

89 - 200 Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8

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TREATMENT EBV-Associated Disease Therapy for IM consists of supportive measures, with rest and analgesia. Excessive physical activity during the first month should be avoided to reduce the possibility of splenic rupture, which often necessitates splenectomy. Glucocorticoid therapy is not indicated for uncomplicated IM and in fact may predispose to bacterial superinfection. Prednisone (40–60 mg/d for 2–3 days, with subsequent tapering of the dose over 1–2 weeks) has been used for the prevention of airway obstruction in patients with severe tonsillar hypertrophy, for autoimmune hemolytic anemia, for hemophagocytic lymphohistiocytosis, and for severe thrombocytopenia. Glucocorticoids have also been administered to rare patients with severe malaise and fever and to patients with severe CNS or cardiac disease. Acyclovir has had no significant clinical impact on IM in controlled trials. In one study, the combination of acyclovir and prednisolone had no significant effect on the duration of symptoms of IM. Acyclovir, at a dosage of 400–800 mg five times daily, has been effective for the treatment of oral hairy leukoplakia (despite common relapses). Posttransplantation EBV lymphoproliferative disease (Chap. 148) generally does not respond to antiviral therapy. When possible, therapy should be directed toward reduction of immunosuppression. Antibody to CD20 (rituximab) has been effective in some cases. Infusions of donor lymphocytes are often effective for stem cell transplant recipients, although graft-versus-host disease can occur. Infusions of HLA-matched EBV-specific cytotoxic T cells have been used to prevent EBV lymphoproliferative disease in high-risk settings as well as to treat the disease. Interferon α administration, cytotoxic chemotherapy, and radiation therapy (especially for CNS lesions) also have been used. Infusion of autologous EBV-specific cytotoxic T lymphocytes has shown promise in small studies of patients with nasopharyngeal carcinoma and Hodgkin's lymphoma. Treatment of several cases of X-linked lymphoproliferative disease with antibody to CD20 resulted in a successful outcome of what otherwise would probably have been fatal acute EBV infection.

PART 5 Infectious Diseases ■ ■ PREVENTION The isolation of patients with IM is unnecessary. A vaccine directed against the major EBV glycoprotein reduced the frequency of IM but did not affect the rate of asymptomatic infection in a phase 2 trial. Additional vaccines are in clinical trials. ■ ■ **FURTHER READING** Bjornevik K et al: Longitudinal analysis reveals high

prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science* 375:296, 2022. Chan KCA et al: Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer. *N Engl J Med* 377:513, 2017. Cohen JL et al: Epstein-Barr virus NK and T cell lymphoproliferative disease: Report of a 2018 international meeting. *Leuk Lymphoma* 61:808, 2020. Dierickx D, Habermann TM: Post-transplantation lymphoproliferative disorders in adults. *N Engl J Med* 378:549, 2018. Li T et al: Anti-Epstein-Barr virus BNLF2b for mass screening for nasopharyngeal cancer. *N Engl J Med* 389:808, 2023. Mahaden JM et al: Tabelecleucel for allogeneic haematopoietic stemcell or solid organ transplant recipients with Epstein-Barr viruspositive post-transplant lymphoproliferative disease after failure of rituximab or rituximab and chemotherapy (ALLELE): A phase 3, multicentre, open-label trial. *Lancet Oncol* 25:376, 2024. Murray PG, Young LS: An etiological role for the Epstein-Barr virus in the pathogenesis of classical Hodgkin lymphoma. *Blood* 134:591, 2019. Tangye SG, Latour S: Primary immunodeficiencies reveal the molecular requirements for effective host defense against EBV infection. *Blood* 135:644, 2020.

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Cytomegalovirus and

Human Herpesvirus

Types 6, 7, and 8 CYTOMEGALOVIRUS ■ ■ **DEFINITION** Cytomegalovirus (CMV), which was initially isolated from patients with congenital cytomegalic inclusion disease, is now recognized as an important pathogen in all age groups. In addition to inducing severe birth defects, CMV causes a wide spectrum of disorders in older children and adults, ranging from an asymptomatic subclinical infection to a mononucleosis syndrome in healthy individuals to disseminated disease in immunocompromised patients. Human CMV is one of several related species-specific viruses that cause similar diseases in various animals. All are associated with the production of characteristic enlarged cells—hence the name cytomegalovirus. CMV, a β -herpesvirus, has double-stranded DNA, four species of mRNA, a protein capsid, and a lipoprotein envelope. Like other herpesviruses, CMV demonstrates icosahedral symmetry, replicates in the cell nucleus, and can cause either a lytic and productive or a latent infection. CMV can be distinguished from other herpesviruses by certain biologic properties, such as host range and type of cytopathology. Viral replication is associated with the production of large intranuclear inclusions and smaller cytoplasmic inclusions. CMV appears to replicate in a variety of cell types in vivo; in tissue culture it grows preferentially in fibroblasts. Although there is little clinical evidence that CMV is oncogenic in vivo, it does transform fibroblasts in rare instances, and genomic transforming fragments have been identified. ■

■ **EPIDEMIOLOGY** CMV has a worldwide distribution. In many low- and middle-income regions, nearly all adults are seropositive for CMV, whereas only half of adults in the United States and Canada are seropositive. Immunocompromised CMV seropositive adults are more likely to undergo reactivation disease rather than primary infection. Data generated in specific regions should be considered in the context of local seropositivity rates, when appropriate. Based on a recent systematic review, the overall prevalence of congenital CMV is estimated to be 0.67%, with a threefold higher prevalence in low- and middle-income countries (1.42%) compared with high-income countries (0.48%). Communal living and poor personal hygiene facilitate spread. Perinatal and early childhood infections are common. CMV may be present in breast milk, saliva, feces, and urine. Transmission can occur among young children in day-care centers and has been traced from

infected toddler to pregnant mother to developing fetus. When an infected child introduces CMV into a household, 50% of nonimmune family members seroconvert within 6 months. CMV is not readily spread by casual contact but rather requires repeated or prolonged intimate exposure for transmission. In late adolescence and young adulthood, CMV is often transmitted sexually, and asymptomatic carriage in semen or cervical secretions is common. Transfusion of CMV-seropositive blood products containing viable leukocytes may transmit CMV, with a frequency of 0.14–10% per unit transfused, although use of leukocyte-reduced or CMV-seronegative blood significantly decreases the risk of CMV transmission. Once infected, an individual generally carries CMV for life, similar to other herpes viruses. The infection usually remains silent. CMV reactivation syndromes develop more frequently, however, when

T lymphocyte-mediated immunity is compromised—for example, after organ transplantation, with lymphoid neoplasms and certain acquired immunodeficiencies (in particular, HIV infection; Chap. 208), or during critical illness in intensive care units. Most primary CMV

infections in organ transplant recipients (Chap. 148) result from transmission via the graft or blood products. In CMV-seropositive transplant recipients, infection results from reactivation of latent virus in the recipients or from infection by a new strain from the donor. CMV infection may be associated with diseases as diverse as coronary artery stenosis and malignant gliomas, although these associations require further validation. ■ ■PATHOGENESIS Congenital CMV infection can result from either primary or reactivation infection of the mother. However, clinical disease in the fetus or newborn is related largely to primary maternal infection (Table 200-1). The major factors determining the severity of congenital infection are unclear, although a deficient capacity to produce precipitating antibodies and to mount T cell responses to CMV is associated with relatively severe disease. Primary infection with CMV in late childhood or adulthood is often associated with a vigorous T lymphocyte response that may contribute to the development of a mononucleosis syndrome similar to that observed with Epstein-Barr virus (Chap. 199). The hallmark of such infection is the appearance of atypical lymphocytes in the peripheral blood; these cells are predominantly activated CD8⁺ T lymphocytes. Polyclonal activation of B cells by CMV contributes to the development of rheumatoid factors and other autoantibodies during mononucleosis. Once acquired, CMV persists indefinitely in host tissues. The sites of persistent infection may include multiple cell types and various organs. Transmission via blood transfusion or organ transplantation is due primarily to silent infection in these tissues. If the host's T cell responses become compromised by disease or by iatrogenic immunosuppression, latent virus can reactivate to cause a variety of syndromes. Chronic antigenic stimulation in the presence of immunosuppression (for example, after organ transplantation) appears to be an ideal setting for CMV activation and CMV disease. Certain particularly potent suppressants of T cell immunity (e.g., antithymocyte globulin, alemtuzumab) are associated with a high rate of clinical CMV syndromes. CMV may itself contribute to further T lymphocyte hyporesponsiveness, which often precedes superinfection with other opportunistic pathogens such as bacteria, molds, other viruses, and *Pneumocystis*. ■ ■PATHOLOGY Cytomegalic cells in vivo (presumed to be infected epithelial cells) are two to four times larger than surrounding cells and often contain an 8- to 10- μ m intranuclear inclusion that is eccentrically placed and is surrounded by a clear halo, producing an "owl's eye" appearance. Smaller granular cytoplasmic inclusions are demonstrated occasionally. Cytomegalic cells are found in a wide variety of organs, including the salivary gland, lung, liver, kidney, intestine, pancreas, adrenal gland, and central nervous system. The cellular inflammatory response to

infection consists of plasma cells, lymphocytes, and monocyte-macrophages. Granulomatous reactions occasionally develop, particularly in the liver. Immunopathologic reactions may contribute to CMV disease. Immune complexes

TABLE 200-1 Cytomegalovirus (CMV) Disease in the Immunocompromised Host

POPULATION RISK FACTORS PRINCIPAL SYNDROME(S) TREATMENT PREVENTION

Fetus/neonate Primary maternal infection/ early pregnancy, reactivation infection Cytomegalic inclusion disease Ganciclovir followed by valganciclovir for symptomatic neonates

Organ transplant recipient Seropositivity of donor and/or recipient; potent immunosuppressive regimen; treatment of rejection Febrile leukopenia (CMV syndrome); gastrointestinal disease; pneumonia; early infection may be asymptomatic Hematopoietic stem cell transplant recipient Graft-vs-host disease; older age of recipient; seropositive recipient; viremia Pneumonia; gastrointestinal disease

Person with HIV <50 CD4+ T cells/ μ L; CMV seropositivity Retinitis; gastrointestinal disease; neurologic disease

have been detected in infected infants, sometimes in association with CMV-related glomerulopathies. Immune-complex glomerulopathy has also been observed in some CMV-infected patients after renal transplantation.

■ ■ **CLINICAL MANIFESTATIONS** Congenital CMV Infection Fetal infections range from subclinical to severe and disseminated. CMV seroconversion rates during pregnancy range from 1% to 7%. Of infants born to mothers with primary CMV infections during pregnancy, 5–20% will develop clinical manifestations, with a mortality rate of ~5%. Petechiae, hepatosplenomegaly, and jaundice are the most common presenting features (60–80% of cases). They can have “blueberry muffin”-like hemorrhagic purpuric eruptions, which when biopsied show histopathology with dermal erythropoiesis. Infections during the first trimester are associated with up to 40–50% of infected neonates developing sensorineural complications. Microcephaly with or without cerebral calcifications, intrauterine growth retardation, and prematurity are reported in 30–50% of cases. Inguinal hernias and chorioretinitis are less common. Laboratory abnormalities include elevated alanine aminotransferase levels in serum, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and elevated protein levels in cerebrospinal fluid. The prognosis for severely infected infants is poor, and few survivors escape intellectual or hearing difficulties later in childhood. The differential diagnosis of cytomegalic inclusion disease in infants includes syphilis, toxoplasmosis, bacterial sepsis, and infection with a variety of viruses, including rubella, Zika, or herpes simplex virus. Most congenital CMV infections are clinically inapparent at birth. Of asymptotically infected infants, 7–11% develop sensorineural hearing loss over a 5-year period.

CHAPTER 200 Perinatal CMV Infection The newborn may acquire CMV at delivery by passage through an infected birth canal or by postnatal contact with infected breast milk or other maternal secretions. Of infants who are breast-fed for >1 month by seropositive mothers, 40–60% become infected. Iatrogenic transmission can result from blood transfusion; use of leukocyte-reduced or CMV-seronegative blood products for transfusion into low-birth-weight seronegative infants or seronegative pregnant women decreases risk. Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8

The great majority of infants infected at or after delivery remain asymptomatic. However, protracted interstitial pneumonitis has been associated with perinatally acquired CMV infection, particularly in premature infants, and occasionally has been accompanied by infection with Chlamydia trachomatis, Pneumocystis, or Ureaplasma urealyticum. Poor weight gain, adenopathy, rash, hepatitis, anemia, and atypical lymphocytosis may also be found, and CMV excretion often persists for months or years.

CMV Mononucleosis The most common clinical manifestation of CMV

infection in immunocompetent hosts beyond the neonatal period is a heterophile antibody-negative mononucleosis syndrome, which may develop spontaneously or follow transfusion of Avoidance of exposure; education of pregnant women about risks Ganciclovir or valganciclovir, $\pm$ CMV immunoglobulin for severe or resistant/refractory disease Prophylaxis with ganciclovir, valganciclovir, or letermovir, or preemptive therapy Maribavir, foscarnet, or cidofovir for resistant/ refractory infection Prophylaxis with letermovir, ganciclovir, or valganciclovir, or preemptive therapy Ganciclovir, valganciclovir, foscarnet, or cidofovir Highly active antiretroviral therapy; prophylaxis with valganciclovir

leukocyte-containing blood products. Although the syndrome occurs at all ages, it most often involves sexually active young adults. With incubation periods of 20–60 days, the illness generally lasts for 2–6 weeks. Prolonged high fevers, sometimes with chills, profound fatigue, and malaise, characterize this disorder. Myalgias, headache, and splenomegaly are common, but in CMV mononucleosis (as opposed to Epstein-Barr virus mononucleosis), exudative pharyngitis and cervical lymphadenopathy are rare. Occasional patients develop rubelliform rashes, often after exposure to ampicillin or certain other antibiotics. Less common are interstitial or segmental pneumonia, myocarditis, pleuritis, arthritis, splanchnic vein thrombosis, and encephalitis. In rare cases, Guillain-Barré syndrome complicates CMV mononucleosis. The characteristic laboratory abnormality of CMV mononucleosis is relative lymphocytosis in peripheral blood, with >10% atypical lymphocytes. Total leukocyte counts may be low, normal, or markedly elevated. Although significant jaundice is uncommon, serum aminotransferase and alkaline phosphatase levels are often moderately elevated. Heterophile antibodies are absent; however, transient immunologic abnormalities are common and may include the presence of cryoglobulins, rheumatoid factors, cold agglutinins, and antinuclear antibodies. Hemolytic anemia, thrombocytopenia, and granulocytopenia complicate recovery in rare instances.

Most patients recover without sequelae, although postviral asthenia may persist for months. The excretion of CMV in urine, genital secretions, and/or saliva often continues for months or years. Rarely, CMV infection is fatal in immunocompetent hosts; survivors can have recurrent episodes of fever and malaise, sometimes associated with autonomic nervous system dysfunction (e.g., attacks of sweating or flushing).

PART 5 Infectious Diseases CMV Infection in the Immunocompromised Host (Table 200-1) CMV is the most common viral pathogen complicating organ transplantation (Chap. 148). In recipients of kidney, heart, lung, liver, pancreas, and vascularized composite (hand, face, other) transplants, CMV infection may result in a variety of clinical manifestations, including fever and leukopenia, hepatitis, colitis, pneumonitis, esophagitis, gastritis, and retinitis. CMV disease is an independent risk factor for both graft loss and death. Without prophylaxis, the period of maximal risk is between 1 and 4 months after transplantation. Disease likelihood and viral replication levels generally are greater after primary infection than after reactivation. Molecular studies indicate that seropositive organ transplant recipients are susceptible to infection with donor-derived, genotypically variant CMV strains. Reactivation infection, although common, is less likely than primary infection to be clinically significant. The overall risk of clinical disease is related to various factors, such as serologic mismatch (donor seropositive, recipient seronegative), degree of immunosuppression, use of antilymphocyte antibodies, lack of anti-CMV prophylaxis, and coinfection with other pathogens. The transplanted organ is particularly vulnerable as a target for CMV infection; thus, there is a tendency for CMV hepatitis to follow liver transplantation and for CMV pneumonitis to follow lung transplantation. CMV viremia occurs in roughly one-third of

hematopoietic stem cell transplant (HSCT) recipients; the risk of severe disease may be reduced by prophylaxis or preemptive therapy with antiviral drugs. The risk is greatest in the first 100 days after transplantation, and identified risk factors include certain types of immunosuppressive therapy, an allogeneic (rather than an autologous) graft, acute graft-versus-host disease, older age, and recipient seropositivity prior to transplant. CMV is an important pathogen in persons with HIV (PWH) (Chap. 208), in whom it may cause retinitis or disseminated disease, particularly when peripheral-blood CD4⁺ T cell counts fall below 50/ μ L. In PWH and CD4⁺ T cells under 200/ μ L, high blood CMV viral loads are a predictor of severe disease and death. As treatment for underlying HIV infection has improved, the incidence of serious CMV infections (e.g., retinitis) has decreased. During the first few weeks after starting highly active antiretroviral therapy, however, acute flare-ups of CMV retinitis may occur secondary to an immune reconstitution inflammatory syndrome (IRIS).

Syndromes produced by CMV in immunocompromised hosts ("CMV syndrome") often begin with fatigue, fever, malaise, anorexia, night sweats, and arthralgias or myalgias. Liver function abnormalities, leukopenia, thrombocytopenia, and atypical lymphocytosis may be observed during these episodes. Without treatment, CMV infection may progress to more severe end-organ disease. The development of tachypnea, hypoxemia, and nonproductive cough signals respiratory involvement. Radiologic examination of the lung often shows bilateral interstitial or reticulonodular infiltrates that begin in the periphery of the lower lobes and spread centrally and superiorly; localized segmental, nodular, or alveolar patterns are less common. The differential diagnosis includes Pneumocystis infection; other viral, bacterial, or fungal infections; pulmonary hemorrhage; and injury secondary to irradiation or to treatment with cytotoxic drugs. Gastrointestinal CMV involvement may be localized or extensive and almost exclusively affects immunocompromised hosts. Colitis is the most common clinical manifestation in organ transplant recipients. Ulcers of the esophagus, stomach, small intestine, or colon may result in bleeding or perforation. Clinicians should be aware that blood tests such as CMV antigenemia and viral load testing may yield negative results in the setting of intestinal disease. CMV infection may lead to exacerbations of underlying ulcerative colitis. Hepatitis occurs frequently, particularly after liver transplantation. Acalculous cholecystitis and adrenalitis also have been described. CMV rarely causes meningoencephalitis in otherwise healthy individuals. Two forms of CMV encephalitis are seen in PWH. One resembles HIV encephalitis and often presents as progressive dementia; the other is a ventriculoencephalitis characterized by cranial-nerve deficits, nystagmus, disorientation, lethargy, and ventriculomegaly. In immunocompromised patients, CMV can also cause subacute progressive polyradiculopathy, which is often reversible if recognized and treated promptly. CMV retinitis is an important cause of blindness in immunocompromised patients, particularly patients with advanced AIDS (Chap. 208). Early lesions consist of small, opaque, white areas of granular retinal necrosis that spread in a centrifugal manner and are later accompanied by hemorrhages, vessel sheathing, and retinal edema (Fig. 200-1). CMV retinopathy must be distinguished from that due to other conditions, including toxoplasmosis, candidiasis, and herpes simplex virus infection. Fatal CMV infections are often associated with persistent viremia and the involvement of multiple organ systems. Progressive pulmonary infiltrates, pancytopenia, hyperamylasemia, and hypotension are characteristic features that are frequently found in conjunction with a terminal bacterial, fungal, or protozoan superinfection. Extensive adrenal necrosis with CMV inclusions is often documented at autopsy, as is CMV involvement of many other organs. **FIGURE 200-1** Cytomegalovirus infection in a patient with AIDS may appear as an arcuate zone of retinitis with hemorrhages and optic disk

swelling. Often CMV is confined to the retinal periphery, beyond view of the direct ophthalmoscope.

■ ■ **DIAGNOSIS** CMV infection usually cannot be diagnosed reliably on clinical grounds alone. Isolation of CMV or detection of its antigens or DNA in appropriate clinical specimens is the preferred approach. The most common method of detection is quantitative nucleic acid testing (QNAT) for CMV by polymerase chain reaction (PCR) technology, for which blood or other specimens can be used; some centers use a CMV antigenemia test, an immunofluorescence assay that detects CMV antigens (pp65) in peripheral-blood leukocytes. CMV DNA in cerebrospinal fluid is useful in the diagnosis of CMV encephalitis or polyradiculopathy. Virus excretion and/or viremia is readily detected by culture of appropriate specimens on human fibroblast monolayers. If CMV titers are high, as is common in congenital disseminated infection and in AIDS, characteristic cytopathic effects may be detected within a few days. However, in some situations (e.g., CMV mononucleosis), viral titers are low, and cytopathic effects may take several weeks to appear. Many laboratories expedite diagnosis with an overnight tissue-culture method (shell vial assay) involving centrifugation and an immunocytochemical detection technique employing monoclonal antibodies to an immediate-early CMV antigen. Isolation of CMV from urine, stool, or saliva does not, by itself, constitute proof of acute infection, since excretion from these sites may continue for months or years after illness. Detection of viremia by QNAT or antigenemia testing is a better predictor of acute infection. A variety of serologic assays detect antibody to CMV. An increased level of IgG antibody to CMV may not be detectable for up to 4 weeks after primary infection. Detection of CMV-specific IgM is sometimes useful in the diagnosis of recent or active infection; however, circulating rheumatoid factors may result in occasional false-positive IgM tests. Serology is more helpful when used to predict risk of CMV infection and disease in transplant recipients and is not recommended to diagnose acute disease in immunocompromised patients. ■ ■ **PREVENTION** Prevention of CMV infection and disease in organ transplant and HSCT recipients is usually based on one of two methods: universal prophylaxis or preemptive therapy. With universal prophylaxis, antiviral drugs are used for a defined period, often 3 or 6 months. One clinical trial demonstrated that, in CMV-seronegative kidney transplant recipients with seropositive donors, prophylaxis with valganciclovir was more effective at prevention when given for 200 days rather than 100 days. With preemptive therapy, patients are monitored weekly for CMV viremia, and antiviral treatment is initiated once viremia is detected. Because of the bone marrow-suppressive effects of universal prophylaxis with ganciclovir/valganciclovir, preemptive therapy has been more commonly employed in HSCT recipients; letermovir provides excellent prophylaxis in higher-risk patients. For PWH, CMV end-organ disease is best prevented by using antiretroviral therapy sufficient to maintain CD4⁺ T-cell counts above 100/μL; primary prophylaxis with ganciclovir or valganciclovir is not recommended. Several additional measures are useful for the prevention of CMV transmission to CMV-naïve, high-risk patients. The use of CMV-seronegative or leukocyte-depleted blood significantly decreases the rate of transfusion-associated transmission. In a placebo-controlled trial, a CMV glycoprotein B vaccine reduced infection rates among 464 CMV-seronegative women; this outcome raises the possibility that a vaccine will reduce rates of congenital infection, but further studies must validate this approach. A conditionally replication-defective CMV, termed V160, was recently shown in a phase 2 clinical trial to be well tolerated and immunogenic although three doses of vaccine did not reduce the incidence of primary CMV infection in CMV-seronegative women compared with placebo. The Triplex vaccine is in clinical trials in stem cell and liver transplant recipients; this vaccine has a recombinant viral vector with genes expressing three immunodominant proteins: UL83 (pp65), UL123 (IE1), and UL122 (IE2). An mRNA

CMV vaccine, mRNA-1647, is in clinical trials; it contains six mRNAs that encode the membrane-bound pentamer complex and the full-length membrane-bound glycoprotein B. CMV immune

globulin (intravenous immunoglobulin enriched from CMV-positive donors) has been studied in a variety of clinical situations (primary CMV infection in pregnancy, HSCT, solid organ transplantation), with conflicting results, and is used much less often in the era of multiple effective antiviral agents. A recent trial in pregnant women using CMV immunoglobulin before 24 weeks' gestation did not result in a lower incidence of congenital CMV infection or perinatal death compared with placebo.

Prophylactic acyclovir or valacyclovir at high doses may reduce rates of CMV infection and disease in renal transplant recipients; neither drug is effective in the treatment of active CMV disease. Valacyclovir may also reduce the risk of maternal-fetal CMV transmission in pregnant women with primary CMV infection. **TREATMENT Cytomegalovirus Infection** Ganciclovir is a guanosine derivative that has considerably more activity against CMV than its congener acyclovir. After intracellular conversion by a viral phosphotransferase encoded by CMV gene region UL97, ganciclovir triphosphate is a selective inhibitor of CMV DNA polymerase. Several clinical studies have indicated response rates of 70–90% among people with HIV who are given ganciclovir for the treatment of CMV retinitis or colitis. In severe infections (e.g., CMV pneumonia in HSCT recipients), ganciclovir is sometimes combined with CMV immune globulin. Prophylactic or suppressive ganciclovir may be useful in high-risk HSCT or organ transplant recipients (e.g., those who are CMV-seropositive before transplantation). In many PWH, those with persistently low CD4⁺ T cell counts, and those with CMV disease, clinical and virologic relapses occur promptly if treatment with ganciclovir is discontinued. Therefore, prolonged prevention regimens may be recommended for such patients. Resistance to ganciclovir is more common among patients exposed to antivirals for >3 months and is usually related to mutations in the CMV UL97 gene (or, less commonly, the UL54 gene, or UL56 after letermovir exposure, or UL27 after maribavir exposure). The advent of CMV genotyping for resistance mutations has made it possible to rapidly obtain information regarding optimal treatment approaches against clinically resistant CMV. **CHAPTER 200 Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8**

Valganciclovir is an orally bioavailable prodrug that is rapidly metabolized to ganciclovir in intestinal tissues and the liver. Approximately 60–70% of an oral dose of valganciclovir is absorbed. An oral valganciclovir dose of 900 mg results in ganciclovir blood levels similar to those obtained with an IV ganciclovir dose of 5 mg/kg. Valganciclovir appears to be as effective as IV ganciclovir for both CMV induction (treatment) and prevention regimens, also offering the advantage of oral dosing. Ganciclovir or valganciclovir therapy for CMV disease consists of a 14- to 21-day induction course (5 mg/kg IV twice daily for ganciclovir or 900 mg PO twice daily for valganciclovir), sometimes followed by suppressive therapy (e.g., valganciclovir, 900 mg/d). Peripheral-blood neutropenia develops in roughly one-quarter of treated patients but may be ameliorated by granulocyte colony-stimulating factor. Guidelines recommend checking weekly blood work for CMV NAT or antigenemia to ascertain virologic response. Whether to use suppressive therapy should depend on the overall level of immunocompromise and the risk of recurrent disease. Discontinuation of preventative regimens should be considered in PWH who, while receiving antiretroviral therapy, have a sustained (3- to 6-month) increase in CD4⁺ T cell counts to >100/μL. Compared with shorter (6-week) courses, prolonged (6-month) courses of valganciclovir had beneficial effects on hearing and developmental outcomes in infants with congenital CMV

infection. For treatment of CMV retinitis, some clinicians use intravitreal injections of ganciclovir or foscarnet (see below) plus oral valganciclovir or intravenous ganciclovir, although no clinical trials have compared these approaches.

Foscarnet (sodium phosphonoformate) inhibits CMV DNA polymerase. Because this agent does not require phosphorylation to be active, it is also effective against most ganciclovir-resistant isolates. Foscarnet is less well tolerated than ganciclovir and causes considerable toxicity, including renal dysfunction, hypomagnesemia, hypokalemia, hypocalcemia, genital ulcers, dysuria, nausea, and paresthesia. Moreover, foscarnet administration requires the use of an infusion pump and close clinical monitoring. With aggressive hydration and dose adjustments for renal dysfunction, the toxicity of foscarnet can be reduced. The use of foscarnet should be avoided when a saline load cannot be tolerated (e.g., in cardiac insufficiency). The approved induction regimen is 60 mg/kg every 8 h for 2 weeks, although 90 mg/kg every 12 h is equally effective and no more toxic. Maintenance infusions should deliver 90–120 mg/kg

once daily. No oral preparation is available. Foscarnet-resistant virus may emerge during extended therapy. This drug is used more frequently after HSCT than in other situations to avoid the myelo suppressive effects of ganciclovir; in general, foscarnet has been the first choice for infections with ganciclovir-resistant CMV. Maribavir is now being used for resistant/refractory CMV infections, as it was shown in a phase 3 trial to be more effective and have less toxicity compared with alternative therapies. Letermovir has efficacy for prophylaxis after HSCT and organ transplantation but induces rapid development of resistance when used during active infection; some experts recommend letermovir for prevention after treatment of resistant/refractory CMV.

Cidofovir is a nucleotide analogue with a long intracellular half-life that allows intermittent IV administration. Induction regimens of 5 mg/kg weekly for 2 weeks are followed by secondary prevention regimens of 3–5 mg/kg every 2 weeks. Cidofovir can cause severe nephrotoxicity through dose-dependent proximal tubular cell injury; however, this adverse effect can be tempered somewhat by saline hydration and probenecid. Cidofovir is used primarily for ganciclovir-resistant virus but is being replaced by maribavir; it may be useful for prevention after treatment of resistant/refractory CMV, as it could be given every 2 weeks. PART 5 Infectious Diseases HUMAN HERPESVIRUS (HHV)

TYPES 6, 7, AND 8 ■ ■ HHV-6 AND HHV-7 HHV-6 and -7 seropositivity rates are generally high throughout the world. HHV-6 was first isolated in 1986 from peripheral-blood leukocytes of six persons with various lymphoproliferative disorders. There are two genetically distinct variants (HHV-6A and HHV-6B). HHV-6 appears to be transmitted by saliva and possibly by genital secretions. HHV-6 DNA integrates into chromosomal telomeres in several cell types, including germ cells, in about 1% of people. As a result, offspring may carry a copy of the viral genome in every nucleated cell (known as inherited chromosomally integrated or iciHHV-6). The full clinical implications of iciHHV-6 remain unclear; clinicians should be aware that they will always be HHV-6 NAT positive. Pregnant women with iciHHV-6 may be at higher risk for pre-eclampsia or spontaneous abortion. Infection with HHV-6 frequently occurs during infancy as maternal antibody wanes. The peak age of acquisition is 9–21 months; by 24 months, seropositivity rates approach 80%. Older siblings appear to serve as a common source of transmission. In addition, congenital infection may occur, and ~1% of newborns are infected with HHV-6; transplacental infection with

HHV-6 accounts for about 14%, with the others related to infection from inherited chromosomally integrated HHV-6. Congenital infection is generally asymptomatic, although subtle neurologic defects have been described. Most postnatally infected children develop symptoms (fever, fussiness, and diarrhea). A minority develop exanthem subitum (roseola infantum; see Fig. A1-5), a common illness characterized by fever with subsequent rash. In addition, ~10–20% of febrile seizures without rash during infancy are caused by HHV-6. After initial infection, HHV-6 persists in peripheral-blood

mononuclear cells as well as in the central nervous system, salivary glands, and female genital tract. In older age groups, HHV-6 has been associated with mononucleosis syndromes; in immunocompromised hosts, encephalitis, pneumonitis, syncytial giant-cell hepatitis, and disseminated disease are seen. In transplant recipients, HHV-6 infection may also be associated with graft dysfunction. Acute HHV-6-associated limbic encephalitis has been reported in hematopoietic stem cell transplant recipients and is characterized by memory loss, confusion, seizures, hyponatremia, and abnormal electroencephalographic and MRI results. High plasma loads of HHV-6 DNA in HSCT recipients are associated with allelic-mismatched donors, use of glucocorticoids, delayed monocyte and platelet engraftment, development of limbic encephalitis, and increased all-cause mortality rates. Mesial temporal lobe epilepsy has been associated with HHV-6 infections, and, like many other viruses, HHV-6 (as well as EBV, another herpes virus) has been implicated in the pathogenesis of multiple sclerosis, although further study is needed to distinguish between association and etiology. HHV-7 was isolated in 1990 from T lymphocytes from the peripheral blood of a healthy 26-year-old man. The virus is frequently acquired during childhood, albeit at a later age than HHV-6. HHV-7 is commonly present in saliva, which is presumed to be the principal source of infection; breast milk and cervical secretions also may carry the virus. Viremia can be associated with either primary or reactivation infection. The most common clinical manifestations of childhood HHV-7 infections are fever and seizures. Some children present with respiratory or gastrointestinal signs and symptoms. An association has been made between HHV-7 and pityriasis rosea, but evidence is insufficient to indicate a causal relationship. Clustering of HHV-6, HHV-7, and CMV infections in transplant recipients can make it difficult to sort out the roles of the various agents in individual clinical syndromes. HHV-6 and HHV-7 appear to be susceptible to ganciclovir and foscarnet, although definitive evidence of clinical response is lacking. Use of the narrower-spectrum, CMV-specific agent letermovir for CMV prevention after HSCT was shown not to result in higher rates of HHV-6. ■ ■ HHV-8 Unique herpesvirus-like DNA sequences were reported during 1994 and 1995 in tissues derived from Kaposi's sarcoma (KS) and body cavity-based lymphoma occurring in people with HIV. The virus from which these sequences were derived is designated HHV-8 or Kaposi's sarcoma-associated herpesvirus (KSHV). HHV-8, which infects B lymphocytes, macrophages, and both endothelial and epithelial cells, appears to be causally related not only to KS and a subgroup of AIDS-related B cell body cavity-based lymphomas (primary effusion lymphomas) but also to multicentric Castleman disease, a lymphoproliferative disorder of B cells. The association of HHV-8 with several other diseases has been reported but not confirmed. HHV-8 seropositivity occurs worldwide, with areas of high endemicity influencing rates of disease. Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic areas (e.g., central and southern Africa) than in others (North America, Asia, northern Europe). Pockets of increased HHV-8 infections have been observed among men who have sex with men (MSM) with HIV in the southern United States; risk factors for dual infections with HIV and HHV-8 in this population include oral/anal or oral/penile sex and methamphetamine use. In high-prevalence areas, infection occurs in childhood, and seropositivity

is associated with families having numerous children who share eating and drinking utensils; HHV-8 may be transmitted in saliva. In low-prevalence areas, infections typically occur in adults, probably via sexual transmission. Concurrent epidemics of HIV-1 and HHV-8 infections among certain populations (e.g., MSM) in the late 1970s and early 1980s appear to have resulted in the frequent association of AIDS and KS. Transmission of HHV-8 may also be associated with organ transplantation, injection drug use, and blood transfusion; however, transmission via organ transplantation or blood transfusion in the United States appears to be quite rare.

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