Cytomegalovirus Infection

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Drs Plosa, Esbenshade, Fuller, and Weitkamp have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

There is wide variation among centers regarding prophylactic versus preemptive therapy for posttransplantation cytomegalovirus infection.

Objectives

After completing this article, readers should be able to:

1. Understand the mother-infant cytomegalovirus (CMV) transmission risk based on maternal antibody status.
2. Recognize the clinical manifestations of congenital and postnatal CMV infection.
3. Explain the appropriate methods for the diagnosis of congenital CMV infection.
4. Describe the specific risk of neurodevelopmental impairment in infants with congenital CMV infection.
5. State the major antiviral agents for treatment of CMV infection in the immunocompromised host.

Introduction

Cytomegalovirus (CMV) has been identified as an important viral pathogen in humans for more than a century. The histopathology of CMV was first described in 1904, but the virus itself was not isolated until 1957 by Craig et al. (1) CMV infects multiple human cell types, including salivary gland epithelial cells, hence the original name of the virus: salivary gland virus. In 1960, Weller designated the virus as CMV based on the appearance of the swollen virus-infected cells labeled as cytomegalia. (2) Over the next several decades, the prevalence and importance of CMV as a human pathogen became more apparent. CMV causes the most common perinatal viral infection in developed countries. CMV infects nearly 1% of all newborns, ~40,000 infants per year, in the United States. Infection with CMV is the most common cause of nonhereditary sensorineural hearing loss (SNHL). (3) In addition to congenital and perinatal infection, CMV causes significant morbidity in immunocompromised patients, including chorioretinitis, pneumonia, colitis, and neuropathy. (4)

The Virus

CMV is a member of the human herpesvirus family. Its large, linear, double-stranded DNA is ~235 kb in size. The genome is divided into a unique long (U_L) region and a unique short region. The U_L region contains two genes whose protein products are important in antiviral therapies, including ganciclovir administration. The U_L54 gene product is a DNA polymerase and is the target of several antiviral agents indicated for the treatment of symptomatic congenital CMV infection. The U_L97 gene product is a phosphotransferase required for phosphorylation of ganciclovir to its active metabolite in vivo. The humoral immune response against CMV is focused on two envelope proteins: glycoprotein B and glycoprotein H. Most human

Abbreviations

CMV: cytomegalovirus
R⁻: recipient negative for CMV infection
SNHL: sensorineural hearing loss
U_L: unique long region

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8 cells are infected by CMV, including fibroblasts, epithelial cells, endothelial cells, macrophages, and myocytes. The exact incubation period is unknown, but is thought to be 1 to 2 months.

Epidemiology

CMV infection is ubiquitous in human populations worldwide. In the United States, the overall CMV seroprevalence is ~50%, leaving many women of reproductive age still at risk for primary CMV infection during pregnancy. Worldwide, CMV seroprevalence among women in the reproductive age ranges from 45% in developed countries to 100% in developing countries. With prolonged, repeated exposure to the virus through saliva or saliva-contaminated surfaces, CMV is spread easily in the child care setting. Toddlers infected postnatally with CMV shed the virus in their urine for a mean of 18 months (range 6–40 months). In contrast, healthy adults infected with CMV will shed the virus for only up to several weeks. Higher socioeconomic status is associated with lower rates of CMV prevalence.

Exposure to young children is a risk factor for infection. In women of childbearing age, infection rates for seronegative child care employees are between 10% and 20% per year. The infection rates for the general seronegative population are 2% per year. In contrast to seronegative child care workers, increased risk of infection for health care workers has not been documented.

Although prevalent, CMV infection often is asymptomatic in the immunocompetent host. Symptomatic CMV infection occurs primarily when the infection occurs congenitally, perinatally in premature infants (but not term), and in immunocompromised individuals, such as HIV-positive patients or transplant recipients receiving immunosuppressive therapy.

Transmission

Exposure to CMV can occur from almost all body fluids, including urine, saliva, tears, and genital secretions, as well as from transplanted organs. CMV can be maternally transmitted during pregnancy, perinatally, or after postnatal exposure. Primary maternal infection during pregnancy has a 40% transmission rate to the fetus. This transmission is thought to occur by the transplacental route. In the setting of maternal viremia, maternally infected leukocytes cross to the placenta. The virus can be isolated from the placenta following congenital infection; placentitis is demonstrated on placental pathologic examination.

In women who are seropositive before pregnancy, reactivation of CMV can lead to congenital infection. The transmission rate to the fetus in a preconceptionally immune mother shedding CMV virus is 1% vs 40% for primary maternal CMV infection, and sequelae in the offspring generally are less severe.

Alternatively, congenital CMV in a preconceptionally seropositive mother may result from acquisition of a new strain of CMV. In addition to in utero transmission, infection can occur during the perinatal period from exposure to genital secretions during delivery.

Shedding of CMV in toddlers in child care centers can be as high as 70%. Standard precautions with good hand hygiene are sufficient to prevent transmission and should be practiced routinely when taking care of young children. The Centers for Disease Control and Prevention Web site gives recommendations for pregnant women on how to avoid transmission of CMV (www.cdc.gov/cmv/).

Postnatal infection can occur after exposure to human milk, blood products, or transplanted organs. Human milk–associated CMV infections typically are asymptomatic in term infants because of passively acquired maternal antibodies. (5) In contrast, extremely premature infants are at higher risk for symptomatic CMV infection acquired from human milk because of their immature immune system and paucity of maternal antibodies. Postnatal CMV disease in this population can present as sepsislike illness, including respiratory symptoms (pneumonitis), hepatomegaly, thrombocytopenia, neutropenia, and lymphocytosis.

The risk of CMV transmission in premature infants can be minimized with the use of pasteurized human milk, leukoreduced blood products, and milk or blood from CMV-negative donors. (6) Transmission of CMV during solid organ transplantation typically occurs when a seronegative recipient receives an organ from a seropositive donor.

Congenital Cytomegalovirus Infection

Ninety percent of congenitally infected infants are asymptomatic at birth. The remaining 10% of infected infants can demonstrate a wide range of manifestations affecting multiple organ systems. The clinical features of congenital CMV infection are more severe following primary maternal CMV infection than from recurrent maternal infection. Common clinical features of congenital CMV infection (Table 1) include jaundice, hepatosplenomegaly, prematurity, intrauterine growth restriction, microcephaly, thrombocytopenia, and skin manifestations (Fig 1), such as petechiae and purpura. Prenatally, congenital CMV infection can be associated with oligo- or polyhydramnios, periventricular calcifications (Fig 2), and hyperechoic bowel on prenatal ultrasonography.

Table 1. Clinical Signs of Congenital CMV Infection

Central nervous system
Microcephaly
Hypotonia
Poor feeding
Ventriculomegaly
Periventricular calcifications
Seizures
Chorioretinitis
Sensorineural hearing loss
Cerebellar hypoplasia
Polymicrogyria
Periventricular pseudocysts
Developmental delay
Skin
Jaundice
Petechiae
Purpura
Gastrointestinal
Direct hyperbilirubinemia
Elevated liver enzymes
Hepatomegaly
Hematologic
Thrombocytopenia
Anemia
Splenomegaly

The possible neurologic manifestations of congenital CMV infection are numerous. Hypotonia, poor feeding, ventriculomegaly, cerebellar hypoplasia, polymicrogyria, periventricular pseudocysts, seizures, spasticity, and developmental delay can occur in infants afflicted with congenital CMV infection. Among infants with symptomatic congenital CMV infection, SNHL will affect 30% at birth. Among the 90% of asymptomatic infants at birth, 7% to 15% will develop progressive SNHL later in childhood. Ophthalmologic manifestations of congenital CMV include chorioretinitis, strabismus, microphthalmia, optic nerve atrophy, and cortical visual impairment.

Diagnosis

Congenital CMV infection can be diagnosed prenatally by detecting CMV immunoglobulin M in fetal blood or by isolating the virus from amniotic fluid. Amniocentesis is most accurate after 21 weeks, when the fetal kidney has matured enough to excrete the virus into the amniotic fluid. Postnatally, congenital CMV is confirmed by detection of the virus in urine, blood, or saliva within the first 3 weeks of life by culture or polymerase chain reaction. The virus can be detected within 24 hours by the shell-vial assay, in which CMV is identified by immunofluoresence against nucleic antigens of infected cells.

The differential diagnosis of congenital CMV infection includes other congenital infections, such as congenital toxoplasmosis. In infants with prominent skin manifestations, bacterial sepsis and erythroblastosis fetalis should be considered.

Routine CMV testing during pregnancy currently is not recommended in the United States. Although experimental treatments for newly infected pregnant women have been reported, most infections (~90%) do not result in symptomatic CMV disease. Furthermore, many cases of the most common complication of congenital CMV infection, SNHL, occur in infants born to mothers with secondary CMV.

Because treatment for CMV has high toxicity and uncertain effectiveness, therapy is recommended only in certain symptomatic cases (eg, central nervous system disease). Although routine CMV testing could facilitate earlier interventions for SNHL or earlier identification of delayed-onset hearing loss, it is unclear currently if these benefits outweigh the risks of parental anxiety, unnecessary treatments, or interventions and social stigmatization.

CMV in the Immunocompromised Host

The increased risk for CMV infection and reactivation in immunocompromised individuals is well recognized. In the pediatric population, apart from congenital transmission, CMV infection can occur following bone marrow transplantation or solid organ transplantation, or in HIV-positive patients. CMV in this setting can present as asymptomatic viremia, as CMV syndrome, or as tissue-invasive disease.

CMV syndrome is defined as CMV viremia associated with one or more clinical signs or symptoms (fever, malaise, leukopenia, thrombocytopenia, atypical lymphocytosis, or elevated liver enzymes) in the absence of another cause. Tissue-invasive disease occurs when there is tissue-specific disease (pneumonitis, colitis, hepatitis, retinitis), defined by detection of the virus from the tissue itself.

Solid organ transplant recipients who are seronegative before transplantation and receive an organ from a seropositive donor (donor-positive/recipient-negative [R^-]) are most at risk for acquiring CMV infection. The incidence of CMV disease in donor-negative/R^- transplantation is <5%; however, without prophylaxis, the incidence of CMV disease in donor-positive/R^- transplantation is estimated to be as high as 40%.

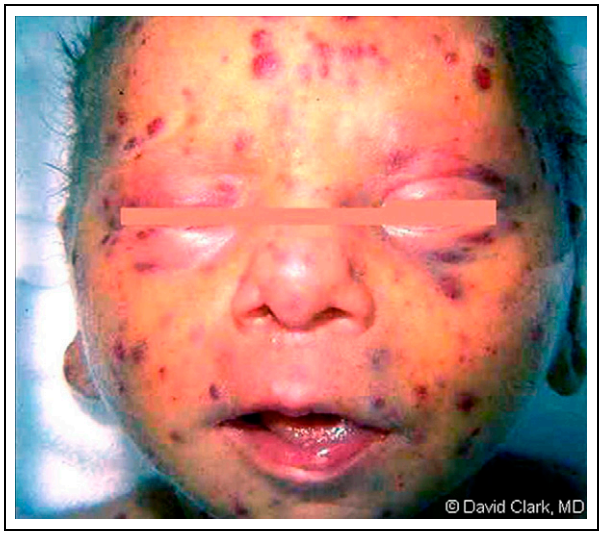

Figure 1. Blueberry muffin rash in congenital CMV infection. Reprinted with permission from the Red Book® Online Visual Library, 2009, © American Academy of Pediatrics. Image 039_11. Available at: http://aapredbook.aappublications.org/visual.

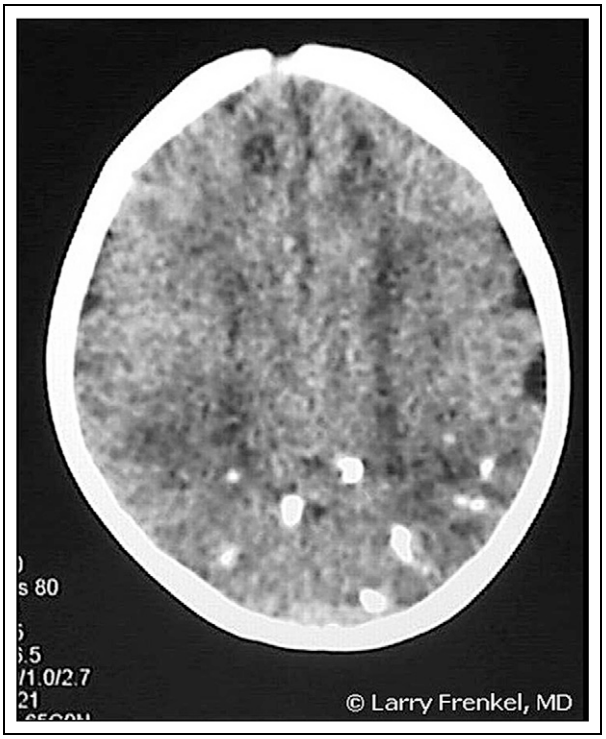

Figure 2. Periventricular calcifications in congenital CMV infection. Reprinted with permission from the Red Book® Online Visual Library, 2009, © American Academy of Pediatrics. Image 039_34. Available at: http://aapredbook.aappublications.org/visual

Because of the varied degree of immunosuppression, the rates of CMV infection vary with the organ transplanted. Lung and small bowel transplants have the highest incidence of posttransplant CMV infection. The disease burden of CMV is not limited to the infection itself. CMV disease increases the risk for bacterial, fungal, or viral superinfections. In addition, there is increased risk of posttransplantation lymphoproliferative disease, graft dysfunction, and graft failure. CMV coinfection of HIV-infected infants in the first 18 months of life can result in greater HIV-related disease progression and central nervous system disease. (7)

There is wide variation among centers regarding prophylactic versus preemptive therapy for posttransplantation CMV infection. Universal prophylaxis involves giving antiviral medications to either all patients or to a select group of at-risk patients after transplantation. This strategy decreases the risk for other viral infections but does so at the increased cost of universal prophylactic therapy, which carries the potential for increased adverse effects from antiviral medication and increased risk for late-onset CMV infection after discontinuation of the prophylactic therapy.

With preemptive therapy, patients are tested weekly for the presence of viremia. Therapy is initiated when early, asymptomatic viremia is detected. With this method, there are decreased drug costs and potentially fewer adverse effects from medications. Weekly testing can be burdensome and costly, however.

There is no strong evidence in pediatric patients to suggest one strategy over another. In fact, most centers have protocols that incorporate elements of both.

A recent study in the adult literature, the IMPACT (IMproved Protection Against CMV in Transplantation) study, reported decreased incidence of CMV infection at 1 year after transplantation, after 200 days of universal prophylactic therapy versus 100 days. (8) For pediatric patients, intravenous ganciclovir and enteral valganciclovir are the most commonly used antiviral agents for posttransplant CMV therapy.

Treatment

The first antiviral agent specifically licensed for treating CMV infection was ganciclovir. Treatment for congenital CMV with ganciclovir is associated with significant toxicity and currently is recommended only for those infants with severe symptomatic disease involving the central nervous system who are able to start treatment within the first month after birth. (9) A synthetic acyclic nucleoside analog of guanosine, ganciclovir blocks viral DNA synthesis by inhibiting CMV DNA polymerase in infected cells and

by incorporating itself into CMV DNA, causing chain termination. Ganciclovir requires in vivo phosphorylation to a triphosphate by the CMV U_L97 gene product.

Adverse effects include myelosuppression (anemia, thrombocytopenia, neutropenia), with occasional dose-limiting toxicity from neutropenia. Ganciclovir is dosed at 12 mg/kg per day intravenously for 6 weeks for severe congenital and perinatal CMV infection (Table 2). The drug is cleared renally, and adjusted dosing for patients with renal insufficiency is recommended. Resistance to ganciclovir has been reported in immunocompromised patients after prolonged treatment. New-generation DNA-sequencing methods may now detect ganciclovir-associated resistance mutations in infants and children with treatment failure against CMV.

Valganciclovir is a valine ester and prodrug of ganciclovir. This medication is available only in enteral form and is very well absorbed. The drug is indicated currently for treatment of CMV chorioretinitis in HIV-positive patients and as CMV prophylaxis in seronegative transplant recipients who have a seropositive donor. (10) Randomized clinical trial data are not yet available for the use of valganciclovir in treating congenital CMV. Similar to ganciclovir, the major adverse effect is myelosuppression.

Table 2. Current Therapies for Pediatric CMV Infection

Drug	Route of Administration	Mechanism of Action	Adverse Effects	Suggested Dosing Regimens[a]
Ganciclovir	Intravenous	Inhibits CMV DNA polymerase	Myelosuppression (particularly neutropenia)	Congenital infection: 12 mg/kg/day divided every 12 h for 6 wk[b] (7)
Valganciclovir	Enteral	Prodrug of ganciclovir; inhibits CMV DNA polymerase	Myelosuppression	Congenital infection in neonates >7 d old and infants 1–3 mo of age: 16 mg/kg/dose every 12 h[c] (8)(9)
Foscarnet	Intravenous	Inhibits CMV DNA polymerase	Nephrotoxicity[d]	HIV-infected infants and children: -disseminated disease or retinitis: Induction: 180 mg/kg/day divided every 8 h for 14–21 d, then maintenance: 90–120 mg/kg/dose once daily -central nervous system disease: 180 mg/kg/day divided every 8 h until symptoms improve followed by chronic suppression (10)
Cidofovir	Intravenous	Inhibits CMV DNA polymerase, incorporates into viral DNA	Nephrotoxicity,[e] neutropenia, and metabolic acidosis	Infection in children: Induction: 5 mg/kg/dose once weekly × 2 consecutive wk Maintenance: 3–5 mg/kg/dose once weekly every 2 wk for 2–4 doses (11)

[a] Suggested doses are based primarily on consensus because no sufficient clinical data exist to name the appropriate dose for use in infants and children. (12)
[b] Some experts use ganciclovir in immunocompromised hosts and extremely premature infants with severe CMV gastrointestinal tract disease and CMV pneumonitis (with or without CMV immune globulin). Dose adjustment or discontinuation of treatment should be considered for severe neutropenia (absolute neutrophil count < 500 cells/mm^3). (7)
[c] A randomized controlled trial comparing 6 weeks versus 6 months of treatment with valganciclovir oral solution to systematically assess the efficacy and safety outcomes associated with longer-term antiviral treatment of symptomatic congenital CMV disease is ongoing (http://clinicaltrials.gov/ct2/show/NCT00466817?term=valganciclovir&rank=7).
[d] Foscarnet sometimes is used in combination with ganciclovir (which increases the risk of adverse effects). (10)
[e] To prevent nephrotoxicity, administration of cidofovir should be given in conjunction with oral probenecid and intravenous hydration.

Foscarnet is second-line antiviral therapy for CMV infection in myelosuppressed patients or in those demonstrating viral resistance to ganciclovir. The mechanism of action is similar to ganciclovir, inhibiting CMV DNA polymerase; however, foscarnet does not require phosphorylation in vivo. Foscarnet causes less myelosuppression than other antiviral therapies for CMV, but it is nephrotoxic, and prehydration with saline is often recommended.

An additional second-line therapy for CMV chorioretinitis in HIV-positive patients is cidofovir. Cidofovir is an acyclic nucleoside phosphonate, a nucleotide analog that requires phosphorylation. Once in its active form, cidofovir is incorporated into the viral DNA and inhibits DNA synthesis. Metabolites of cidofovir are cleared by the kidney and have very long half-lives, allowing weekly dosing schedules.

The adverse effects of cidofovir are nephrotoxicity (requiring prehydration with saline), neutropenia, metabolic acidosis, and ocular hypotony. (11) It is recommended that clinicians adjust the dosage in patients with renal insufficiency and avoid use with other nephrotoxic agents. Cidofovir administration must be accompanied by oral probenecid to reduce possible nephrotoxicity. Reportedly, cidofovir is carcinogenic and teratogenic in animals.

CMV immunoglobulin G has been used as prophylaxis in seronegative solid organ transplant recipients whose donor was seropositive. CMV immunoglobulin is pooled, high-titer intravenous immunoglobulin is extracted from donors with high CMV titers. The agent is presumed to interact with the CMV viral envelope glycoproteins. CMV has also been used as adjunctive therapy in immunocompromised patients with severe systemic CMV infection. It is effective in treating CMV pneumonia in bone marrow transplant recipients. CMV immunoglobulin has been tested as a treatment for women or fetuses infected with CMV during pregnancy. Data from randomized controlled clinical trials have not yet been published, but CMV immunoglobulin is sometimes considered for treating high-risk cases of fetal injury and as a possible alternative to pregnancy termination.

Prevention of Sensorineural Hearing Loss

Over the past decade, investigations have been ongoing to determine the safety and efficacy of antiviral treatment for prevention of SNHL in patients having congenital CMV infections. In 2003, Kimberlin et al (9), for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group, published a phase III randomized controlled trial of a 6-week course of intravenous ganciclovir versus no treatment in infants who have symptomatic congenital CMV infection. Despite differential loss to follow-up rates, the data suggested that ganciclovir may prevent hearing deterioration at 6 months and may prevent hearing deterioration at ≥1 year, as measured by brainstem-evoked response.

In 2010, Amir et al published a retrospective case series of 23 infants with symptomatic congenital CMV infection with central nervous system involvement treated with 6 weeks of intravenous ganciclovir, followed by long-term oral valganciclovir to 1 year of age. (12) This most recent retrospective study suggests that a prolonged treatment course with the addition of oral valganciclovir to intravenous ganciclovir may lessen hearing impairment at 1 year of age when compared with intravenous ganciclovir alone. A phase III, randomized, placebo-controlled blinded investigation for safety and efficacy comparing a 6-week course to a 6-month course of oral valganciclovir is in progress (ClinicalTrials.gov: NCT00466817).

Vaccines

Given the ubiquitous nature of CMV and the potentially devastating neurodevelopmental consequences of congenital infection, development of a CMV vaccine is a high priority. The first human study of a CMV vaccine was completed in the 1970s using the laboratory strain AD169 to make a live, attenuated vaccine. Although study participants produced CMV-specific antibody, this CMV strain was highly weakened in its virulence (attenuated), and as a result was not sufficiently immunogenic to be an effective vaccine candidate.

The next live, attenuated strain studied was the CMV Towne strain. Efficacy studies have been completed in renal transplant candidates and healthy CMV-seronegative adult men. Similar to the AD169 vaccine, the immune response was inadequate when challenged with the naturally occurring CMV Toledo strain. This vaccine prevented infection after a low-dose Toledo strain challenge, but did not prevent infection during a high-dose challenge.

Work is ongoing on development of subunit vaccines against several viral proteins. The viral protein that has been most studied is glycoprotein gB, the gene product of the CMV U_L55 gene. This protein is the target of neutralizing antibodies occurring after natural infection. Initial safety studies in both adults and toddlers are reassuring, and a phase III efficacy study is ongoing in seronegative women of childbearing age. Other viral proteins under investigation as potential vaccine targets are pp65, pp150, pp28, pp50/52, and pp71.

Summary

- Although commonly asymptomatic, congenital CMV infection is the leading cause of nonhereditary SNHL. Other sequelae that may be evident only after the neonatal period can include chorioretinitis, neurodevelopmental delay with mental or motor impairment, and microcephaly. (13)
- Congenital CMV infection is confirmed by detection of the virus in urine, blood, or saliva within the first 3 weeks of life by culture or polymerase chain reaction. A positive test does not necessarily confirm symptomatic CMV disease or need for treatment. (13)
- Postnatal CMV infections transmitted through human milk have been reported and may be clinically relevant in extremely premature infants; however, the risk-benefit ratio of pasteurizing human milk for the prevention of postnatal CMV infection is unclear.
- Ganciclovir, valganciclovir, foscarnet, cidofovir, and CMV hyperimmune globulin are effective in treating or preventing CMV infections in the immunocompromised host, but require close monitoring for associated toxicities. Treatment for congenital CMV is associated with significant toxicity and uncertain effectiveness.
- Based on strong evidence, anticipatory guidance for congenital CMV infection should include hearing tests and neurodevelopmental assessments until school age. (3) In patients with symptomatic congenital CMV infection, lifelong ophthalmologic screening should be included. (4)
- Based primarily on consensus, owing to lack of relevant clinical studies, it is not recommended to withhold human milk produced by CMV-seropositive mothers from healthy term infants. (5)(6)
- Based on some research evidence, as well as consensus, treatment for congenital CMV is recommended only in symptomatic infants with central nervous system involvement. (9)

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PIR Quiz

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1. The mother of one of your patients has recently started work at a day care center. She is known to be CMV-seronegative and is thinking about having more children. She asks you about the likelihood of contracting CMV over the next year. Of the following, the most accurate estimate of her risk of CMV infection per year is:
   A. 2%.
   B. 10%.
   C. 35%.
   D. 50%.
   E. 75%.

2. Of the following, which is the best explanation for avoiding recommendation of routine CMV testing during pregnancy?
   A. Complications of intrauterine CMV infection are rare.
   B. Medical therapy of intrauterine CMV is highly toxic to the mother.
   C. Most intrauterine CMV infections do not result in symptomatic disease.
   D. No reliable diagnostic test for CMV in utero exists.
   E. The virus is not secreted into the amniotic fluid.

3. Of the following, which is the most common complication of congenital CMV infection?
   A. Cholestasis.
   B. Chorioretinitis.
   C. Hearing loss.
   D. Hypotonia.
   E. Thrombocytopenia.

4. A 3-year-old girl receives a cadaveric liver transplant for biliary atresia. She is placed on systemic immunosuppression with corticosteroids and tacrolimus. Of the following situations, which places her at the highest risk of CMV infection posttransplantation?
   A. The organ donor is CMV antibody–negative, the recipient is CMV antibody–negative.
   B. The organ donor is CMV antibody–negative, the recipient is CMV antibody–positive.
   C. The organ donor is CMV antibody–positive, the recipient is CMV antibody–negative.
   D. The organ donor is CMV antibody–positive, the recipient is CMV antibody–positive.
   E. The above scenarios all have a similar risk of CMV transmission.

5. Of the following therapies for CMV, which carries the lowest risk of myelosuppression?
   A. Cidofovir.
   B. Foscarnet.
   C. Gancyclovir.
   D. Immunoglobulin.
   E. Valgancyclovir.