Cytomegalovirus and Epstein-Barr Virus Infections

Swetha Pinninti, MD,* Catherine Hough-Telford, MD,† Sunil Pati, PhD,† Suresh Boppana, MD†

*Department of Pediatrics, University of Nebraska Medical Center/Children's Hospital and Medical Center, Omaha, NE.
†Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL.

Educational Gaps

1. Although most infants with symptomatic congenital cytomegalovirus (cCMV) infection are at risk of developing sensorineural hearing loss, 10% to 15% of asymptomatic infants also develop hearing loss and require audiologic screening at regular intervals in the first few years after birth.
2. Unlike with other congenital infections, CMV seropositivity is not protective for fetal transmission. An estimated 75% of infants with cCMV are born in the United States following nonprimary maternal infections.
3. Most individuals with Epstein-Barr virus-associated infectious mononucleosis recover with supportive therapy; contrary to common belief, corticosteroid use is not the mainstay of treatment because airway compromise and splenic rupture can be rare complications.

Objectives

After completing this article, the reader should be able to:

1. Recognize routes of acquisition of cytomegalovirus (CMV) in the neonatal and postneonatal periods.
2. Recognize differences in presentations of congenital CMV infection, childhood infections, and infections in the immunocompromised individual.
3. Plan the diagnostic evaluation for congenital or acquired CMV infection in immunocompetent and immunocompromised children of various ages.
4. Understand management and long-term follow-up plans for infants with congenital CMV infection.
5. Describe the management and treatment of CMV infections in the immunocompromised host.
6. Explain the epidemiology of Epstein-Barr virus (EBV) infections and identify the clinical features associated with EBV infection in immunocompetent and immunocompromised children of various ages.

AUTHOR DISCLOSURE Drs Pinninti, Hough-Telford, Pati, and Boppana have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

7. Recognize the potential complications of EBV infection in immunocompetent and immunocompromised children of various ages.
8. Plan management of children with uncomplicated infectious mononucleosis.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is the most common cause of congenital infection and the leading nongenetic cause of sensorineural hearing loss (SNHL). CMV is also a significant cause of morbidity in preterm neonates who acquire infection postnatally and in individuals with compromised immune systems.

The Virus

CMV, also known as human herpesvirus-5 (HHV-5), is a β herpesvirus, the largest known member of the Herpesviridae family. The virus has double-stranded DNA that is wrapped in a nucleoprotein core and surrounded by matrix proteins, including the pp65 antigen, which is important for diagnosis. A lipid bilayer envelope surrounds the matrix, and the inner core of the envelope contains viral glycoproteins that are important in virus attachment and entry and in generating immune responses. The genome is divided into unique long and unique short regions, flanked by repeat regions. CMV infects a broad range of cell types in humans, including epithelial cells, endothelial cells, neuronal cells, smooth muscle cells, fibroblasts, monocytes, and macrophages. During productive infection, a cascade of transcriptional events leads to the synthesis of 3 categories of viral proteins: 1) immediate-early (IE or α); 2) early (E or β); and 3) late (L or γ). The unique long region contains 2 important targets for antiviral therapy: UL54, which codes for DNA polymerase, and UL97, which codes for phosphotransferase.

Epidemiology

CMV acquisition in a population is characterized by an age-dependent increase in seroprevalence and correlates most closely with race, socioeconomic level, and residence in developing versus developed countries. CMV seroprevalence in developing countries reaches more than 90% by adolescence and exceeds 95% by early adulthood. Consequently, most infants with congenital CMV (cCMV) infection in these populations are born to women with preconceptional immunity to CMV. In contrast, the CMV seroprevalence rate among women of childbearing age in the United States is approximately 50%, but the rates differ considerably according to race and income level. Significantly higher seroprevalence has been documented in low-income groups and individuals of African American race. Unlike congenital rubella and toxoplasmosis, the prevalence of cCMV is directly proportional to seroprevalence in women of childbearing age such that increased cCMV prevalence is observed in populations with higher seroprevalence. The cCMV prevalence varies from 0.5% to 1% in the developed world, with lower maternal seroprevalence, to 1% to 5% in developing nations, with near-universal seropositive rates. In the United States, urban young African American women are at significantly higher risk of delivering infants with cCMV infection.

Transmission

CMV is shed in, and thus can be transmitted through, most body fluids, including saliva, urine, human milk, genital secretions, and blood. Pregnant women with primary CMV infection have a 30% to 40% risk of transmission to the fetus, whereas a nonprimary infection (virus reactivation or acquisition of a new viral strain) is associated with an approximately 1% transmission rate to the fetus. However, a systematic review of the data over a 10-year period showed that more than 75% of all infants with cCMV in the United States were born to mothers with nonprimary maternal infections. Perinatal transmission of CMV can occur in newborns exposed to genital secretions of seropositive mothers.

CMV acquisition in the postnatal period occurs most commonly through human milk. Transfusion of blood products from seropositive donors can lead to CMV disease, but leukoreduction or use of blood products from seronegative donors has virtually eliminated this risk. Nearly all seropositive women secrete CMV in their milk and about 50% of infants exposed to the virus through human milk acquire the virus in the postnatal period. Human milk-associated CMV infection is usually asymptomatic in term infants, but preterm or very low-birthweight (VLBW) infants are at risk for developing disease.

Infants and young children with congenital or postnatally acquired CMV infection shed large amounts of virus for prolonged periods and are important sources of CMV transmission to day care workers, caregivers of young children, and other children. Immunosuppressed patients, especially those

with AIDS or those who have received a solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT), are at increased risk for this opportunistic infection in the first 3 to 4 months after transplant.

Nosocomial transmission has not been found to be a significant cause due to good hand hygiene practices and standard precautions. Therefore, health-care workers, including nursing personnel caring for newborns and infants, are not at increased risk for acquiring CMV.

Clinical Presentation

Congenital CMV Infection. Ninety percent of infants with cCMV infections have no clinical abnormalities at birth (asymptomatic infection); approximately 10% display 1 or more clinical findings suggestive of congenital infection at birth (symptomatic infection). Results of studies of women with primary CMV infection during pregnancy suggest that infection during the first and early second trimesters is more likely to be associated with severe fetal infection than late gestational maternal infection. However, intrauterine transmission occurs more frequently with later gestational maternal infections. The clinical manifestations of symptomatic cCMV can vary widely from mild disease to multiorgan involvement. Such manifestations include generalized petechial rash, purpura, jaundice with elevated direct bilirubin, hepatosplenomegaly, thrombocytopenia, transaminitis, neurologic findings that include microcephaly and seizures, and chorioretinitis (Table 1). An elevated aspartate aminotransferase, elevated conjugated bilirubin, hemolysis, and thrombocytopenia are the most common laboratory abnormalities. Abnormal brain imaging has been reported in 50% to 70% of symptomatic infants who undergo imaging studies.

Outcomes. Although earlier investigations reported that most (~90%) infants with symptomatic infection developed sequelae, recent data that included more infants with cCMV infection identified on newborn CMV screening have indicated that approximately 50% of symptomatic infants develop long-term sequelae. The most frequent sequela is SNHL, which has been reported in approximately 50% of symptomatic infants and 10% of asymptomatic infants. Symptomatic infants are also at risk for intellectual and motor disabilities and less frequently, seizures and chorioretinitis. Microcephaly, chorioretinitis, and neurologic abnormalities at birth or early in infancy and neuroimaging abnormalities have been associated with poor neurologic outcomes.

Infants with evidence of disseminated disease are at increased risk for SNHL, although even asymptomatic infants are at risk for SNHL. Because most infants with cCMV infection are asymptomatic, most children with CMV-associated SNHL have no clinical findings at birth. The pathogenesis of CMV-associated SNHL is poorly understood, and the condition can be present at birth or manifest later during early childhood. The hearing loss can range from severe bilateral to mild unilateral. Clinicians must monitor infants with cCMV infection (whether asymptomatic or symptomatic) with audiologic testing at regular intervals during the first 4 to 6 years after birth. This highlights the need for developing strategies, including newborn CMV screening, for early identification of asymptomatic infants at risk for future hearing loss to improve speech and language function.

Generally, infants with asymptomatic cCMV have better neurologic outcomes compared to infants with symptomatic disease, but a small proportion of asymptomatic infants can develop motor deficits, microcephaly, and chorioretinitis in addition to SNHL.

Postnatal CMV Infections. Primary modes of postnatal CMV acquisition are through human milk and occasionally

TABLE 1. **Clinical Findings in Infants With Symptomatic Congenital Cytomegalovirus Infection (1)**

FINDING	%
Clinical	
• Petechiae	76
• Jaundice	67
• Hepatosplenomegaly	60
• Chorioretinitis/optic atrophy	20
• Prematurity (<38 weeks' gestational age)	34
• Purpura	13
• Neurologic findings (one or more of the following):	68
– Microcephaly	53
– Lethargy/hypotonia	27
– Poor suck	19
– Seizures	7
Laboratory	
• Elevated aspartate aminotransferase (80 U/L [1.3 μkat/L])	83
• Conjugated hyperbilirubinemia (conjugated bilirubin >4 mg/dL [68.4 μmol/L])	81
• Thrombocytopenia (<100 × $10^3/\mu$L [100 × 10^9/L])	77

via blood product transfusions. Term infants who acquire CMV postnatally do not usually manifest severe disease, most likely due to passive placental transfer of antibodies during the third trimester of pregnancy. However, infants weighing less than 1500 g and/or preterm infants (<32 weeks' gestational age) are more likely to develop symptomatic postnatal CMV infection. The condition is characterized by symptoms similar to those of cCMV infection, including petechial rash, hepatitis, thrombocytopenia, and neutropenia as well as pneumonitis and sepsislike syndrome. Studies have reported an incidence of 0.3% to 4.5% for CMV sepsislike syndrome in infants born preterm in the United States. However, in contrast to cCMV infection, postnatal CMV acquisition through human milk has not been associated with long-term sequelae. The incidence of transfusion-related CMV has declined substantially since the introduction of leukoreduction and/or transfusion of CMV-negative blood products and no longer remains a major cause of postnatal CMV infections.

Mononucleosis Syndrome. Most healthy individuals (including children) who acquire CMV are asymptomatic. However, CMV has been shown to be the most frequent cause of heterophile antibody-negative mononucleosis. Symptoms are identical to Epstein-Barr virus (EBV) mononucleosis, including fever, malaise, headache, and fatigue. Fevers can persist for longer than 14 days. CMV infrequently causes pharyngitis, lymphadenopathy, and splenomegaly. Most cases of CMV mononucleosis are associated with mildly elevated transaminases, lymphocytosis, and anemia. Severe sequelae are extremely rare but can include interstitial pneumonitis, myocarditis, pericarditis, hemolytic anemia, thrombocytopenia, splenic infarction, adrenal insufficiency, colitis, Guillain-Barré syndrome, and meningoencephalitis.

Immunocompromised Individuals. SOT and HSCT recipients, those who have human immunodeficiency virus (HIV) infection/AIDS, and individuals with impaired T-cell and/or natural killer (NK)-cell function are at a substantial risk for symptomatic CMV infection.

CMV in SOT recipients usually occurs within the first 3 to 4 months after transplantation, when levels of immunosuppression are the highest. However, CMV infection and disease can be delayed among individuals receiving CMV prophylaxis. Patients who are CMV-seronegative and receive a transplant from a seropositive donor are at the highest risk. Symptoms include fever, malaise, myalgias, arthralgias, leukopenia or pancytopenia, and laboratory evidence of hepatitis. CMV can disseminate and can cause end-organ disease, including pneumonitis, retinitis, gastrointestinal disease, and graft rejection. SOT recipients who are CMV-seronegative are at highest risk for severe CMV disease after transplantation.

HSCT recipients are at risk for acquiring CMV both during the early and late posttransplant periods and can experience symptoms similar to those seen in SOT recipients, such as fever, thrombocytopenia, hepatitis, and end-organ damage that can include interstitial pneumonitis, central nervous system (CNS) disease, retinitis, and colitis. Seropositivity in the HSCT recipient, histocompatibility of the donor and recipient, graft-versus-host disease, myeloablative conditioning treatments, and therapies that impair function of the recipient's T lymphocytes are risk factors for CMV disease in this population. Nonautologous HSCT recipients who are CMV-seropositive are at greatest risk for severe CMV disease if the donor was seronegative. CMV was the most common viral opportunistic infection in HIV/AIDS patients before the advent of highly active antiretroviral therapy (HAART). The risk is highest in those with CD4 counts less than 50/mm^3. These patients develop CMV retinitis (most common manifestation), pneumonitis, esophagitis, and/or colitis. Patients receiving HAART with HIV viral load suppression and improved CD4 counts are at much lower risk for the development of CMV disease.

Diagnosis

Serology. Serologic tests have no utility in the diagnosis of cCMV. In allograft recipients, serologic testing is useful to determine serostatus before transplantation and identify primary infections during pregnancy. Although detection of immunoglobulin (Ig)M antibodies is suggestive of acute or recent infection, IgM can persist for months after primary infection. Moreover, studies have shown wide variability in sensitivity and specificity of commercial IgM assays. Given these limitations, IgG avidity assays are being used to distinguish primary from nonprimary infections during pregnancy. These assays are based on the observation that IgG antibodies of low avidity are present during the first few months after the onset of infection and avidity increases over time, reflecting maturation of the immune response.

Congenital CMV. Viral isolation by culture from urine or saliva has long been the gold standard for identifying infants with cCMV infection. Studies investigating the role of urine polymerase chain reaction (PCR) for the diagnosis of cCMV infection report sensitivities ranging from 93% to 100%. Recent investigations have demonstrated that real-time PCR of newborn saliva and urine specimens has high sensitivity and specificity for screening and diagnosis of cCMV infection. PCR assays are less expensive than other tests, have rapid turnaround time, and do not require maintenance of tissue culture facilities. Furthermore, the DNA extraction step is not required for the real-time PCR assay of newborn saliva specimens. PCR is also unlikely to be affected by storage and

transport conditions and can be adapted for high-throughput newborn screening. However, there is an urgent need for standardization of PCR assays to reduce variability among different assays. The specimens for testing should be collected within the first 2 to 3 weeks after birth to distinguish congenital from postnatally acquired CMV infection.

Postnatal CMV. Postnatal CMV infection can be diagnosed by demonstrating virus shedding in urine or saliva. However, it is important to exclude congenital infection. Viral culture or PCR are the preferred diagnostic methods. Recently, quantitative plasma PCR assays have been used for diagnosing infants with postnatal acquisition. However, similar to PCR assays from blood for diagnosis of cCMV infection, not all infants who shed virus in their urine or saliva as a result of perinatal infection have detectable CMV DNA in their blood. Serologic assays have no role in the diagnosis of postnatal CMV infection.

Treatment.

Congenital CMV Infection. For infants with symptomatic cCMV infection, 6 months of valganciclovir therapy has been shown to be more beneficial for long-term hearing and neurodevelopmental outcomes than 6 weeks of treatment (Table 2). Because of the potential toxicities associated with antiviral therapy, treatment with oral valganciclovir should be initiated in symptomatic infants with CNS involvement (ie, the most severely affected infants) who were born at greater than 32 weeks' gestation and are younger than age 1 month. Experts disagree about whether isolated SNHL should be considered symptomatic disease, but because antiviral benefit was not demonstrated in these infants, therapy generally is not recommended for infants with isolated SNHL. Infants who undergo treatment should receive regular monitoring for myelosuppression, with frequent complete blood cell counts recommended throughout the 6-month course of therapy.

Several observational and nonrandomized studies have suggested that CMV hyperimmune globulin (HIG) at a dose of 100 IU/kg intravenously monthly until 36 weeks of gestation prevents intrauterine CMV transmission in women with primary CMV infection during pregnancy. However, data from a recent randomized trial using this dosage regimen of HIG did not show a significant reduction in fetal infection. A large multicenter randomized trial of CMV HIG is underway in the United States, and results from that trial could provide a definitive answer on the role of HIG in the prevention of cCMV infection.

Ganciclovir can be used to treat preterm or VLBW infants who develop severe postnatal CMV infections. Currently some experts recommend treatment for 2 weeks, and if benefit is shown, extend treatment for an additional 1 to 2 weeks. Close monitoring for myelosuppression is recommended.

Immunosuppressed Patients. Ganciclovir is the treatment of choice in the setting of severe disease in those who have undergone SOT and HSCT, and oral valganciclovir is used for nonlife-threatening CMV infections (Table 2). Foscarnet and cidofovir are reserved for resistant viral infections due to associated toxicities. For those who have received SOT, a reduction in immunosuppression and CMV immune globulin are additional strategies that can be employed. Ganciclovir and valganciclovir remain first-line agents for HIV/AIDS patients with invasive CMV disease; foscarnet and cidofovir are reserved for infection with resistant viral strains. Because immunosuppressed individuals are at high risk for the development of viral resistance, resistance should be suspected and tested for in patients who do not respond as expected to ganciclovir or valganciclovir. Consultation with an infectious disease specialist is recommended for an immunosuppressed patient with CMV disease.

Prevention

Vaccine development for CMV has been considered a high priority by the Institute of Medicine. However, no effective vaccine for CMV has been developed to date; several candidate vaccines are in trials. Currently, the primary risk factors for CMV acquisition are contact with young children and sexual activity. Thus, practicing standard precautions with good handwashing and limiting exposure to nasal-oral secretions of young children can be considered as precautions against acquiring this disease. Pregnant women, especially those with young children or who work in a child care setting, should take steps to minimize exposure to CMV in saliva and urine by practicing good handwashing techniques, especially after diaper changes, feedings, wiping a child's nose or mouth, and handling a child's toy, as well as avoidance of kissing a toddler on the mouth and sharing of food, drinks, or other objects that the child has put in his or her mouth (eg, pacifier, toothbrush).

Using CMV-negative or leukoreduced blood products in neonatal intensive care units has dramatically reduced the rates of postnatal CMV disease. However, transmission via human milk remains a cause of CMV-related disease in preterm and VLBW infants. Pasteurization eliminates CMV from human milk, and freezing can reduce but not eliminate the viral load in milk, but these actions do not seem to decrease the incidence of CMV-associated sepsislike syndrome. In addition, these methods may reduce the beneficial properties of human milk for preterm infants. Currently no guidelines exist for screening human milk routinely to

TABLE 2. **Antiviral Agents Used for Treatment of Cytomegalovirus Infection**

	INDICATION	PRIMARY TOXICITIES	COMMENTS
Ganciclovir (intravenously)	cCMV: CNS involvement Postnatal CMV: Severe disease in preterm, VLBW infants Treatment and prophylaxis of CMV in immunosuppressed patients (including HIV/AIDS patients, HSCT or solid organ transplant patients)	Myelosuppression(especially neutropenia) CNS adverse effects (headaches, confusion, altered mental status, convulsions, coma) Carcinogenic, teratogenic in animal studies	Postnatal CMV: Treatment should be reserved for preterm and VLBW infants with severe disease. A trial of 2 weeks and reassessment for improvement is recommended by experts. If improvement is seen, an additional 1-2 weeks of therapy should be given. Frequent monitoring for myelosuppression should be performed. Has been replaced by valganciclovir, except in preterm infants.
Valganciclovir (orally)	cCMV: CNS involvement CMV treatment and prophylaxis in immunosuppressed patients (including HIV/AIDS patients, HSCT or solid organ transplant patients)	Myelosuppression (especially neutropenia, thrombocytopenia) GI adverse effects Carcinogenic, teratogenic in animal studies	cCMV: 6 months of therapy has been shown to improve hearing outcomes and neurodevelopmental outcomes in patients with symptomatic cCMV over 6 weeks of ganciclovir (2). Patients should be monitored for myelosuppression with regular CBC count/differential count throughout 6 months of therapy.
Foscarnet (intravenously)	Treatment of ganciclovir/valganciclovir-resistant CMV infection in immunosuppressed patients	Nephrotoxicity Electrolyte abnormalities CNS adverse effects (seizures, tremors, altered sensorium) Possibly teratogenic, mutagenic	Second-line therapy due to toxicities
Cidofovir (intravenously)	Treatment of ganciclovir/valganciclovir-resistant CMV in immunosuppressed patients	Nephrotoxicity Neutropenia Teratogenic	Its use has not been studied in children. Second-line therapy due to toxicities.

CBC=complete blood cell, CMV=cytomegalovirus, cCMV=congenital cytomegalovirus, CNS=central nervous system, GI=gastrointestinal, HIV=human immunodeficiency virus, HSCT=hematopoietic stem cell transplant, VLBW=very low-birthweight.

prevent postnatal CMV disease, and this remains a topic of discussion given the numerous benefits of human milk in this population. In SOT recipients, CMV antiviral prophylaxis is used by most transplant centers for at least the first 3 to 6 months posttransplant to prevent CMV-related disease.

EPSTEIN-BARR VIRUS

EBV or HHV-4 is a ubiquitous virus with worldwide distribution. EBV is a well-established causative agent of heterophile-positive mononucleosis in children and young adults and based on seroepidemiologic data and the detection of EBV genomes, has been associated with the development of African Burkitt lymphoma, nasopharyngeal carcinoma, lymphoproliferative disease, and Hodgkin lymphoma in individuals with compromised immune systems.

The Virus

EBV is a γ-herpesvirus that belongs to the Herpesviridae family. It possesses a double-stranded DNA genome that encodes for almost 100 proteins and is encased in an icosahedral protein nucleocapsid surrounded by a lipid envelope embedded with viral glycoproteins. Primary infection results from exposure to the oral secretions of infected individuals. Initial lytic infection of tonsillar crypt epithelial cells and B lymphocytes leads to rapid viral replication and subsequent transformation or immortalization of infected B cells. Infected B lymphocytes incite an intense CD4+ and CD8+ T-cell response. The atypical lymphocytosis, a characteristic of infectious mononucleosis, is composed primarily of antigen-stimulated CD8+ cytotoxic T-cells and contributes significantly to the signs and symptoms of infectious mononucleosis. Subsequently, the infected B lymphocytes enter a

state of viral latency, where the genome circularizes in the nucleus and replicates as an episome. Even though the infection at this stage is latent, limited viral gene expression persists. Latent EBV produces few viral proteins, primarily the EBV nuclear antigens (EBNAs). Similar to other members of the Herpesviridae family, infection with EBV is characterized by lifelong latency and periodic asymptomatic reactivations. For unclear reasons, some latently infected B lymphocytes enter the viral replicative, or lytic, cycle that begins with EBV early antigen (EA) production; proceeds to viral DNA replication followed by structural glycoprotein production, including the manufacture of viral capsid antigens (VCAs); and culminates in cell death with release of mature virions that are shed through secretions and systemically infect other B lymphocytes.

Epidemiology

EBV seroconversion has been documented worldwide, with 90% to 95% seroprevalence rates in adults. In industrialized countries and higher socioeconomic groups, 50% of the population seroconverts before age 5 years, with a second peak occurring midway through the second decade of life. Seroconversion is relatively rare during infancy, most likely due to protection provided by passive transfer of maternal antibodies. Most childhood infections are asymptomatic compared to primary infections delayed beyond the first decade of life. No clear seasonal incidence or gender preference has been documented. The incidence in the United States is about 500 cases per 100,000 persons per year, with the highest incidence among individuals 15 to 24 years old.

Transmission

EBV is ubiquitous and has been isolated from oral secretions of individuals with acute infection and 10% to 20% of previously infected healthy adults. The incidence of shedding exceeds 50% in immunocompromised hosts. EBV DNA has also been isolated from lower genital tract epithelia, but whether the virus is transmitted by the sexual route remains unknown. The virus is labile and has not been isolated from environmental sources. The most likely mode of spread in children is by contact with oral secretion of individuals with salivary shedding and in young adults by transfer of saliva with kissing. EBV has also been reported to spread by blood transfusion.

Clinical Presentation

Infectious Mononucleosis. Primary EBV infections are often asymptomatic in young children, with almost 50% of symptomatic infections being heterophile antibody-negative. The incubation period of infectious mononucleosis in adolescents and adults is 30 to 50 days and may be shorter in children. Classic infectious mononucleosis is characterized clinically by a triad of pharyngitis, fever, and lymphadenopathy, with marked atypical lymphocytosis and serologic evidence of heterophile- and EBV-specific antibodies. Symptoms and signs of infection are preceded by several days of prodromal symptoms of anorexia, chills, and malaise. Fever is present in more than 90% of individuals, and tonsillar enlargement and cervical lymphadenopathy are evident in 80% to 90% of symptomatic patients. Periorbital edema, pharyngitis, and palatal petechiae are present in 33% of cases and are not diagnostic of infectious mononucleosis. Splenomegaly is variably detected on physical examination and a maculopapular or urticarial rash is present in 5% of patients. Most symptoms resolve spontaneously over a 2- to 3-week period.

Differential Diagnosis. Heterophile antibody-negative mononucleosis may be caused by other entities, most commonly CMV infection. Differentiating features include lack of pharyngitis with less intense lymphocytosis and transaminitis in CMV- compared to EBV-associated infectious mononucleosis. Other possible causes are viral hepatitis, toxoplasmosis, and acute HIV infection. Group A *Streptococcus* is the most common bacterial cause of pharyngitis. Distinguishing from other viral entities is important because antibiotic treatment for streptococcal pharyngitis reduces infectivity, alleviates symptoms, and prevents rheumatic fever and suppurative complications.

Associated Lymphoproliferative Disorders. Chronic active EBV infection (CAEBV) is a lymphoproliferative disease that is noted more frequently in Asia and South America and is associated with EBV infection of NK and T cells. It is characterized by severe illness lasting more than 6 months, elevated EBV lytic antigens and EBV DNA in the blood, and histologic evidence of organ involvement (pneumonitis, hepatitis, or lymphadenitis). The pathogenesis of this entity is not well understood and the prognosis remains poor.

EBV is the most common cause of virus-associated hemophagocytic lymphohistiocytosis (HLH), which is a nonmalignant but serious generalized histiocytic proliferation associated with marked hemophagocytosis. The HLH syndrome is characterized by excessive lymphocyte and macrophage activation and infiltration of bone marrow and reticuloendothelial organs. Children usually present with fevers, pancytopenia, coagulopathy, and transaminitis after primary EBV infection. Familial forms with autosomal recessive inheritance patterns have been described. Treatment regimens with etoposide with or without corticosteroids have been associated with reduced mortality rates.

Immunocompromised Individuals. An X-linked syndrome, unrelated to other immune deficiencies, has been

described in boys who develop severe primary EBV infections and is designated X-linked lymphoproliferative syndrome or Duncan syndrome. This disorder has been linked to mutations in the signaling lymphocyte activation molecule-associated protein gene, which mediates signal transduction in T and NK cells. Affected boys present with fulminant hepatitis and hemophagocytic syndrome (HLH). Boys who survive the primary infection frequently develop progressive agammaglobulinemia or lymphomas in the long term. The overall prognosis is poor, but early bone marrow transplantation may be beneficial.

Uncontrolled proliferation of EBV-infected B lymphocytes, which can occur in the absence of immune surveillance in individuals after transplantation or persons receiving intense immunotherapy with severe cellular immune depletion, is referred to as posttransplant lymphoproliferative disease (PTLD). The risk is much lower in HSCT recipients due to the relatively shorter duration of immunosuppression compared to SOT recipients. The risk is highest in recipients of multivisceral transplantation (33%) compared to renal, liver, or heart transplant recipients (1%-2.5%). The incidence is higher among children with lower seropositivity rates. Individuals typically present with symptoms of infectious mononucleosis or fever with infiltration of reticuloendothelial and solid organs.

The overall mortality in individuals with PTLD remains high at 50% and the treatment approach depends on the type of transplant (stem cell versus solid organ). The mainstay of treatment is reduction of immunosuppression. Surgical resection and radiotherapy are used in conjunction for localized PTLD. Cytotoxic chemotherapy is often administered after failure of initial approaches. Antiviral therapy with or without immunoglobulin has not been found to be effective because the infection is predominantly due to latent EBV infection rather than lytic virus and the drugs target DNA polymerase, which is only expressed during the lytic cycle.

Four EBV-associated entities are observed in HIV patients, but the incidence has drastically decreased since the introduction of HAART. Children with lymphocytic interstitial pneumonitis present with generalized lymphadenopathy, parotitis, and bilateral diffuse pulmonary nodules. The diagnosis is made by lung biopsy, with EBV DNA isolated from 80% of children. It is rarely observed in adults because it is a manifestation of a primary EBV infection. Acyclovir with or without corticosteroids is beneficial for treatment.

Non-Hodgkin lymphoma (NHL) is more common in immunocompromised patients and is more aggressive in the HIV population. EBV has been reported to be associated with nearly 50% of NHL lesions and 90% of CNS lymphomas in this population.

Oral hairy leukoplakia is a nonmalignant lesion that arises as a white hairy lesion on the lateral side of the tongue in individuals with severe immunosuppression or HIV. It is caused by lytic replication of EBV, and the differential diagnosis includes oral candidiasis. Lesions regress with acyclovir.

Leiomyosarcoma are malignant cancers of smooth muscle that have been reported in children with AIDS and in transplant recipients. Serology results in affected children suggest EBV reactivation. Surgery is the mainstay of therapy.

EBV-associated Malignant Tumors and Autoimmune Disorders. EBV, in conjunction with various genetic and environmental factors, has been implicated in the pathogenesis of malignancies such as Hodgkin lymphoma, nasopharyngeal carcinoma, gastric carcinoma, and Burkitt lymphoma. Moreover, a history of infectious mononucleosis has been associated with an increased risk for multiple sclerosis. Antiviral drugs have no proven efficacy in EBV-associated malignant disorders. EBV immunotherapy has been shown to have limited benefit in patients with EBV-positive Hodgkin lymphoma and nasopharyngeal carcinoma.

Congenital and Perinatal Infections. Anecdotal reports have suggested that embryopathy may occur in very rare cases of primary maternal EBV infection in early gestation. However, the exact risk of congenital infection with EBV remains unknown. Various congenital defects have been described in the few reported infants with documented congenital EBV infection or whose mothers had infectious mononucleosis during pregnancy. No specific pattern has been recognized, but abnormalities include micrognathia, congenital heart disease, cataract, microphthalmia, hip dysplasia, biliary atresia, and CNS abnormalities. Subsequently, various studies of women with infectious mononucleosis or primary asymptomatic EBV infection in early pregnancy failed to document serologic or virologic evidence of EBV infection in their offspring. The possibility of EBV acquisition by neonates during passage through the birth canal has been raised by the results of a study in which cervical shedding of EBV was demonstrated in 18% of seropositive women. However, no clear data address the incidence of perinatal transmission of EBV. The diagnosis of congenital EBV infection can be established serologically or by attempting virus identification using lymphocyte transformation assays. More recently, PCR has been used for the detection of EBV DNA in infants.

Diagnosis

Hematologic Findings. Infectious mononucleosis is characterized by significant lymphocytosis that peaks between weeks 2 and 3 of illness. Most patients have absolute and relative mononuclear lymphocytosis. Atypical lymphocytes are the hallmark of infectious mononucleosis and are largely composed of reactive CD8+ cytotoxic T lymphocytes. However, this finding is not pathognomonic of infectious mononucleosis; it is seen in other syndromes, including CMV and HIV infection, toxoplasmosis, and viral hepatitis. A self-limited mild neutropenia is noted in 60% to 90% of individuals. Mild thrombocytopenia is observed in 50% of patients. Abnormalities of liver function tests are noted in almost 90% of patients, with values in the range of 2 to 3 times the upper limit of normal. The values usually peak during the second week of illness and normalize over a 3- to 4-week period.

Serology. Laboratory diagnosis of EBV infections is based primarily on serology. The detection of heterophile antibodies in patients with infectious mononucleosis is considered diagnostic of a primary EBV infection. These antibodies, initially described as sheep erythrocyte agglutinins, are present in about 90% of cases at some point in the illness. Although a substantial proportion of young children with infectious mononucleosis are heterophile antibody-negative, by age 4 years, 80% of children with primary infection are heterophile antibody-positive. EBV-specific serology can be used in those with a negative heterophile antibody test. Antibodies against several EBV antigens are produced at different times during the course of an infection. Typically, antibodies to EBV VCA and EA appear during the acute phase of the infection while those against EBNA develop weeks to months later. Primary infections can be diagnosed by detecting IgM antibodies against VCA. If no IgM antibodies are detected, the presence of IgG antibodies to VCA and EA in the absence of antibodies against EBNA is strongly suggestive of either a primary or post-acute infection. These findings are summarized in Table 3.

Detection of EBV EBV may be cultured from oropharyngeal secretions or lymphocytes of patients with infectious mononucleosis. However, due to the ubiquity of EBV shedding in previously infected individuals, it is of little clinical utility and is not routinely offered in most diagnostic virology laboratories. EBV DNA detection from blood, plasma, peripheral mononuclear cells, or cerebrospinal fluid by real-time PCR is currently hampered by lack of standardization. Despite the lack of standard protocols, this methodology has been used in patients receiving HSCT to monitor development of PTLD, nasopharyngeal carcinomas, and CNS lymphomas in patients with HIV.

Treatment

Treatment of infectious mononucleosis is largely supportive, with 95% of affected individuals recovering uneventfully without specific therapy. Acetaminophen or nonsteroidal anti-inflammatory agents are helpful in relieving pharyngitis symptoms and fever. Most instances of splenic rupture, a dreaded complication of infectious mononucleosis, occur within the first month after infection. The exact duration to avoid contact sports to prevent this complication remains unknown. Neither physical examination nor ultrasonography is a reliable predictor to assess risk for rupture and neither is recommended in follow-up evaluations. Experts currently recommend avoiding contact sports for at least 3 to 4 weeks after the onset of infection, given the rarity of this complication beyond 3 weeks.

Despite documented *in vitro* efficacy, randomized, controlled trials of acyclovir, which targets viral DNA polymerase, have not reported efficacy in the treatment of patients with infectious mononucleosis. Likely, symptoms in infectious mononucleosis are due to the robust host immune response rather than viral replication. Individuals with primary infections shed large amounts of virus in oral secretions for 6 to 12 months following primary infection, but no special precautions are recommended because most individuals are seropositive. Antiviral therapy has been found to be effective in oral hairy leukoplakia because the

TABLE 3. **Serologic Findings in EBV Infections**

	EBV ANTIGENS		
EBV INFECTION	**VCA**	**EA**	**EBNA**
Acute	+ (IgM ± IgG)	+ (High)	Negative
Convalescent/Past	+ (IgG)	+ (Low)	+
Reactivation	+ (IgG)	+ (High)	+

EA=early antigen, EBNA=Epstein-Barr nuclear antigen, EBV=Epstein-Barr virus, Ig=immunoglobulin, VCA=viral capsid antigen.

virus is in the lytic phase of infection. In individuals with HIV, lesions regress with initiation of antiretroviral therapy.

Corticosteroids are often advocated for patients of infectious mononucleosis, but a Cochrane review of the utility of corticosteroids in infectious mononucleosis found insufficient evidence of a clinically relevant benefit to recommend their use. Use of corticosteroids has been shown to decrease the duration of fever and severity of pharyngeal symptoms without any effect on other symptoms. Despite lack of strong evidence, corticosteroids might be efficacious in individual cases of severe upper airway obstruction, autoimmune hemolytic anemia, severe thrombocytopenia, and neurologic complications.

Complications

Autoimmune hemolytic anemia (0.5%-3%) and mild thrombocytopenia (50%) are anticipated complications of EBV infection that usually resolve spontaneously. Splenic rupture, which usually occurs during the first 3 weeks of illness, is rare (<0.5%) and presents with pain in the left upper quadrant or, in very rare instances, as shock. Tonsillar swelling with progressive airway obstruction occurs in 5% of affected patients and is the most common reason for hospitalization. It is usually managed conservatively, with instances of impending obstruction treated with tonsilloadenoidectomy and systemic corticosteroids. Neurologic complications of EBV infection include encephalitis or aseptic meningitis and are seen in 1% to 5% of patients. An unusual symptom is perceptual distortions of sizes, shapes, and spatial relationships, known as the "Alice in Wonderland syndrome" or metamorphopsia. Occasionally fulminant hepatitis, renal dysfunction, pericarditis, myocarditis, and pneumonitis have been reported with EBV infections. Death is a very rare complication and is usually due to splenic rupture or severe upper airway obstruction.

Antibiotic administration, particularly ampicillin, has been associated with the development of a maculopapular pruritic rash in individuals with infectious mononucleosis. Although the incidence of a nonspecific rash without antibiotic administration in infected individuals is only 4% to 8%, the incidence rises to 90% to 100% in older children who receive ampicillin. The incidence of rash is relatively lower with amoxicillin and other β-lactam antibiotics (50%-60%). The exact pathogenesis of this rash remains unknown, but it is believed to be due to a transient rise in benzyl penicilloyl-specific antibodies due to immune dysregulation. However, the development of this rash is not predictive of development of penicillin allergy.

Chronic fatigue syndrome/myalgic encephalomyelitis consists of marked fatigue associated with subjective complaints that result in impaired daily functioning. Persistent EBV infection has been suggested as a cause of fatigue and malaise in young and middle-aged adults, which led to the use of terms such as "chronic mononucleosis" and "chronic EBV infection." Such terms should be avoided because of a lack of causal relationship with EBV based on serologic and epidemiologic observations. Recently, the Institute of Medicine convened an expert committee that recommended the name of this entity be changed to systemic exertion intolerance disease to accurately capture the central characteristics of the illness and provided new diagnostic criteria to facilitate timely diagnosis and care of affected individuals.

Summary

- On the basis of strong research evidence, congenital cytomegalovirus (cCMV) infection is a leading cause of sensorineural hearing loss (SNHL) and neurologic disabilities in children worldwide. Infants with symptomatic and asymptomatic infection are at risk of developing SNHL. Confirmation of cCMV is by isolation of the virus in saliva or urine by culture or polymerase chain reaction. (3)(4)(5)
- On the basis of strong research evidence, postnatal CMV infection acquired through consumption of human milk is clinically relevant in extremely preterm infants. However, the benefit of withholding or pasteurizing human milk to prevent postnatal CMV infection has not been determined. (6)
- On the basis of strong research evidence, antiviral treatment improves hearing outcome in children with symptomatic cCMV. (2)(7)
- On the basis of expert opinion consensus, antiviral therapy is not recommended for infants with asymptomatic cCMV.
- Epstein-Barr virus is a ubiquitous virus that causes a wide spectrum of illnesses ranging from infectious mononucleosis in young adults to lymphoproliferative disorders in the immunocompromised host and several malignancies.
- On the basis of strong research evidence, management of infectious mononucleosis predominantly involves supportive therapy, with no clear benefit demonstrated with use of corticosteroids or antiviral therapy. (8)(9)

CME quiz, References, and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/37/6/223.

PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

1. You are rounding with a group of medical students in the newborn nursery. One student notes that a mother of a term newborn has cytomegalovirus (CMV)-positive serology. She asks whether a mother who is CMV-positive should breastfeed her newborn. Which of the following is the BEST response?
    A. Human milk should be routinely screened to avoid postnatal transmission of CMV.
    B. CMV virus is not transmitted through human milk.
    C. Postnatal CMV acquisition through human milk has been shown to be associated with sensorineural hearing loss later in life.
    D. Preterm infants (<32 weeks gestational age) are less likely to develop symptomatic postnatal CMV infection than term infants if they are breastfed.
    E. Term infants who are breastfed and acquire CMV postnatally do not usually manifest severe disease.
2. In women with primary CMV infection during pregnancy, studies suggest that infection during the first and early second trimester is more likely to be associated with severe fetal infection than late gestational maternal infection, but there is more frequent transmission with later gestational infection. Of the following, the most common sequela seen in congenital CMV infection is:
    A. Chorioretinitis.
    B. Developmental delay.
    C. Meningoencephalitis.
    D. Pneumonitis.
    E. Sensorineural hearing loss.
3. A 15-year-old girl presents with fever, sore throat, and malaise for the past week. On physical examination, you note bilateral posterior cervical lymphadenopathy and an erythematous posterior pharynx with tonsillar enlargement. The complete blood cell count shows a hemoglobin of 11.5 g/dL (115 g/L) and white blood cell count of 2400/μL (2.4×10^9/L), with 70% lymphocytes, 25% neutrophils, and multiple atypical lymphocytes noted on the peripheral smear. Of the following, a true statement regarding the diagnosis of EBV infection is that:
    A. Atypical lymphocytes are the hallmark of infectious mononucleosis and if seen on a peripheral blood smear, a definitive diagnosis of infectious mononucleosis can be made without the need for serologic testing.
    B. EBV cultures from oropharyngeal secretions or lymphocytes of patients previously infected with EBV are useful in making a diagnosis.
    C. EBV-specific serology is not considered useful in those with a negative heterophile antibody test.
    D. If a patient with symptoms of fever, pharyngitis, and lymphadenopathy is treated with amoxicillin and develops a rash, a definitive diagnosis of infectious mononucleosis can be made without the need for serologic testing.
    E. The detection of heterophile antibodies in patients with infectious mononucleosis is considered diagnostic of a primary EBV infection.
4. A 6-year-old boy presents with fever, sore throat, fatigue, and general malaise for 1 week. He denies difficulty breathing or swallowing. Physical examination reveals an axillary temperature of 38.3°C (101°F), respiratory rate of 24 breaths per minute, and heart rate of 120 beats per minute. The oropharynx is diffusely erythematous. The tonsils are 3+ bilaterally with white-gray exudates. There are several posterior cervical nodes palpable that are all smaller than 1 cm and mildly tender. The spleen tip is palpable 3 cm below the left costal margin. A complete blood cell count shows a hemoglobin of 12 mg/dL (120 g/L) and a white blood cell count of 10,000/μL (10×10^9/L), with 10% neutrophils, 65% lymphocytes, and 10% atypical lymphocytes. A rapid heterophile antibody test is positive

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2016 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*^{TM}, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

and you diagnose infectious mononucleosis. His mother asks what treatments will be recommended for her son. Which of the following is the BEST answer?

A. Acetaminophen.
B. Acyclovir.
C. Amoxicillin.
D. Corticosteroids.
E. Ganciclovir.

5. A 15-year-old boy presents with 6 days of fever, sore throat, general malaise, and mild left lower quadrant pain. He denies vomiting, diarrhea, or difficulty swallowing. On physical examination, his spleen tip is palpable approximately 4 cm below the left costal margin and is mildly tender to palpation. He has tender posterior cervical lymphadenopathy. His pharynx is erythematous and there are gray-white exudates. A complete blood cell count shows a hemoglobin of 9.8 g/dL (98 g/L) and a platelet count of $70 \times 10^3/\mu L$ (70×10^9/L). You suspect infectious mononucleosis that is confirmed by a positive heterophile antibody test. He tells you that he plays football for his high school team and wants to know when he can participate again in the sport. Of the following, the best recommendation is that he may return to contact sports when:

A. Ultrasonography ensures the spleen is no longer enlarged.
B. He is no longer febrile.
C. At least 3 to 4 weeks have passed since the onset of infection.
D. His spleen tip is no longer palpable on physical examination.
E. His platelet count increases above $100 \times 10^3/\mu L$ (100×10^9/L).

Cytomegalovirus and Epstein-Barr Virus Infections

Swetha Pinninti, Catherine Hough-Telford, Sunil Pati and Suresh Boppana

Pediatrics in Review 2016;37;223
DOI: 10.1542/pir.2015-0072

Cytomegalovirus and Epstein-Barr Virus Infections

Swetha Pinninti, Catherine Hough-Telford, Sunil Pati and Suresh Boppana

Pediatrics in Review 2016;37;223
DOI: 10.1542/pir.2015-0072