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Advances in the Prevention and Treatment of Congenital Cytomegalovirus Infection

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Abstract

Purpose of review—Cytomegalovirus (CMV) is the most common cause of congenital infection in the world. Symptomatic infants are at increased risk of developing permanent sequelae, including sensorineural hearing loss (SNHL) and neurodevelopmental delay. Advances in the treatment and prevention of congenital CMV infection are a high priority nationally and globally.

Recent findings—In symptomatic infants, antiviral therapy with 6 months of oral valganciclovir (VGCV) improves hearing and neurodevelopmental outcomes. Strategies to prevent congenital or maternal CMV infections, including the use of CMV hyperimmune globulin (HIG) and development of a maternal vaccine, have yet to yield positive results.

Summary—The clinical significance of congenital CMV infection, developments in antiviral therapy, and efforts to prevent congenital disease are herein reviewed.

Keywords

Congenital cytomegalovirus; Antiviral therapy; Valganciclovir; Vaccine; Mother-to-child transmission

Introduction

Cytomegalovirus (CMV) is ubiquitous in humans and, while it commonly leads to asymptomatic or self-limited infection in healthy children and adults, it is a major cause of sequelae in congenitally infected infants and immunocompromised populations. Congenital CMV infection contributes to a large global burden of disease, including permanent hearing loss and neurocognitive disabilities. In this review, we will highlight the clinical significance of congenital CMV infection, developments in antiviral therapy aimed at improving long-term outcomes in symptomatic infants, and efforts to prevent congenital disease by interrupting maternal-fetal transmission or preventing maternal infection during pregnancy.

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Conflicts of Interest

None declared.

Clinical Significance of Congenital CMV Infection

CMV is the most common cause of congenital infection worldwide [1]. The incidence of congenital CMV infection ranges from 0.5% to 2% of all live births, affecting upwards of 30,000 infants per year in the United States [1, 2]. Maternal CMV seroprevalence varies widely, ranging from 45 to 100%, with higher prevalence and earlier CMV acquisition associated with non-white race and lower socioeconomic status [3, 4]. In utero transmission of CMV occurs in mothers with no evidence of CMV immunity who become infected during pregnancy (primary infection), but can also occur in women with preexisting antibody to CMV either by reactivation of previous maternal infection or by acquisition of a different viral strain during pregnancy [5]. Primary maternal CMV infection during pregnancy is associated with a greater risk of in utero transmission, but due to the high prevalence of disease in the overall population, nearly two-thirds of infants with congenital CMV infection are born to mothers with preexisting antibody to CMV [6].

In infants congenitally infected with CMV, approximately 10–15% have clinically apparent disease at birth (“symptomatic” neonates). Clinical manifestations can range from mild, transient findings to severe multi-system dysfunction and may include intrauterine growth restriction, petechiae, jaundice, hepatosplenomegaly, microcephaly, chorioretinitis, and sensorineural hearing loss (SNHL). These symptomatic infants are at increased risk of developing permanent sequelae, most commonly SNHL and neurodevelopmental delay. Even in the 85–90% of infants without clinically apparent disease at birth (“asymptomatic” neonates), approximately 10–15% go on to develop late-onset sequelae, primarily SNHL [7, 8]. Although primary infection is associated with more severe sequelae, prior maternal immunity is only partially protective, and does not completely protect from hearing loss [9, 10].

Inclusive of symptomatic disease and asymptomatic infection, congenital CMV infection is the leading non-genetic cause of SNHL, estimated to be responsible for one-third of all cases in children [11]. Hearing loss occurs in nearly 50% of infants with symptomatic congenital CMV infection, while 7% of asymptomatically infected infants develop hearing loss [12, 13]. CMV-related hearing loss is often delayed in onset, presenting after the newborn period, and can produce a progressive or fluctuating course. In addition to SNHL, vestibular disorders have also been found to occur frequently in children with congenital CMV infection [14].

One of the challenges of assessing the clinical impact of congenital CMV infection is identifying which patients will go on to have permanent sequelae. Infants with severe symptomatic infection are more likely to develop permanent disability, but as of yet, no reliable biomarker has been identified to predict which infants with mild to moderate symptomatology or with asymptomatic infection will develop SNHL. Viral load, as determined by polymerase chain reaction (PCR) assay in blood (reported as DNAemia in some studies) may have the most potential in this regard, but has yet to be clearly established. In a treatment trial of infants with symptomatic congenital CMV infection, lower viral loads over time correlated with better short-term and long-term (24 months) hearing outcomes, illustrating proof of concept but failing to identify a clinically helpful

threshold below which outcomes are better and above which outcomes are worse [15**]. Another recent study followed a small group of infants with asymptomatic congenital CMV infection through 6 years of age and found that asymptomatic infants with viral loads at birth greater than or equal to 17,000 copies/mL were more likely to develop SNHL, but the study was handicapped by a sample size of only 33 infants [16*]. Further studies are needed to delineate the utility of viral load as a predictor of sequelae. If such a marker could be validated, it would provide a reasonable rationale for designing clinical trials in which a biomarker is used to initiate targeted antiviral therapy in asymptotically infected infants who are at higher risk for SNHL.

Treatment of Congenital CMV Infection

Initial investigations into antiviral therapeutics aimed at mitigating the long-term sequelae of congenital CMV infection have centered upon the acyclic deoxyguanosine nucleoside analog ganciclovir (GCV), and its oral prodrug valganciclovir (VGCV). An early study performed by the Collaborative Antiviral Study Group (CASG) demonstrated that 6 weeks of intravenous GCV (6mg/kg/dose given every 12 hours) improved hearing outcomes in symptomatic infants with central nervous system (CNS) involvement [17]. In this study, no patients receiving GCV had worsening of their hearing between baseline and 6 months. Despite the promising improvement in outcome, the utility of this intervention was limited by the high rate of clinically significant neutropenia that developed in patients receiving intravenous GCV, as well as the challenge of maintaining long-term intravenous access. A follow-up pharmacokinetic study from the same group determined that VGCV at a dose of 16mg/kg/dose given orally twice daily attained comparable systemic exposure as intravenous GCV, thus providing an oral option for the treatment of symptomatic congenital CMV infection [18].

Based upon the fact that infants with congenital CMV infection demonstrate prolonged viral shedding and delayed or progressive sequelae [19], the CASG hypothesized that a longer duration of viral suppression during the first months of life may further improve outcomes. To test this, the CASG conducted a randomized, placebo-controlled trial comparing 6 weeks of oral VGCV therapy with 6 months of oral VGCV therapy in infants with symptomatic congenital CMV infection [15**]. VGCV was evaluated at the dose of 16mg/kg/dose given twice daily, and the primary end point of the study was the change in best-ear hearing from baseline to 6 month (assessed by brainstem auditory evoked response). Secondary endpoints included change in hearing from baseline to follow-up at 12 and 24 months, as well as comparison of neurodevelopmental impairment between the study groups at 12 and 24 months. Endpoint analyses were adjusted to account for the presence of CNS involvement at baseline. While no difference in hearing outcome was detected between baseline and follow-up at 6 months, there was a modest, statistically significant improvement in hearing in the 6-month group at both 12 and 24 months. Neurodevelopmental outcomes, as measured by the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III), at 24 months were also significantly better in the 6-month group as compared with the 6-week group. There was no difference in the frequency of neutropenia between the study groups, and the overall rate of neutropenia over the course of the study was lower than that which had previously been seen with intravenous GCV. Based upon this study, it can be concluded that

a 6-month course of oral VGCV is a safe and effective therapeutic option for infants with symptomatic congenital CMV infection. As always, the decision to treat newborns with symptomatic congenital CMV infection must be individualized and should involve counsel regarding the potential risks (neutropenia in approximately 20% of treated babies; carcinogenicity and gonadotoxicity in some animal models, but not seen in humans) and benefits (improved hearing and developmental outcomes) of prolonged antiviral therapy.

Infants with asymptomatic congenital CMV infection should not receive antiviral therapy. As previously mentioned, the design of a clinical trial investigating antiviral therapy for asymptomatic patients would be greatly aided by the identification of a biomarker that predicts those infants who are at increased risk for permanent sequelae.

It is important to identify all infants with congenital CMV infection so that appropriate developmental interventions and long-term follow up can be established. Children found to have congenital CMV infection should have hearing tested every 6 months for 3 years and then yearly for at least an additional 1–2 years. Any defects, including those in hearing and language, should be identified and promptly addressed with appropriate nonpharmacologic intervention (e.g., physical therapy, occupational therapy, audiology amplification).

Prevention of Congenital and Maternal CMV Infections

In addition to the ongoing optimization of antiviral treatment aimed at reducing long-term sequelae of symptomatic congenital CMV infection, complementary efforts also are underway to prevent infections altogether or at least to ameliorate severe sequelae. Strategies to reduce the burden of congenital CMV disease include early detection and intervention in newborns by universal screening, prevention of mother-to-child transmission (MTCT), and prevention of maternal infection. In addition to these strategies, the mainstay of infection prevention involves education regarding sources of exposure and methods of behavioral risk modification to limit exposure.

Universal newborn screening is one method aimed at preventing long-term disability by early recognition and treatment of congenital CMV infection. Viral culture diagnostic modalities are labor intensive and time consuming, making routine universal screening using this modality infeasible in most facilities. Recent data from the CMV and Hearing Multicenter Screening (CHIMES) study have shown that real-time PCR assays in saliva and urine perform as well as viral culture, which provides a scalable diagnostic tool for high-volume screening [20**]. As such, a recent review considered universal newborn CMV screening as a strategy for early detection and therapeutic intervention to improve clinical outcomes in congenitally infected infants and projected that there was potential benefit to be gained [21*]. The authors estimated the number of children in the United States affected by CMV-related long-term sequelae and modeled the impact of nonpharmaceutical interventions and antiviral therapy on hearing and neurodevelopmental outcomes, concluding that newborn CMV screening would positively impact the outcomes of several thousand children per year [21*].

Antenatal interventions as a means of preventing fetal CMV infection are also under investigation. In pregnant women with primary CMV infection, prevention of MTCT via passive immunization with CMV hyperimmune globulin (HIG) has been theorized but efficacy remains unproven. An initial cohort study suggested a lower rate of fetal infection in pregnant women who chose to receive HIG, but as this was an uncontrolled, nonrandomized study [22]. A subsequent phase 2, randomized, placebo-controlled, double blind study evaluated the efficacy of HIG for the reduction of MTCT of CMV infection in 124 women with primary CMV infection during pregnancy. The study group that received HIG was found to have fetal transmission rate of 30%, while the placebo group's rate of transmission was slightly higher at 44% [23*]. The difference between these rates of maternal-fetal transmission in the 2 study groups did not reach statistical significance, however, indicating that CMV HIG does not effectively prevent congenital CMV infection in pregnant women with primary infection. Mothers who received HIG also experienced greater frequency of obstetric-related adverse events. Given the lack of demonstrated efficacy and the increased risk of adverse events, CMV HIG should not routinely be used during pregnancy for the prevention of congenital CMV infection. Further investigation of HIG as a means of prevention congenital CMV infection is underway with a large-scale phase 3, randomized, placebo-controlled, double blind study that is currently seeking to enroll 800 pregnant women in the United States (www.clinicaltrials.gov/show/NCT01376778).

Even as further studies seek to reduce maternal-fetal transmission of CMV, a more fundamental method for reducing the incidence of congenital CMV infection involves prevention of maternal CMV infection through an effective vaccination program. Based on cost analyses and the significant public health impact of congenital CMV disease, the Institute of Medicine ranked the development of a CMV vaccine as the highest priority in its 2000 report [24].

Investigation into CMV vaccines began over 4 decades ago with live-attenuated virus candidates, but these failed to yield adequate protection. More recent efforts with recombinant live-attenuated CMV vaccines with deletion of genes responsible for immune evasion have shown promise in animal model [25**]. This recombinant virus was demonstrated to be substantially attenuated in an immunocompromised guinea pig model, yet it induced antibody responses comparable to wild-type infection, reduced the rate of transplacental infection, and reduced the mortality of guinea pig pups as compared with the control pups born to unvaccinated mothers. These promising results support further development of recombinant live-attenuated CMV vaccine candidates.

Subunit vaccines are another class of CMV vaccine candidates and are largely focused on the immunogenic capacity of surface glycoprotein B (gB). A previous phase 2 study of a gB/MF59 adjuvant subunit vaccine in seronegative postpartum women demonstrated vaccine efficacy of approximately 50% [26]. This study demonstrated the potential for maternal vaccination as a means of preventing congenital CMV infection. A recent guinea pig model has been developed in which glycoprotein homologs can be studied individually or in glycoprotein complex formation in order to better understand function and immunogenicity [27]. Models such as this may prove vital to the development of future CMV vaccine candidates.

Recent analyses of clinical isolates have underscored the genomic diversity of CMV strains, with high rates of recombination and the establishment of naturally circulating genetic variants demonstrated to be hallmarks of its viral evolution [28, 29]. Given this molecular diversity, it is unlikely that a single antigenic component will generate a sufficiently broad immunogenicity to protect against CMV infection. Multivalent vaccine candidates may overcome this challenge by eliciting a broadened immunogenicity. One such subunit vaccine candidate combined gB and pp65 and was studied in guinea pig model. Interestingly, the gB/pp65 combination vaccine induced antibody responses that were significantly lower than the monovalent gB comparator vaccine [30*]. The gB/pp65 combination vaccine also failed to reduce transplacental transmission of infection. Several other multi-component subunit and DNA vaccine candidates aimed at achieving broad cross-neutralizing humoral and cellular immune responses are in the early stages of investigation [2]. Ultimately, the complex nature of maternal protective immunity, including the risk of reinfection with genetically distinct viral strains in women with prior immunity, indicates that many challenges remain to the development of an effective CMV vaccine program [31*].

Conclusion

Recent advancements in the treatment of symptomatic congenital CMV infection demonstrate that 6 months of oral VGCV improves hearing and neurodevelopmental outcomes. Infants with asymptomatic infection should not receive antiviral therapy but should be prospectively monitored for late-onset hearing loss and developmental delay. Strategies to prevent congenital and maternal CMV infections have included the use of CMV HIG in pregnant women with primary CMV infection and the development of an effective vaccine program. These preventative strategies have failed to yield substantially positive results in human subjects to date, though there have been some promising developments.

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Abbreviations

CASG	Collaborative Antiviral Study Group
CHIMES	CMV and Hearing Multicenter Screening Study
CMV	Cytomegalovirus
CNS	Central nervous system
GCV	Ganciclovir
gB	Glycoprotein B
HIG	Hyperimmune globulin

MTCT	Mother-to-child transmission
PCR	Polymerase chain reaction
SNHL	Sensorineural hearing loss
VGCV	Valganciclovir

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highlights the challenges that remain in the development of an effective CMV vaccine. [PubMed: 24639230]

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Key Points

- Infants with symptomatic congenital CMV infection are at increased risk of developing permanent sequelae, including hearing loss and neurodevelopmental delay.
- A reliable biomarker that can predict which infants with asymptomatic congenital CMV infection will develop hearing loss has yet to be identified.
- Antiviral therapy with 6 months of oral valganciclovir improves hearing and neurodevelopmental outcomes in infants with symptomatic congenital CMV infection.
- Developing an effective vaccine to prevent maternal CMV infection and reduce the incidence of congenital infection is a high priority, but no candidate vaccines are currently near licensure.