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Congenital Cytomegalovirus Infection: Update on Management Strategies

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Introduction

CMV infection is ubiquitous in the general population, and rarely produces symptoms in the immunocompetent infant, child, or adult. CMV-induced illness may in contrast be serious in individuals with impaired immune systems, including HIV-infected individuals, solid organ and hematopoietic transplant patients, and infants infected *in utero*. In the developed world, congenital CMV infection is present in approximately 1% (0.5–2%) of all live births, making this the most common congenital viral infection¹. 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, and spina bifida². Rates of congenital CMV infection tend to parallel those of maternal seropositivity. It is estimated that in the United States every year, approximately 27,000 women acquire primary CMV infection during pregnancy³. Young maternal age, single marital status, and non-white race are associated with higher rates of congenital CMV infection. Women with occupational exposure that are associated with increased exposure to young children, including teachers and day-care providers, may be at increased risk of acquiring primary CMV infections⁴.

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 30–40% of cases, compared to a risk of ~1% in women with preconceptual immunity who are re-infected during pregnancy (non-primary 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 non-primary 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 during newborn screening. Caution must be exercised in interpreting the results of virological tests obtained beyond 14–21 days of age, since the identification of CMV in such infants may represent post-natal acquisition of infection, typically acquired through breastfeeding¹¹.

Early signs and symptoms are apparent at birth in 10–15% of all children with congenital CMV infection. Each year in the United States this corresponds to 4,000–6,000 infants born with symptomatic congenital CMV disease. 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 mortality¹². Fulminant illness is characterized by jaundice, hepatosplenomegaly, lethargy, respiratory distress, seizures, and petechial rash, and infants may exhibit a wide spectrum of disease, including hemolysis, bone marrow suppression, hepatitis, pneumonitis, enteritis, and nephritis^{13–15}. Antiviral therapy may be life-saving for infants with overwhelming infection and severe organ disease.

Of major importance is the issue of 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 hypoplasia¹⁶ (Table 1). CNS disease usually results in at least one of the following signs and symptoms: lethargy, microcephaly, intracranial calcifications, hypotonia, seizures, hearing deficit, and abnormal eye exam. CNS involvement as may be reflected by the clinical finding of microcephaly, and corroborated by abnormal imaging studies (cranial CT, brain MRI, or head ultrasound)^{17, 18}. An example of an abnormal MRI scan of a symptomatic congenitally infected infant is demonstrated in Fig. 1. The risk of long-term neurodevelopmental disabilities is high in this setting, and is observed in 50–90% of children who are symptomatic at birth. Long-term sequelae may occur, and 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 neurodevelopment injury is less likely in congenitally infected infants who are asymptomatic at birth, and when it occurs, it is typically limited to hearing deficits (see below)^{19–22}. Sensorineural hearing loss (SNHL), which is the most frequent sequelae of congenital CMV infection, and may occur in both symptomatic and asymptomatically infected infants. The bulk of the evidence regarding the potential benefits of antiviral therapies (reviewed below) 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 10–15% of those infants who are asymptomatically infected at birth, to up to 60% of symptomatic congenitally infected infants^{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 suggestive of disseminated infection at birth such as petechiae, hepatosplenomegaly, and CNS abnormalities, as well as those with high viral load as measured by quantitative PCR, appear to have an increased risk of developing SNHL^{28, 29}. Interestingly, CMV-induced SNHL may be present at birth or can become evident later in childhood; in this delayed-onset group, hearing loss usually occurs prior to 4 years of age³⁰. All congenitally infected infants, irrespective of the results of functional newborn hearing screening, should be monitored regularly for SNHL. This issue is likely to become of increasing importance over the next few years as more efforts are undertaken to implement universal newborn screening of newborns for congenital CMV infection, using newborn blood spot cards for PCR-based detection of viral genome³¹. As such infants are identified, serial audiologic and neurodevelopmental assessments will be necessary, and selected infants will be candidates for antiviral drug treatment.

Treatment

Although much of the injury produced by congenital CMV infection, particularly to the fetal brain, occurs *in utero*, it is likely that antiviral therapy of the newborn will have only modest impact on the long-term outcomes for the most severely affected infants. However, recent evidence suggests that treatment of pregnant woman with primary CMV infection can

improve the outcome for the fetus. The roles of therapy for both the newborn infant (with ganciclovir) and the pregnant patient (with CMV immune globulin) are discussed below.

Pharmacologic Treatment

Ganciclovir

Standard dose: 12 mg/kg/day

Contraindications: Neutropenia, renal insufficiency

Main Drug Interactions: None

Main Side Effects: Neutropenia

Special Points: Use of ganciclovir in infants is not FDA-approved. Evidence to support efficacy is limited. Use in infants with congenital CMV infection appears to be justified in newborns with neurologic manifestations at the time of diagnosis (see below).

Cost: Cytovene® (ganciclovir; manufactured by Roche) is supplied in 500 mg dose vials. The cost for 25 unit dose vials is \$1491.60 (Drug Topics Red Book 2007, Medical Economics Co., Montvale, NJ).

Cost Effectiveness: Since the agent is not FDA approved for use in children, the cost effectiveness is unknown at this time.

Notes of Interest Regarding Antiviral Therapy for Congenital CMV

The prototypic antiviral for CMV infection is the nucleoside analog, ganciclovir, and considerable experience has been accrued with this drug over the past 20 years, particularly in immunosuppressed patients, particularly solid organ and bone marrow transplant recipients, and patients with HIV infection³². To examine whether the benefits of antiviral therapy could be extended to newborns, in 1991 the first Phase III, randomized, non-blinded controlled trial of ganciclovir for infants with congenital CMV disease was initiated³³. A six-weeks course of ganciclovir (6 mg/kg/dose every 12 hrs) was given to a randomized group of newborns with virologically confirmed congenital CMV who also had documented CNS involvement. The primary endpoint 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 6 months of age. With respect to drug toxicities, almost two-thirds of the treated infants developed neutropenia, which was reversible. These data provided strong support for consideration of therapy of congenital CMV infection in infants with CNS abnormalities. What remains to be determined is whether or not asymptomatic congenitally infected infants can benefit from ganciclovir therapy, with respect to the risk of development of SNHL. It will also be an important priority to determine if the oral formulation of ganciclovir, valganciclovir, is an acceptable alternative in newborns, thus obviating the need for central venous access for prolonged intravenous ganciclovir administration. 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.org).

In infants with life- or sight-threatening organ disease, CNS involvement, or in those with persistent or reoccurring disease, ganciclovir therapy should be utilized [33; Class I study]. There is still a need for further evidence that early treatment prevents, delays, or alters the onset of late or progressive SNHL, particularly in the asymptomatic congenitally infected infant. In addition to ganciclovir (and its oral prodrug, valganciclovir) there are currently

two other anti-virals licensed for the treatment of CMV infection, foscarnet and cidofovir (Table 2). Experience with these agents in the setting of congenital CMV infection is extremely limited³².

Surgery

Standard procedure: Cochlear implantation.

Contraindications: None.

Complications: CSF leak/fistulae. Meningitis.

Special points: Use for congenital CMV infection with hearing loss is undefined. Case series indicate benefit with normalization of speech and language development.

Cost / cost effectiveness: Unknown.

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 should have periodic assessments of hearing and development throughout early childhood.

Cost / cost effectiveness: Undefined.

Emerging Therapies

Specific emerging therapy: Cytomegalovirus Immune Globulin

Standard procedure: Undefined (see below).

Contraindications: Allergy or anaphylaxis to any components; known IgA deficiency.

Complications: Unknown.

Special points: Investigational.

Cost: The cost of the Ig described by Nigro et al. (34) is unknown because the product used in this study is not commercially available. An analogous product, Cytogam® (CMV-Ig; manufactured by MedImmune) is \$1057.51 for a 50 ml vial (Drug Topics Red Book 2007, Medical Economics Co., Montvale, MN).

Cost effectiveness: Unknown; intervention has not yet been subject to double-blind placebo-controlled study.

In contrast to the approach of treating the congenitally infected newborn, there has been recent evaluation of a strategy of treatment of 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 obstetrical programs for maternal CMV screening during pregnancy. The intervention that has been evaluated is that of a CMV-specific immune globulin [34; Class III]. In a recent, prospective, non-randomized trial, which

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 infection³⁴. The study cohort was divided into therapy and prevention groups. The therapy group comprised 55 women with CMV-positive amniotic fluid and who were offered HIG. A prevention group, consisting of 102 women who did not undergo amniocentesis, was also offered HIG. In the therapy group 3% of the women elected to receive HIG gave birth to an infant with symptomatic congenital CMV disease, as 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, as compared to 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 the treatment and prevention of congenital CMV infection. Although HIG cannot be considered at this time 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 for prevention of congenital CMV transmission³⁵.

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. Careful physical exam evaluating for head circumference, weight, growth rate, and neurological deficits in combination with cranial imaging is essential.
- Several cranial imaging modalities such as cranial ultrasound (US), head computed tomography (CT) and brain magnetic resonance imaging (MRI), are available for detecting brain lesions associated with congenital CMV infection; abnormal head CT is a predictor for an adverse neurodevelopmental outcome, while a normal CT scan has an excellent predictive value for good long-term outcome.
- Since sensorineural hearing loss (SNHL) is the most common late sequelae 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, since 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 consist of a multidisciplinary approach; in addition to a pediatric infectious diseases specialist, a pediatric otolaryngology specialist, a child behavioral-developmental specialist, a physical therapy, an ophthalmologist, and a neurologist may all be important members of the care team.

Opinion Statement

Congenital cytomegalovirus (CMV) infections are under-recognized as a cause of serious morbidity in newborn infants. The era of therapeutic nihilism regarding these infections has come to an end, since useful therapies are available that may modify the outcome. Therapeutic interventions may be provided to treat the infected fetus *in utero*, or to treat

the newborn infant when CMV is recognized in the neonatal period. Expanded newborn screening programs for congenital CMV will further heighten the importance of clinicians being aware of current therapeutic options.

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