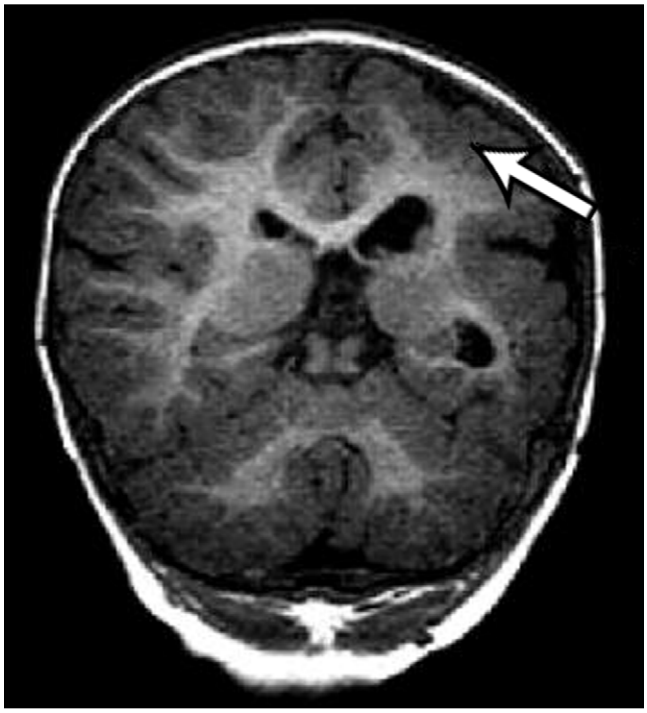

Figure 1. Brain MRI of an infant born with symptomatic congenital cytomegalovirus (CMV) infection. Cortical dysplasia is noted on this T1-weighted coronal section; the left hemisphere shows loss of sulci and gyri (polymicrogyria) and thickened gray matter (*arrow*). White matter abnormalities reflecting neural migration anomalies are also present.

Table 1. Long-term sequelae of congenital cytomegalovirus infection in children with and without symptoms at birth*

	Affected children, %	
Sequelae	**Symptomatic**	**Asymptomatic**
Overall incidence	50–90	10–15
Hearing loss	50–60	7–15
Cognitive deficits	50–70	~ 4
Microcephaly	35–40	~ 2
Ocular abnormalities	25–50	~ 3
Seizures	15–20	~ 1
Motor deficits (mild to moderate)	25–30	< 1
Motor deficits (severe)	15–25	< 1

*Rates reflect a range of incidence data reported in the pediatric literature.
(*Adapted from* Sharon and Schleiss [16].)

screening. Caution must be exercised in interpreting the results of virologic tests obtained beyond 14 to 21 days of age, because the identification of CMV in such infants may represent postnatal acquisition of infection, typically through breast-feeding [11].

Early signs and symptoms are apparent at birth in 10% to 15% of all children with congenital CMV infection. Thus, 4000 to 6000 infants are born with symptomatic congenital CMV disease each year in the United States. Infection in the symptomatic infant may involve any organ and ranges from mild, isolated, transient illness to severe, fulminant dissemination resulting in up to 20% perinatal mortality [12]. Fulminant illness is characterized by jaundice, hepatosplenomegaly, lethargy, respiratory distress, seizures, and petechial rash. Infants may exhibit a wide spectrum of disease, including hemolysis, bone marrow suppression, hepatitis, pneumonitis, enteritis, and nephritis [13–15]. Antiviral therapy may be lifesaving for infants with overwhelming infection and severe organ disease.

Of major importance is the issue of central nervous system (CNS) involvement in congenital CMV infection. Infants who are symptomatic in the newborn period commonly present with cerebral lesions, including meningoencephalitis, calcifications, microcephaly, disturbances in neuronal migration, germinal matrix cysts, ventriculomegaly, and cerebellar hypoplasia [16]. CNS disease usually results in at least one of the following signs and symptoms: lethargy, hypotonia, seizures, hearing deficit, or abnormal eye examination. CNS involvement may be corroborated by abnormal imaging studies (cranial CT, brain MRI, or head ultrasound) [17,18]. Figure 1 shows an example of an abnormal MRI scan of a symptomatic, congenitally infected infant. The risk of long-term neurodevelopmental disabilities is high in this setting; they are observed in 50% to 90% of children who are symptomatic at birth. Possible long-term sequelae include microcephaly, hearing loss, motor deficits (paresis/paralysis), cerebral palsy, mental retardation, seizures, ocular abnormalities (chorioretinitis, optic atrophy), and learning disabilities (Table 1).

In contrast, long-term neurodevelopmental injury is less likely in congenitally infected infants who are asymptomatic at birth. Such injury is typically limited to hearing deficits [19–22]. Sensorineural hearing loss (SNHL), the most frequent sequela of congenital CMV infection, may occur in both symptomatic and asymptomatic infected infants. The bulk of the evidence regarding the potential benefits of antiviral therapies for congenital CMV infection relates to the issue of SNHL; thus, this is an area of unique importance in the assessment of the role of treatment of congenital CMV infection. The incidence of hearing loss among children with congenital CMV infection ranges from 10% to 15% among infants who are asymptomatic at birth to as many as 60% of infants with symptomatic congenital infection [23,24]. SNHL can be progressive and fluctuating and can range in severity from a unilateral, mild hearing deficit to severe, bilateral, profound deafness [25–27]. Patients with symptomatic congenital CMV disease with clinical and laboratory findings suggesting disseminated infection at birth (eg, petechiae, hepatosplenomegaly, CNS abnormalities)

and those with high viral load as measured by quantitative polymerase chain reaction (PCR) testing appear to have an increased risk of developing SNHL [28,29]. CMV-induced SNHL may be present at birth or can become evident later in childhood, usually before 4 years of age [30]. Therefore all congenitally infected infants, regardless of the results of functional newborn hearing screening, should be monitored regularly for SNHL. This issue is likely to become increasingly important over the next few years as more efforts are undertaken to implement universal screening of newborns for congenital CMV infection, using PCR-based detection of viral genome [31]. As infected infants are identified, serial audiologic and neurodevelopmental assessments will be necessary, and selected infants will be candidates for antiviral drug treatment.

Treatment

- Much of the injury produced by congenital CMV infection, particularly injury to the fetal brain, occurs in utero, so antiviral therapy in newborns is likely to have only modest impact on long-term outcomes for the most severely affected infants. However, recent evidence suggests that treatment of pregnant women with primary CMV infections (using CMV immune globulin) can improve the outcome for the fetus.

Pharmacologic treatment

Ganciclovir

Ganciclovir, a nucleoside analogue, is the prototypic antiviral for CMV infection. Considerable experience with this drug has been accrued over the past 20 years, particularly in immunosuppressed patients (solid-organ and bone marrow transplant recipients and patients with HIV infection) [32]. To examine whether the benefits of antiviral therapy could be extended to newborns, in 1991 the first phase 3, randomized, nonblinded, controlled trial of ganciclovir for infants with congenital CMV disease was initiated [33]. A 6-week course of ganciclovir (6 mg/kg every 12 hours) was given to a randomized group of newborns with virologically confirmed congenital CMV infection who also had documented CNS involvement. The primary end point was improved hearing or retention of normal hearing. Small but significant differences between treated and untreated groups were noted, including normal or improved hearing at age 6 months. Almost two thirds of the treated infants developed reversible neutropenia. These data provided strong support for consideration of treatment of congenital CMV infection in infants with CNS abnormalities.

Still to be determined is whether asymptomatic congenitally infected infants at risk of developing SNHL can benefit from ganciclovir therapy. Another priority will be determining whether the oral formulation of ganciclovir, valganciclovir, is an acceptable alternative in newborns, eliminating the need for central venous access for prolonged administration of intravenous ganciclovir. Studies by the Collaborative Antiviral Study Group (CASG), a multi-institutional collaborative network funded by the National Institute of Allergy and Infectious Diseases, should answer these questions in the coming years (www.casg.uab.edu).

Ganciclovir should be used in infants with life- or sight-threatening organ disease, CNS involvement, or persistent or reoccurring disease [33, Class I]. Further evidence that early treatment prevents, delays, or alters the onset of late or progressive SNHL is still needed, particularly for asymptomatic congenitally infected infants.

In addition to ganciclovir (and its oral prodrug, valganciclovir), two other antivirals, foscarnet and cidofovir, are licensed for the treatment of CMV infection (Table 2). Experience with these agents in the setting of congenital CMV infection is extremely limited [32].

Table 2. Antivirals used to treat cytomegalovirus infection

Antiviral agent	Mechanism of action	Dosage	Indications	Toxicities	Comments
Ganciclovir	Inhibit CMV DNA polymerase. Synthetic guanine analogue. Phosphorylated by specific CMV protein.	10–12 mg/kg/d, divided twice a day (IV)	CMV retinitis; end-organ disease in immunosuppressed patients; congenital CMV infection with symptomatic CNS involvement	Hematologic: neutropenia, thrombocytopenia	Consider concomitant use of G-CSF or GM-CSF.
Valganciclovir	Inhibit CMV DNA polymerase. Valine ester of ganciclovir, metabolized into ganciclovir rapidly after oral dosing.	10–12 mg/kg/d, divided twice a day (po)	CMV retinitis in HIV+ patients; prevention of CMV disease in transplant recipients.	Hematologic: neutropenia, thrombocytopenia	Excellent oral bioavailability. Limited experience in infants. Available in tablet forms; suspension available for investigational use.
Foscarnet	Inhibit CMV DNA polymerase. Drug acts directly.	180 mg/kg/d; 2–3 divided doses for 14–21 d, then 90–120 mg/kg/d (IV)	CMV retinitis; end-organ disease in immunosuppressed patients; ganciclovir-resistant infection or inability to tolerate ganciclovir toxicities	Renal; may also be associated with toxicity for developing bones and teeth. Avoid use in pregnancy.	Prehydration minimizes nephrotoxicity. Limited experience in infants.
Cidofovir	Inhibit CMV DNA polymerase. Phosphorylated into active form.	5 mg/kg once weekly for 2 wk followed by biweekly doses (IV)	CMV end-organ disease in immunosuppressed patients; ganciclovir-resistant infection or inability to tolerate ganciclovir toxicities	Renal	Prehydration and pretreatment with probenecid minimizes nephrotoxicity. Limited experience in infants.

CMV—cytomegalovirus; CNS—central nervous system; G-CSF—granulocyte colony-stimulating factor; GM-CSF—granulocyte-macrophage colony-stimulating factor; IV—intravenous; po—oral.

Standard dose 12 mg/kg per day.

Contraindications Neutropenia, renal insufficiency.

Main drug interactions None.

Main side effects Neutropenia.

Special points Use of ganciclovir in infants has not been approved by the US Food and Drug Administration (FDA). Evidence to support efficacy is limited. Use appears to be justified in newborns with congenital CMV infection who have neurologic manifestations at the time of diagnosis.

Cost/cost-effectiveness Cytovene (ganciclovir, Roche Laboratories, Nutley, NJ) is supplied in vials containing a 500-mg dose. The cost for 25 vials is $1491.60 [34]. Because this agent is not FDA-approved for use in children, its cost-effectiveness is unknown.

Surgery

Standard procedure Cochlear implantation.

Contraindications None.

Complications CSF leak/fistulae, meningitis.

Special points	Cochlear implantation is of value in the setting of CMV-associated SNHL, although the precise indications remain incompletely defined. Case series indicate benefit with normalization of speech and language development.

Physical/speech therapy and exercise

Specific therapy	Speech therapy should be provided to children with congenital CMV infection with hearing loss. Physical therapy should be provided to children with cerebral palsy and developmental delay.
Usage	Individualized, depending upon extent of child's disability.
Special points	Children with known congenital CMV infection should have periodic assessments of hearing and development throughout early childhood.

Emerging therapies

Rather than treating the congenitally infected newborn, a strategy has recently been evaluated that involves treating the pregnant patient who has evidence of primary CMV infection and fetal infection in utero. These studies have been performed in Italy, a country with well-organized obstetric programs for maternal CMV screening during pregnancy. The intervention that has been evaluated is the use of a CMV-specific immune globulin [35•, Class III]. In a prospective, nonrandomized trial that studied 157 pregnant women with confirmed primary CMV infection and their newborn infants, administration of CMV-specific hyperimmune globulin (HIG) to the pregnant women was followed by evaluation of the newborn for the presence and clinical presentation of congenital CMV infection [35•]. The study cohort was divided into therapy and prevention groups. The therapy group comprised 55 women with CMV-positive amniotic fluid; they were offered HIG. A prevention group, 102 women who did not undergo amniocentesis, was also offered HIG. In the therapy group, 3% of the women receiving HIG gave birth to an infant with symptomatic congenital CMV disease, compared with 50% of women who did not receive HIG. In the prevention group, 16% of the women who received HIG had infants with congenital CMV infection, compared with 40% who did not receive HIG. No adverse events were associated with HIG infusion. This trial showed that CMV-specific HIG is safe and may be effective in treating and preventing congenital CMV infection. Although HIG cannot now be considered to be a standard of care for CMV infection documented during pregnancy, additional randomized, controlled trials are warranted to further validate the protective effect and the clinical practicality of using passive immunization to prevent congenital CMV transmission [36].

Specific emerging therapy	Cytomegalovirus immune globulin.
Standard procedure	Undefined.
Contraindications	Allergy or anaphylaxis to any components; known IgA deficiency.
Complications	Unknown.
Special points	Investigational.
Cost/cost-effectiveness	The product used in the study by Nigro et al. [35•] is is not commercially available, so its cost is unknown. An analogous product, CytoGam (CSL Behring, King of Prussia, PA) is $1057.51 for a 50-mL vial [34]. Because this intervention has not yet been subject to a double-blind, placebo-controlled study, its cost-effectiveness is unknown.

Other considerations

- Infants with virologically confirmed congenital CMV infection should undergo complete physical examination and focused laboratory and imaging studies to determine the extent of the disease.

- Appropriate counseling of parents should be provided and early intervention undertaken to maximize performance in children with high risk for disabilities. Cranial imaging and careful physical examination evaluating the head circumference, weight, growth rate, and neurologic deficits is essential.
- Several cranial imaging modalities such as cranial ultrasound, head CT, and brain MRI are available for detecting brain lesions associated with congenital CMV infection. Abnormal findings on head CT are predictors of an adverse neurodevelopmental outcome; a normal CT scan has an excellent predictive value for good long-term outcome.
- Because SNHL is the most common late sequela of congenital CMV infection, careful monitoring for this complication is required. Hearing evaluation should be a component of the initial evaluation, and age-appropriate evaluations should be repeated throughout early childhood because the hearing deficit is often progressive and may fluctuate.
- Early recognition of SNHL and interventions like ganciclovir, speech/language therapy, centers for deafness education, and cochlear implants may markedly improve the developmental, social, and language skills of a child with hearing impairment.
- Long-term follow-up should take a multidisciplinary approach. In addition to a pediatric infectious diseases specialist, other important members of the care team may include a pediatric otolaryngology specialist, a child behavioral-developmental specialist, a physical therapist, an ophthalmologist, and a neurologist.

Disclosure

No potential conflict of interest relevant to this article was reported.

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