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-strand 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 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 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. Of newborns in the United States, ~1% are infected with CMV; the percentage is higher in many less-developed countries. Communal living and poor personal hygiene facilitate early spread. Perinatal and early childhood infections are common. CMV may be present in breast milk, saliva, feces, and urine. Transmission has occurred 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 susceptible 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. Antibody to CMV is present at detectable levels in a high proportion of sexually active men and women, who may harbor several strains simultaneously. Transfusion of whole blood or certain blood products containing viable leukocytes may transmit CMV, with a frequency of 0.14–10% per unit transfused.

Once infected, an individual generally carries CMV for life. The infection usually remains silent. However, CMV reactivation syndromes develop frequently when T lymphocyte-mediated immunity is compromised—for example, after organ transplantation or in association with lymphoid neoplasms and certain acquired immunodeficiencies (in particular, HIV infection; Chap. 182). Most primary CMV infections in organ transplant recipients (Chap. 126) result from transmission in the graft itself. In CMV-seropositive transplant recipients, infection results from reactivation of latent virus or, less commonly, from reinfection by a new strain. CMV infection may be associated with coronary artery stenosis following heart transplantation or coronary angioplasty, but this association requires 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 almost exclusively related to primary maternal infection (Table 175-1). The factors determining the severity of congenital infection are unknown; a deficient capacity to produce precipitating antibodies and to mount T cell responses to CMV is associated with relatively severe disease.

Table 175-1 CMV Disease in the Immunocompromised Host

<table>
<thead>
<tr>
<th>Population</th>
<th>Risk Factors</th>
<th>Principal Syndromes</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus</td>
<td>Primary maternal infection/early pregnancy</td>
<td>Cytomegalic inclusion disease</td>
<td>None (?) ganciclovir</td>
<td>Avoidance of exposure or maternal treatment with CMV immunoglobulin during pregnancy</td>
</tr>
<tr>
<td>Organ transplant recipient</td>
<td>Serostatus of donor and recipient; immunosuppressive regimen; degree of rejection</td>
<td>Febrile leukopenia; pneumonia; gastrointestinal disease</td>
<td>Ganciclovir or valganciclovir</td>
<td>Donor matching; prophylaxis or preemptive therapy with ganciclovir or valganciclovir</td>
</tr>
<tr>
<td>Bone marrow transplant recipient</td>
<td>Graft-vs.-host disease; older age; seropositive recipient; viremia</td>
<td>Pneumonia; gastrointestinal disease</td>
<td>Ganciclovir plus CMV immunoglobulin</td>
<td>Donor matching; prophylaxis or preemptive therapy with ganciclovir or valganciclovir</td>
</tr>
<tr>
<td>Person with AIDS</td>
<td>&lt;100 CD4+ T cells per microliter; CMV seropositivity</td>
<td>Retinitis; gastrointestinal disease; neurologic disease</td>
<td>Ganciclovir, valganciclovir, foscarnet, or cidofovir</td>
<td>Oral valganciclovir</td>
</tr>
</tbody>
</table>

Primary infection 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 after Epstein-Barr virus (EBV) infection (Chap. 174). 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 probably include multiple cell types and various organs. Transmission via blood transfusion or organ transplantation is due to silent infections in these tissues. Autopsy studies suggest that salivary glands and bowel may be sites of latent infection.

If the host's T cell responses become compromised by disease or by iatrogenic immunosuppression, latent virus can be reactivated to cause a variety of syndromes. Chronic antigenic stimulation in the presence of immunosuppression (for example, after tissue transplantation) appears to be an ideal setting for CMV activation and CMV-induced disease. Certain particularly potent suppressants of T cell immunity (e.g., antithymocyte globulin) are associated with a high rate of clinical CMV syndromes, which may follow either primary or reactivation infection. CMV may itself contribute to further T lymphocyte hyporesponsiveness, which often precedes superinfection with other opportunistic pathogens, such as *Pneumocystis*. CMV and *Pneumocystis* are frequently found
together in immunosuppressed patients with severe interstitial pneumonia.

**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-μm 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 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 inapparent to severe and disseminated. Cytomegalic inclusion disease develops in ~5% of infected fetuses and is seen almost exclusively in infants born to mothers who develop primary infections during pregnancy. Petechiae, hepatosplenomegaly, and jaundice are the most common presenting features (60–80% of cases). 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, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and elevated cerebrospinal fluid protein levels. The prognosis for severely infected infants is poor; the mortality rate is 20–30%, and few survivors escape intellectual or hearing difficulties later in childhood. The differential diagnosis of cytomegalic inclusion disease in infants includes syphilis, rubella, toxoplasmosis, infection with herpes simplex virus or enterovirus, and bacterial sepsis.

Most congenital CMV infections are clinically inapparent at birth. Of asymptomatically infected infants, 5–25% develop significant psychomotor, hearing, ocular, or dental abnormalities over the next several years.

**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 neonatal blood transfusion; screening of blood products before transfusion into low-birth-weight seronegative infants or seronegative pregnant women decreases risk.

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 normal hosts beyond the neonatal period is a heterophile antibody–negative mononucleosis syndrome, which may develop
spontaneously or follow transfusion of 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 (as opposed to EBV) 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, and encephalitis. In rare cases, Guillain-Barré syndrome complicates CMV mononucleosis. The characteristic laboratory abnormality 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).

**CMV INFECTION IN THE IMMUNOCOMPROMISED HOST**

(Table 175-1) CMV appears to be the most common and important viral pathogen complicating organ transplantation (Chap. 126). In recipients of kidney, heart, lung, and liver transplants, CMV induces a variety of syndromes, including fever and leukopenia, hepatitis, pneumonitis, esophagitis, gastritis, colitis, and retinitis. CMV disease may be an independent risk factor for both graft loss and death. The period of maximal risk is between 1 and 4 months after transplantation, although retinitis may be a later complication. Disease likelihood and viral replication levels generally are greater after primary infection than after reactivation. In addition, molecular studies indicate that seropositive transplant recipients are susceptible to re-infection with donor-derived, genotypically variant CMV, and such infection often results in disease. Reactivation infection, although common, is less likely than primary infection to be important clinically. The risk of clinical disease is related to various factors, such as the degree of immunosuppression; the use of antibodies to T cell receptors; and co-infection 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 pneumonia occurs in 15–20% of bone marrow transplant recipients; the case-fatality rate is 84–88%, although the risk of severe disease may be reduced by prophylaxis or preemptive therapy with antiviral drugs. The risk is greatest 5–13 weeks after transplantation, and identified risk factors include certain types of immunosuppressive therapy, acute graft-versus-host disease, older age, viremia, and pretransplantation seropositivity.

CMV is an important pathogen in patients with advanced HIV infection (Chap. 182), in whom it often causes retinitis or disseminated disease, particularly when peripheral-blood CD4+ T cell counts fall below 50–100/μL. As treatment for underlying HIV infection has improved, the incidence of serious CMV infections (e.g., retinitis) has decreased. However, during the first few weeks after institution of highly active antiretroviral therapy, acute flare-ups of CMV retinitis may occur secondary to an immune reconstitution inflammatory syndrome.

Syndromes produced by CMV in immunocompromised hosts often begin with prolonged fever, malaise, anorexia, fatigue, night sweats, and arthralgias or myalgias. Liver function abnormalities,
leukopenia, thrombocytopenia, and atypical lymphocytosis may be observed during these episodes. The development of tachypnea, hypoxia, and unproductive 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 compromised hosts. Ulcers of the esophagus, stomach, small intestine, or colon may result in bleeding or perforation. CMV infection may lead to exacerbations of underlying ulcerative colitis. Hepatitis occurs frequently, particularly after liver transplantation, and acalculous cholecystitis and adrenalitis have been described.

CMV rarely causes meningoencephalitis in otherwise-healthy individuals. Two forms of CMV encephalitis are seen in patients with AIDS. One resembles HIV encephalitis and 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. 182). 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. 175-1). CMV retinopathy must be distinguished from that due to other conditions, including toxoplasmosis, candidiasis, and herpes simplex virus infection.

**Figure 175-1**

![Image of CMV retinitis](image_url)


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* 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
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.

**Diagnosis**

The diagnosis of CMV infection usually cannot be made reliably on clinical grounds alone. Isolation of CMV or detection of its antigens or DNA in appropriate clinical specimens is the preferred approach. Virus excretion 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 patients with 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 virus from urine 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 is a better predictor of acute infection.

Detection of CMV antigens (pp65) in peripheral-blood leukocytes or of CMV DNA in blood or tissues may hasten diagnosis. Such assays may yield a positive result several days earlier than culture methods. The most sensitive way to detect CMV in blood or other fluids may be by amplifying CMV DNA by polymerase chain reaction (PCR). PCR detection of CMV DNA in blood may predict the risk for disease progression, and PCR detection of CMV DNA in cerebrospinal fluid is useful in the diagnosis of CMV encephalitis or polyradiculopathy.

A variety of serologic assays detect increases in titers of antibody to CMV antigens. An increased antibody level may not be detectable for up to 4 weeks after primary infection, and titers often remain high for years after infection. For this reason, single-sample antibody determinations are of no value in assessing the acuteness of infection. Detection of CMV-specific IgM is sometimes useful in the diagnosis of recent or active infection; circulating rheumatoid factors may result in occasional false-positive IgM tests.

**Cytomegalovirus Infection: Treatment**

Several measures are useful for the prevention of CMV infection in high-risk patients. The use of blood from seronegative donors or of blood that has been frozen, thawed, and deglycerolized greatly decreases the rate of transfusion-associated transmission. Matching of organ or bone marrow transplants by CMV serology, with exclusive use of organs from seronegative donors in seronegative recipients, reduces rates of primary infection after transplantation. Both live attenuated and CMV subunit vaccines have been evaluated, but neither is close to approval for general use.

CMV immune or hyperimmune globulin has been reported (1) to reduce rates of CMV-associated syndromes and of fungal or parasitic superinfections among seronegative renal transplant recipients and (2) to prevent congenital CMV infection in infants of women with primary infection during pregnancy. Studies in bone marrow transplant recipients have produced conflicting results. Prophylactic acyclovir or valacyclovir may reduce rates of CMV infection and disease in certain seronegative renal transplant recipients, although neither drug is effective in the treatment of active CMV disease.
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 patients with AIDS who are given ganciclovir for the treatment of CMV retinitis or colitis. In bone marrow transplant recipients with CMV pneumonia, ganciclovir is less effective when given alone, but it elicits a favorable clinical response 50–70% of the time when combined with CMV immune globulin. Prophylactic or suppressive ganciclovir may be useful in high-risk bone marrow or organ transplant recipients (e.g., those who are CMV-seropositive before transplantation or who are CMV culture–positive afterward). In many patients with AIDS, persistently low CD4+ T cell counts, and CMV disease, clinical and virologic relapses occur promptly if treatment with ganciclovir is discontinued. Therefore, prolonged maintenance regimens are recommended for such patients. Resistance to ganciclovir is common among patients treated for >3 months and is usually related to mutations in the CMV UL97 gene.

Valganciclovir is an orally bioavailable prodrug that is rapidly metabolized to ganciclovir in intestinal tissues and the liver. Approximately 60% 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. Oral valganciclovir appears to be as effective as IV ganciclovir for both CMV retinitis induction and maintenance regimens. Furthermore, the adverse-event profiles and rates of resistance development for the two drugs are similar.

Ganciclovir or valganciclovir therapy for CMV retinitis consists of a 14- to 21-day induction course (5 mg/kg IV twice daily for ganciclovir or 900 mg twice daily for valganciclovir) followed by prolonged maintenance therapy. For parenteral maintenance, the ganciclovir dose is 5 mg/kg daily or 6 mg/kg 5 days per week; for oral maintenance, 900 mg of valganciclovir once daily is recommended. Peripheral-blood neutropenia develops in 16–29% of treated patients but may be ameliorated by granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor.

Discontinuation of maintenance therapy should be considered in patients with AIDS who, while receiving antiretroviral therapy, have a sustained (>6-month) increase in CD4+ T cell counts to >100–150/μL.

Ganciclovir may also be administered via a slow-release pellet sutured into the eye. Although this intraocular device provides good local protection, contralateral eye disease and disseminated disease are not affected, and early retinal detachment is possible. A combination of intraocular and systemic therapy may be better than the intraocular implant alone.

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 cardiomyopathy). 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.

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 maintenance 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.
It is not clear whether universal prophylaxis or preemptive therapy is the preferable approach in CMV-seropositive immunocompromised hosts. Both ganciclovir and valganciclovir have been used successfully for prophylaxis and preemptive therapy in transplant recipients. For patients with advanced HIV infection (CD4+ T cell counts of <50/μL), some authorities have advocated prophylaxis with oral ganciclovir or valganciclovir. However, side effects, lack of proven benefit, possible induction of viral resistance, and high cost have precluded the wide acceptance of this practice. Preemptive ganciclovir or valganciclovir therapy based on detection of CMV viremia by either antigenemia or PCR techniques is under study.

HUMAN HERPESVIRUS TYPES 6, 7, AND 8

Human herpesvirus (HHV) type 6 was first isolated in 1986 from peripheral-blood leukocytes of six persons with various lymphoproliferative disorders. The virus has a worldwide distribution, and two genetically distinct variants (HHV-6A and HHV-6B) are now recognized. HHV-6 appears to be transmitted by saliva and possibly by genital secretions.

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 source of transmission. Congenital infection may also occur. Most infected children develop symptoms (fever, fussiness, and diarrhea). A minority develop exanthem subitum (roseola infantum), a common illness characterized by fever with subsequent rash. Approximately 10–20% of febrile seizures without rash during infancy are caused by HHV-6.

In older age groups, HHV-6 has been associated with mononucleosis syndromes, focal encephalitis, and (in immunocompromised hosts) pneumonitis and disseminated disease. In transplant recipients, HHV-6 infection may be associated with similar syndromes and with graft dysfunction. High plasma loads of HHV-6 DNA in stem cell transplant recipients are associated with allelic-mismatched donors, use of steroids, delayed monocyte and platelet engraftment, development of limbic encephalitis, and increased all-cause mortality. Like many other viruses, HHV-6 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 can also 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.

HHV-6, HHV-7, and CMV infections may cluster in transplant recipients, making 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 responses is lacking.

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 patients with AIDS. The virus from which these sequences were derived is designated HHV-8 or Kaposi's sarcoma–associated herpesvirus (KSHV). HHV-8, which infects certain B lymphocytes and endothelium-derived spindle cells, appears to be causally related not only to KS but also to a subgroup of AIDS-related B cell body cavity–based lymphomas (primary effusion lymphomas) and to multicentric Castleman's disease, a lymphoproliferative disorder of B cells. Initial suggestions that HHV-8 is associated with primary pulmonary hypertension have not been confirmed by subsequent studies.

Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic