Treatment of congenital cytomegalovirus: where are we now?

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Congenital cytomegalovirus (CMV) is the most common congenital infection in the USA, affecting approximately 1% of all live births. While the majority of infants will remain asymptomatic, approximately 10% will be symptomatic at birth and another 10–15% will go on to develop problems during the first 6 years of life. Congenital CMV is now the most common cause of nonhereditary sensorineural hearing loss in children. Accordingly, researchers and clinicians have long been interested in identifying strategies to prevent or treat symptomatic congenital CMV infection. This article reviews congenital CMV with a focus on treatment strategies.


Congenital cytomegalovirus (CMV) is the most common congenital infection in the USA affecting approximately 1% of all live births and resulting in 30,000–40,000 congenitally infected children each year [1]. Approximately 10% of infants with congenital CMV are symptomatic at birth and another 10–15% will go on to develop sensorineural hearing loss or developmental problems. While the majority of congenitally infected infants will be without sequelae, the cumulative number of the 20–25% with symptoms remains substantial. It is believed that congenital CMV is the most common cause of nonhereditary sensorineural hearing loss in children [2–5]. The cost associated with symptomatic congenital CMV infection has been estimated to be US$4 billion a year [6]. For these reasons, researchers and clinicians have long been interested in identifying strategies to prevent or treat symptomatic congenital CMV infection. This article reviews congenital CMV with a focus on treatment strategies.

Cytomegalovirus & congenital infection

Cytomegalovirus is a member of the beta-herpesvirus family and, similar to other herpesviruses, results in a life-long infection [7]. Its biology, shared by other members of the Herpesviridae family, is characterized by a highly orchestrated system of transcription, active viral replication and an ability to persist for the life of its host in a latent form punctuated by periods of reactivation. Infection can occur in utero, perinatally or by acquisition of infected secretions later in life. Epidemiologic studies have shown substantial variation in rates of seropositivity in different populations even within the USA, with rates in adults varying from 40 to 80% [8]. Antenatal transmission, as well as risk of sequelae, is influenced by the maternal serologic status during pregnancy. Transmission is frequent in women who undergo primary infection during pregnancy, being 20–50% compared with rates of 0.15–1.5% in pregnant women who have remote infection [1,3,4,6–8]. The rate of disease transmission to the fetus is particularly high when primary infection occurs before the 20th week of gestation [9,10]. Sequelae from congenital infection are also impacted by whether or not the maternal disease was primary or reactivated. Infants infected during a primary infection have long been reported to have a 25% rate of long-term sequelae compared with an 8% rate observed in women who had serologic evidence of previous infection [11]. Interestingly, one study found the rate of hearing loss to be similar in infants born to women with and without prior immunity; however, disease severity and progression were increased in those
born to mothers who had primary infection [11]. These data confirm that while prior immunity has some protective effect, it is not complete. More recent data also suggest that short intervals between the time of CMV acquisition and pregnancy may increase the risk of fetal transmission [12]. Likewise, it has been recognized that women undergoing reinfec tion with a new strain of CMV have an increased risk of having infants with symptomatic disease [13].

Predictors of long-term adverse outcome are not completely known. However, it has long been recognized that infants who are symptomatic at birth are at an increased risk for sequelae compared with those who are asymptomatic [1,3,5,10,14,15]. Children with thrombocytopenia and intrauterine growth retardation, suggesting a more disseminated disease process, have an increased risk of sensorineural hearing loss [14], while microcephaly and abnormal cranial CT scan predict abnormal neurodevelopmental outcomes [16,17].

Progression of disease, once present, is the norm: 30–80% of children with unilateral hearing deficits develop hearing loss in the normal ear or experience progressive loss in the affected ear [18-21]. This progression has been noted to occur as late as 6 years of age [22,23]. Late onset of hearing loss has also been noted up to 5 years of age [22]. In addition, children can have progressive motor or cognitive impairment. The precise pathogenesis of disease progression in congenital CMV is unclear. It is not known whether progressive disease is due to reactivation of virus, the immunologic response of the host or the delayed clinical appearance of damage already present from the time of the initial infection [25]. While neurological damage that occurred in utero may not be expected to reverse, it is possible that antiviral treatment may prevent disease progression. Accordingly, there has long been a desire to treat this infection in newborns.

The early era of treatment

Almost 40 years ago, clinicians caring for infants with severe symptomatic disease used a variety of agents for infants with congenital CMV infection [22-26]. The reports were all anecdotal cases or small case series, using medications that did not have particularly robust activity against CMV in vitro and, perhaps not surprisingly, the outcomes were not very encouraging. Idoxuridine was used for 5 days in a 14-week-old infant with microcephaly and significant irritability [22]. While the authors report that the infant became clinically more comfortable coincident with treatment and that there was transient decrease in virus excretion, the infant continued to have significant microcephaly and developmental delay on follow-up. In 1971, flouxuridine was used to treat a 12-day-old infant who presented with petechiae, thrombocytopenia and hepatosplenomegaly [25]. The virus was isolated from urine, saliva and cerebrospinal fluid despite treatment. The infant’s outcome was poor, with microcephaly becoming apparent over time and significant developmental delay. McCracken and Luby reported their use of cytosine arabinoside (ARA-C) in three infants with congenital CMV infection in 1972 [14]. Two of the three children were noted to have modest clinical improvement and only one, treated with a higher dose, had a decrease in viral shedding. In their discussion, the authors noted that ARA-C produced no decrease in CMV shedding in five other infants treated earlier at a low dose, whereas a final infant treated with high-dose ARA-C had a reduction in viral shedding and a modest clinical response. Similarly, five infants treated with adenine arabinoside displayed only transient cessation of viremia [25].

Researchers were also interested in the use of interferon for treatment, as it appeared to have an in vitro inhibitory effect on CMV. In addition, immunologic studies of infants with congenital CMV infection showed them to have a deficiency of serum interferon and an impaired production response to viral stimulation [25]. However, treatment trials in small case series did not show a beneficial response and did incur toxicity [25]. The development of acyclovir, which was known to have excellent activity against other herpesviruses, led to its use in vitro and in vivo against CMV [27]. While acyclovir did have activity against mouse CMV and in vivo against human CMV at over 10 µg/ml, there was little benefit found in four infants treated. The treatment was given to three neonates who were all asymptomatic at birth and one 18-month-old child who developed symptoms at 6 months of age; duration was short, ranging between 2 and 10 days. While all had transient decreases in viremia, there was no clinical benefit noted. Taken together, while viremia was transiently halted in some instances with these various therapies, no improvement was observed and the enthusiasm for treatment diminished.

Ganciclovir era of CMV treatment

Ganciclovir is an antiviral agent with activity against members of the herpesvirus family but in particular against CMV. It is a nucleoside analog of guanosine and is structurally related to acyclovir, having the addition of a 3'-hydroxy-methyl group [28,29]. It was the first antiviral agent with efficacy against disease from CMV infection and is approved for use in the USA for the treatment of CMV retinitis and prevention of CMV disease after solid organ transplantation [30]. Since the late 1980s, it has been the medication of choice for treating significant CMV disease in immunocompromised hosts [29,31]. In order to be active, ganciclovir needs to be triphosphorylated. In cases of herpes simplex infection, the viral thymidine kinase phosphorylates ganciclovir initially followed by cellular enzymes converting the monophosphate form to ganciclovir triphosphate. Since CMV does not have a thymidine kinase, it is believed that the UL97 gene is responsible for the initial phosphorylation. In vitro ganciclovir has ten- to 20-fold more activity against CMV than acyclovir. This is felt to be related to the fact that the ganciclovir triphosphate concentrates significantly in CMV-infected cells [28,29]. Ganciclovir inhibits most strains of CMV in concentrations that range between 0.1 and 1.6 µg/ml [28,29]. The peak concentrations of ganciclovir, when given intravenously at 5 mg/kg every 12 h, range between 4.5 and 10 µg/ml. Ganciclovir likewise penetrates the CNS and has been used to treat immunocompromised patients with CNS infection from CMV [28,29,31].
Oral ganciclovir, while available and approved for maintenance use in individuals with CMV retinitis, has poor bioavailability [32,33]. In addition, it was noted that children required higher relative oral doses of ganciclovir than adults to achieve similar targeted serum drug levels [32]. While the advantage of not requiring intravenous access was substantial, the poor bioavailability of oral ganciclovir was a significant hindrance to its use.

Valganciclovir is an orally bioavailable, monovalyl ester prodrug of ganciclovir that is rapidly converted to ganciclovir upon absorption [33]. It is approved by the US FDA in a tablet formulation for treatment of CMV retinitis and for prevention of CMV disease in heart, kidney or kidney-pancreas transplant recipients and has been used in a number of studies of treatment and prophylaxis of CMV in immunocompromised hosts [31]. Studies using an oral formulation are being conducted in both pediatric transplant patients [34] and pediatric patients with congenital CMV infection. Analysis of both of these studies is ongoing and further data are anticipated in the near future.

Ganciclovir/valganciclovir safety issues
The major toxicities noted for ganciclovir and valganciclovir are related to bone marrow depression [30,33]. In particular, granulocytopenia has been found frequently in association with ganciclovir products, followed by thrombocytopenia and anemia. Renal toxicity has likewise been noted in ganciclovir trials; however, patients receiving ganciclovir are frequently using other nephrotoxic agents, which makes it difficult to ascribe the toxicity specifically to the antiviral agent. Since ganciclovir is excreted by the kidneys, dosing adjustments may be required if renal impairment occurs. Hematologic and renal monitoring is recommended for individuals treated with ganciclovir or valganciclovir. Animal studies have found ganciclovir products to cause impaired fertility in both male and female mice, along with decreased spermatogenesis in mice and dogs [30,33]. Of particular concern when considering the treatment of infants and young children as studies in mice that have noted ganciclovir to be carcinogenic, particularly to reproductive tissues. Similar findings have not been reported in humans receiving ganciclovir or valganciclovir therapy. Most pediatric transplant centers routinely use ganciclovir or valganciclovir as prophylaxis against CMV. Even with young transplant recipients, the medications are used at many centers for a minimum of 100 days and some centers use ganciclovir products for over 1-2 years [35-37]. Despite the prolonged administration of ganciclovir products in pediatric transplant patients, reports of malignancy associated with their use have not been reported.

The FDA has listed ganciclovir as a Pregnancy Category C; with animal studies demonstrating the potential for teratogenic and embryogenic toxicity but no adequate and well-controlled studies performed in pregnant humans [30,33].

Ganciclovir/valganciclovir treatment of children with congenital CMV infection
The first reported case of the use of intravenous ganciclovir for treatment of congenital CMV was by Fan-Havard and colleagues in 1989 [28]. These authors treated an infant with intraventricular growth retardation and respiratory compromise whose lung biopsy on day 15 of life showed numerous CMV inclusions. Ganciclovir was administered intravenously for 14 days. Shedding of virus stopped at day 5 of treatment but recurred 10 days after ganciclovir was discontinued. The infant’s clinical condition improved slowly and he was removed from mechanical ventilatory support at 3 months of age. Follow-up at 5 months revealed significant bionchopulmonary dysplasia; his neurodevelopmental status was not commented upon [28]. A second infant in this manuscript was also treated with intravenous ganciclovir for CMV pneumonia; however, the infant was 5 weeks old when the diagnosis of CMV was made and he was born at 26 weeks’ gestation; accordingly, it is not possible from the available data to know if this infant had congenital infection or postnatal acquisition of CMV. While neither child had a dramatic clinical response, neither of them experienced clinical or laboratory adverse effects from the drug [28]. Subsequently, other physicians caring for infants with significant symptomatic disease from congenital CMV reported single or small case series using intravenous ganciclovir for various time periods (usually 1-2 weeks) to ameliorate the acute symptoms of CMV infection, such as pneumonitis, hepatitis or disseminated disease with thrombocytopenia or other hematologic abnormalities [38-43]. One of these reports also rationalized treatment to potentially prevent progressive neurological deterioration [41]. Halwachs-Baumann and colleagues reported their experience of treating infants with congenital CMV for the purpose of preventing long-term sequelae [44]. Symptomatic children were treated for at least 3 weeks, or longer if symptoms persisted. The authors note that infants with congenital infection who were asymptomatic were randomized to treatment or no treatment. A total of 12 out of 17 children received ganciclovir. Self-limited side effects of diarrhea and leukopenia occurred in only two patients. However, long-term efficacy was not reported, limiting the usefulness of this study.

In 1991, the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG) embarked on a large, randomized controlled study of 6 weeks of intravenous ganciclovir compared with no treatment in infants with congenital CMV who were less than 30 days old at enrollment and had evidence of CNS involvement [45]. Infants were treated with 6 mg/kg of ganciclovir every 12 h for 6 weeks with dose modifications if needed for bone marrow suppression. This dose was based on results from a previous Phase II evaluation of two dose regimens (4 or 6 mg/kg every 12 h) [46]. Similar to previous studies, transient cessation of viral shedding in the urine was noted but a more pronounced antiviral effect was found with the higher dose. Audiologic evaluations were performed at the time of study entry, 6 weeks and 6 months, and at 1 and 2 years for the primary outcome assessment of hearing loss. A total of 100 infants were enrolled in the study over a 10-year period. However, only 42 and 43 subjects were available for evaluation of hearing change at the 5- and 12-month periods of follow-up, respectively. Despite the substantial dropout rate, some important outcome data can be obtained from this study. Comparison
of the hearing tests for the ‘best ear’ at 6 months and at baseline showed that the infants treated with ganciclovir were more likely to have protection of hearing or even improvement compared with those infants who received no treatment [45]. None of the treated infants had deterioration of hearing at 6 months compared with 41% of the untreated infants (p < 0.01). At the 1-year follow-up hearing assessment, 21% of infants in the treated group had some hearing deterioration in the best ear compared with 68% in the untreated control group. While it was disappointing that some audiologic deterioration began to be seen in the treated group, the data still demonstrate, that even up to 1 year, it is possible that early treatment with 6 weeks of ganciclovir gives a protective advantage for audiologic outcome. Comparison of the infants treated with ganciclovir with those who were untreated for secondary measures of clinical efficacy showed that treated infants also had faster resolution of splenomegaly and hepatomegaly [45]. In addition, the infants who received ganciclovir had a median increase in their head circumference of 3.6 cm at the completion of 6 weeks of therapy compared with only a 2.5-cm increase in the untreated controls (p < 0.01) [45]. While formal developmental assessment were not performed as part of this study, the improved head growth results led to some optimism that treatment may have a prognostic benefit in this area as well. Sheding of CMV ceased simultaneously with therapy but resumed again after therapy was stopped. The major toxicity was related to neutropenia while patients were on ganciclovir. In total, 14 treated patients required dose adjustments; four discontinued the medication prematurely and two patients were treated with granulocyte colony-stimulating factor because of the neutropenia [49]. A study evaluating initial viremia at the time of entry into the two CASG trials found the presence of viremia to correlate with hearing loss at baseline and at 6-month follow-up [17].

Rationale for longer therapy
Recognition that disease from congenital CMV infection can be progressive over years and that the pathogenesis might be due to reactivation of the virus has led to the hypothesis that prolonged therapy might be required for maximal benefit [48]. The rationale for prolonged therapy is also supported by knowledge of another infection acquired in utero; congenital toxoplasmosis. It has long been recognized that congenital toxoplasmosis can be progressive over years and can have late manifestations of clinical symptoms, similar to congenital CMV infection. In addition, children with congenital toxoplasmosis infection benefit from prolonged therapy with drugs directed against Toxoplasma gondii even if not started early in life [49,50]. Currently, the recommendations are to treat these babies with 1 year of therapy, even when identified belatedly [48]. Similar to toxoplasmosis, there has long been interest in whether or not prolonged treatment would be beneficial for infants infected with CMV in utero.

Nigro and colleagues evaluated 12 infants with congenital infection who were randomized to receive 2 weeks of therapy at 5 mg/kg every 12 h or a more prolonged regimen including 7.5 mg/kg every 12 h for 2 weeks followed by 10 mg/kg given three-times a week for 3 months [50]. Children were between 14 days and 6 months of age (mean 2.7 months) at the start of therapy. Four of the six infants in the short-course group had persistent detection of CMV DNA in the peripheral blood and persistent symptoms at 18 months follow-up. The other two infants had cessation of CMV shedding and, likewise, had improved clinical outcome. All infants in the prolonged higher-dose group had cessation of CMV DNA in the blood during treatment. Five of the six children treated with the more prolonged course had improved outcomes, although one later had mild psychomotor retardation. The other infant with severe disease at the start of treatment remained abnormal [51].

In 2003, Michaels and colleagues reported their case series, treating nine symptomatic infants with congenital CMV. Ganciclovir was started between 7 days and 11 months of age (median 10 days) [48]. Treatment was prolonged in all cases, being intravenous for 6–18 months followed by oral ganciclovir for a median of 6 months. Follow-up was between 1 and 7 years with a median of 2 years. Five of the nine children had hearing loss at the time of initiating therapy; none had progressive disease and two had improvement at follow-up [45]. While neurologic evaluation was not rigorously performed in this retrospective review, three of the children who initially had abnormal neurological examinations were later found to be normal and were meeting appropriate milestones at follow-up examinations. Adverse events from prolonged intravenous access were common, with six children having infections of the central line and four having line malfunction [48].

Alternative antidi-CMV therapies
Foscarnet and cidofovir are antiviral medications that also have activity against CMV, and are alternate therapies for CMV disease in immunocompromised hosts that cannot tolerate ganciclovir or have infections with CMV resistant to ganciclovir [31]. Both of these drugs have significant toxicities, particularly to the kidney, which have limited their use in humans trials. A case report using foscarnet for treatment of symptomatic congenital CMV with liver fibrosis had a favorable outcome [52]. Cidofovir has also been used in a guinea pig model of congenital CMV showing potential benefit in preventing maternal transmission during pregnancy [53,54]. However, further data are lacking at this time.

Treatment during pregnancy
Preventing transmission of CMV to the fetus would be ideal. Studies of congenital toxoplasmosis show that prevention of fetal infection by treating pregnant women identified with a primary infection can be successful [50]. Unlike toxoplasmosis, wherein transmission to the fetus only occurs during primary infection, CMV can be transmitted even in women who have had previous immunity [1,55]. However, it has long been recognized that the greatest risk of transmission still occurs with primary infection. For this reason, the strategy of screening women during pregnancy and treating those who develop a
primary infection may still be of benefit. There is a paucity of data on antiviral CMV therapy during pregnancy in the literature. Intrauterine administration of ganciclovir to an affected fetus for 12 days at 29 weeks gestation led to a decrease in viral titer in the amniotic fluid and fetal urine but did not prevent disease; stillbirth occurred at 32 weeks gestation and CMV inclusions were present at autopsy [10]. Several anecdotal cases are available of pregnant women being treated with ganciclovir because they have underlying immunosuppression and CMV disease [56-58]. Laffer and colleagues described fatal outcomes in the fetuses of three women with CMV disease after liver transplantation [56]. Patient 2 in their series was diagnosed with primary CMV during pregnancy; transmission to the fetus occurred despite administration of several cycles of intravenous ganciclovir. Brady and colleagues reported its use in a pregnant woman with acquired immunodeficiency syndrome who had CMV retinitis and pneumonitis [58]. The woman was treated between 30 and 34 weeks gestation with intravenous ganciclovir. At delivery at 34 weeks gestation, the infant was without symptoms of CMV infection and had detectable levels of ganciclovir in plasma at 2 and 8 h after delivery. Despite the favorable clinical outcome in the infant, in situ hybridization for CMV was found in the syncytiotrophoblast and endothelial cells of the placenta and the infant's urine was positive for CMV on day 20 of life. Contradicting the reports of transmission regardless of ganciclovir administration, a third report documents clearance of the amniotic fluid from CMV concurrent with maternal receipt of oral ganciclovir and delivery of an uninfected newborn [57]. Despite this positive case report in an immunocompromised host, the risk of teratogenic effect in pregnant animals makes it unlikely that human trials of ganciclovir will be initiated during pregnancy. Newer antiviral agents with less toxicity, such as maribavir, may hold promise for future efforts.

Intrauterine CMV hyperimmune globulin has also been considered as a potential treatment to ameliorate disease in the fetus. Administration to an affected fetus was associated with a positive outcome in one case report [59]. Of greater importance is an article by Nigro and colleagues in 2005 in which they report the positive results from their prospective non-randomized trial using passive immune globulin during pregnancy to prevent transmission of CMV from mother to fetus [60]. Pregnant women who were found to have primary CMV infection were offered amniocentesis to look for evidence of CMV infection of the fetus; if found to be positive they were offered treatment with CMV-specific hyperimmune globulin. The authors identified 55 women with primary CMV infection who had PCR-positive amniocentesis suggesting fetal infection. A total of 31 women elected to have the treatment. 14 did not and ten chose to have a termination. Of the 31 treated women, 15 had fetal ultrasounds that were abnormal prior to treatment but at follow-up only one of these children had abnormalities. None of the infants with normal fetal ultrasounds developed symptoms later. These results contrast with the nontreated women; seven of the 14 had fetal abnormalities by ultrasound, none were normal at birth and two died. Again, the infants who had normal fetal ultrasound remained normal at follow-up [60].

The study also described offering CMV-hyperimmune globulin as prophylaxis to women with primary infection but who did not undergo amniocentesis, so that fetal infection was not proven. Six of the 37 women (16%) who chose this prophylaxis therapy had infected infants, while 19 of the 47 women (40%) who did not agree to prophylaxis had infants who were infected at birth. These findings are provocative; however, the major critique is the lack of randomization [61,62] and a randomized controlled trial to ascertain the true potential of this therapy has been advocated. Further work by the same group noted that the placentas of women with primary CMV during pregnancy were enlarged compared with those of women who were previously infected [63]. This enlargement was pronounced in women who transmitted the virus to the fetus. Of great interest was the finding that the thickness of the placenta decreased in those women who received hyperimmune globulin, leading to the hypothesis that hyperimmune globulin might act by improving placental health [63,64].

Expert commentary & five-year view

Congenital CMV infection is common and disease impact is considerable. Numerous data are now available to help us assess the risk factors for poor outcome, particularly for those infants found to be symptomatic at birth. Infants identified as having congenital infection with CMV should be evaluated for symptoms and screened for hearing deterioration during the first 5-6 years of life so that early intervention can be instituted appropriately. Furthermore, data are sufficient so that many pediatric infectious disease consultants would recommend routinely treating symptomatic infants with a minimum of 6 weeks of ganciclovir or valganciclovir.

Controlled multicenter studies are clearly required to systematically review whether prolonged therapy will offer better outcomes. Toward this end, the CASG is in the process of beginning a new trial evaluating 6 weeks versus 6 months of valganciclovir for children with symptomatic congenital CMV

Key issues

- Congenital cytomegalovirus (CMV) is a common infection.
- Congenital CMV is a major cause of sensorineural hearing loss.
- Ganciclovir has specific antiviral activity against CMV.
- Ganciclovir therapy in infants with symptomatic congenital CMV infection appears to be effective.
- Studies to determine the optimal duration and timing of ganciclovir therapy are still required.
- Preventive strategies during pregnancy need to be studied further.
infection. Hopefully, this study will offer insight into both the efficacy and safety of longer duration treatment in young children. However, this proposed study will not address those caring for children who were asymptomatic at birth but develop hearing loss or neurological deterioration after the first 30 days of life. Anecdotal data from case series suggest that ganciclovir may be efficacious even later in life but studies examining this population need to be developed. Further understanding of the virologic and immunologic aspects of disease progression will assist in understanding which children may benefit from later receipt of antiviral agents.

Preventive strategies, while not the major purview of this article, deserve mention. Increasingly, young children in the USA are attending daycare centers, which are excellent sources for primary infection by many infectious agents, including CMV. Accordingly, women with toddlers in daycare who have a subsequent pregnancy are at increased risk of CMV infection being brought home by the toddler. While some have recommended advising pregnant women to avoid contact with toddlers in daycare, this is an extreme measure in a family environment. Despite this, education regarding good hygienic practices, including hand washing after diaper changes and avoiding saliva contamination by not sharing eating utensils, is reasonable. Studies examining these educational prevention measures show that they can be beneficial for pregnant women [69]. Vaccine development continues, but as yet there is no vaccine on the horizon that safely prevents primary infection in a seronegative pregnant woman. Research in the area of vaccine development should be encouraged.

Disclosure
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References
Papers of special note have been highlighted as:
• of interest
•• of considerable interest
• Clear, detailed review of cytomegalovirus (CMV) with emphasis on its importance as a congenital infection and as a perinatal or postnatal infection in the newborn.
• Large study confirming that even infants with congenital CMV infection who are asymptomatic at birth can go on to develop sensorineural hearing loss.
• Using a very large cohort, this study confirms that previously acquired immunity to CMV has a significant protective effect for future pregnancies.
• Excellent, encyclopedic review of congenital CMV.
• Large cohort study based on a screened population of infants suggesting that the risk of hearing loss in infants infected from mothers who had been immune may be higher than initially described.
• Analysis of serum from consecutive pregnancies demonstrated that women who had previous immunity to CMV but still transmitted CMV in a subsequent pregnancy often had evidence of acquisition of a new strain of CMV, suggesting that newly acquired strains of CMV could be a risk for intratresine transmission and symptomatic congenital infection.
• Prospective evaluation of almost 200 symptomatic newborns showed that findings suggestive of disseminated infection (petechiae and intratresine growth retardation) were predictive of later hearing loss.
• Longitudinal study showing that microcephaly was a strong predictor of long-term mental retardation and motor disability.
Treatment of congenital cytomegalovirus


Large nonrandomized study investigating different outcomes between the infants born to pregnant women with primary CMV infection who chose to receive CMV hyperimmune globulin compared with women who chose not to receive hyperimmune globulin.


• Suggests a hypothesis for how and why immunoglobulin might work as a preventive strategy during pregnancy.


• Demonstrates that behavioral intervention can be effective for pregnant women to prevent transmission of infection. This gives strong support to the concept that women should be screened early in pregnancy to know their CMV status.

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