Herpesvirus Respiratory Infections in Immunocompromised Patients: Epidemiology, Management, and Outcomes

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Abstract

Among immunocompromised individuals, members of the human Herpesviridae family are frequently encountered pathogens. Cytomegalovirus, herpes simplex virus 1 and 2, varicella zoster virus, Epstein–Barr virus, and human herpesvirus-6, -7, and -8 all establish latency after infection and can reactivate during periods of immunosuppression, leading to both direct and indirect adverse effects on the host including severe organ dysfunction as well as allograft rejection and loss after transplantation. While not all herpesviruses are primary respiratory pathogens, many of their manifestations include involvement of the respiratory tract. This article discusses the individual viruses, their epidemiology, and clinical manifestations as well as recommended treatment and preventive strategies.

Keywords
► herpesviruses
► transplantation
► immunodeficiency
► viral infection

Cytomegalovirus

Epidemiology and Prevalence

Cytomegalovirus (CMV), also known as HHV-5, is a ubiquitous human DNA virus of the subfamily β-Herpesviridae. It typically infects individuals early in life, with rates of seropositivity varying from 40% in industrialized countries to 100% in some underdeveloped countries.1,2 Acute CMV infection in immunocompromised hosts such as SOT or HCT recipients and those with acquired immunodeficiency syndrome (AIDS) not only causes direct morbidity and mortality, it may have widespread indirect effects on the host.3 Despite progress in the management of CMV infection, it remains a leading complication of transplantation, and prevention and treatment of active CMV can positively impact transplant outcomes.4

Respiratory infections remain a common and serious complication of transplantation and chronic immunosuppressive therapy. Manifestations are often more severe than in immunocompetent hosts and may be atypical. Human herpesviruses (HHVs) cause a major burden of disease in patients with impaired immunity and cause a wide spectrum of disease, including pulmonary infection. In addition, Epstein–Barr virus (EBV) and HHV-8 are oncogenic viruses, and in certain settings, infection with these pathogens may evolve into malignancy that can include respiratory tract involvement. This review will focus on the epidemiology, clinical manifestations, treatment, and preventive strategies for infection by HHVs in immunocompromised persons, including hematopoietic cell transplant (HCT) and solid organ transplant (SOT) recipients.
Because of the frequency with which CMV is encountered after transplantation, its wide-ranging effects, and its impact on morbidity and mortality, it is one of the most significant infections that can occur in transplant recipients. After primary infection occurs, CMV establishes persistent latency in various cells including monocytes, dendritic cells, megakaryocytes, and progenitor myeloid cells in bone marrow, leading to the lifelong potential for reactivation. Primary infection in immunocompetent hosts typically occurs with no symptoms or a mononucleosis-type illness, but can be much more severe in immunocompromised persons.

CMV-seronegative SOT recipients may develop primary CMV infection from the donor organ, from blood transfusions or via contact with infected body fluids including saliva, semen, and breast milk. Reactivation of latent infection may also occur after transplant, as can coinfection by a donor’s CMV strain. Organ transplant recipients who are CMV-seropositive before transplantation often develop less severe manifestations of infection compared with those who develop primary infection after transplantation. CMV infection, characterized by the presence of viremia, should be viewed separately from “CMV disease”; the latter refers to CMV infection accompanied by signs and symptoms such as fever, leukopenia, or organ dysfunction.

If antiviral prophylaxis is not administered, CMV infection occurs within the first 3 months of transplant in SOT recipients who are seropositive or those who receive an organ from a seropositive donor as this is generally the period of greatest immunosuppression. Infection may be asymptomatic or associated with the disease. However, because CMV prophylaxis is commonly used after solid organ transplantation if the donor or recipient is seropositive, late-onset infection may occur after prophylaxis is discontinued, and has been identified in 17 to 37% of CMV D+/R- recipients. Late-onset infection usually occurs in the first year after transplant, but can sometimes occur much later. The late-onset disease is associated with mortality and graft loss.

**Clinical Manifestations**

CMV infection after transplant can lead to asymptomatic infection or life-threatening disease. Some patients develop what is termed “CMV syndrome,” a nonspecific presentation characterized by fever and myelosuppression in association with CMV viremia. CMV also causes tissue-invasive disease, including the most common manifestation in SOT recipients, enteritis. This is characterized by symptoms, such as abdominal pain, nausea, and diarrhea with endoscopically identified gastrointestinal (GI) lesions and identification of CMV in a GI tissue specimen. In addition, CMV pneumonitis can be a particularly severe disease with a high mortality, and it most commonly occurs in allogeneic HCT recipients and lung transplant recipients. Pancreatitis, retinitis, nephritis, hepatitis, and encephalitis are additional manifestations of CMV infection that may occur in immunocompromised hosts. The transplanted allograft may become infected, possibly due to dysregulation of the immune response in the graft and/or the fact that the graft can be a reservoir for the virus.

CMV infection has been associated with increased mortality in transplant recipients, both due to direct tissue damage as well as immunomodulatory effects. CMV interacts with the host immune system in a complex manner. It can induce inflammatory cytokines and upregulate major histocompatibility complex antigens and proinflammatory adhesion molecules, and this may enhance immunogenicity of the organ. This is a potential mechanism for the acute and chronic rejection and long-term graft dysfunction associated with CMV infection. CMV-seronegative SOT recipients may develop primary CMV infection after transplant, as can coinfection by a donor’s CMV strain. Organ transplant recipients who are CMV-seropositive before transplantation often develop less severe manifestations of infection compared with those who develop primary infection after transplantation. CMV infection, characterized by the presence of viremia, should be viewed separately from “CMV disease”; the latter refers to CMV infection accompanied by signs and symptoms such as fever, leukopenia, or organ dysfunction.

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**Diagnosis**

The most frequently used method for diagnosing CMV infection is quantitative nucleic acid testing (QNAT) via polymerase chain reaction (PCR) assays. QNAT can be used to rapidly detect infection, monitor response to antiviral therapy, assess severity of infection and the likelihood of tissue invasive disease, since higher viral loads correlate with risk of tissue-invasive disease. Due to differences in quantitative methods between laboratories, there are no established viremia thresholds above which it is agreed treatment should be initiated. However, a World Health Organization CMV international standard has been developed to calibrate assays for consistent viral load reporting. Identifying a rapidly increasing viral load is more helpful in predicting disease than any single value, and changes in viral loads of < 0.5 log_{10} copies/mL are not considered significant variations.

PCR assays for CMV viremia may be less sensitive in patients with localized tissue-invasive disease such as enteritis; in one review of studies reporting transplant recipients with GI disease due to ganciclovir-susceptible CMV, viremia was detected in only 44 to 75% of the cases. Therefore, CMV
disease cannot be excluded by negative QNAT, and endoscopy and biopsy may be required to establish the diagnosis in patients with compatible clinical syndromes. In fact, the gold standard of diagnosis of tissue-invasive CMV disease is biopsy, with the appearance of “owl’s eye” viral inclusion bodies, viral antigen staining by immunohistochemical methods and/or the detection of viral nucleic acids in specimens confirming the diagnosis. Tissue culture can be useful if positive, but is slower and less sensitive than molecular assays. Identifying CMV in BAL fluid in lung transplant recipients may be a sign of asymptomatic viral replication rather than indicative of tissue-invasive disease, but quantitative assays may be more specific for diagnosing disease.

The pp65 antigenemia test detects viral antigen in peripheral white blood cells. Higher levels of pp65 antigenemia have been correlated with disease. However, the test is labor and time intensive, does not perform well in patients with neutropenia, and is less sensitive than QNAT at lower viral load ranges. Therefore, most centers use QNAT for diagnosis of CMV infection. Testing for antibody responses to CMV is not recommended for diagnosing transplant-related CMV infection as it takes time for antibodies to develop after infection, and antibody responses may be impaired in immunocompromised individuals. Furthermore, CMV IgM assays are known to lack specificity, with frequent false-positive reactions.

Risk Factors
The most important predictor of developing CMV infection or disease in solid organ transplantation is the CMV serostatus of the donor–recipient pair; the highest risk of developing CMV disease occurs when a CMV-seronegative recipient receives an organ from a seropositive donor. CMV IgG testing is performed routinely on organ donors and recipients before transplant to stratify the risk of the recipient and inform the prophylaxis strategy. Approximately 20% of solid organ transplantation procedures performed in the United States occur in high-risk serodiscordant pairs. For HCT recipients, CMV-seropositive recipients of grafts from seronegative donors have been noted to be at higher risk from CMV disease and death compared with recipients of grafts from seropositive donors, presumably because the latter type of recipient receives CMV-specific donor CD4+ and CD8+ T cells which can help contain infection. However, the results of studies of CMV-related outcomes in CMV-mismatched donor–recipient HCT pairs are inconsistent. Other risk factors for CMV infection in HCT recipients include umbilical cord blood transplantation, receipt of T cell-depleted stem cells, graft-versus-host disease (GVHD), total body irradiation, and fludarabine-containing chemotherapy regimens. CMV-seronegative transplant recipients receiving allografts from seronegative donors are at the lowest risk for CMV disease after transplantation and they should receive leukoreduced and/or CMV-seronegative blood products.

The level of host immunosuppression is an important risk factor for CMV infection. Transplant recipients who receive antilymphocyte antibodies, such as thymoglobulin or alemtuzumab, or those receiving high-dose corticosteroids for treatment of rejection are at an increased risk of CMV infection and disease. Comorbidities can also enhance risk as can the type of organ transplanted, with lung and small intestine allograft recipients at highest risk among SOT recipients, perhaps due to the amount of lymphoid tissue in the organs and the intensity of immunosuppression.

Finally, certain host genetic factors have also been shown to confer variable risks for CMV infection. Polymorphisms in genes of the innate immune system, including those for Toll-like receptors and mannose-binding lectin have been shown to affect the risk for CMV in organ transplant recipients. Deficiencies in CMV-specific T-lymphocyte responses and hypogammaglobulinemia after transplantation have also been identified as risk factors for CMV disease.

Prognosis and Therapy
The standard of care for treatment of CMV infection and disease is intravenous (IV) ganciclovir or its oral prodrug, valganciclovir. The mechanism of action of ganciclovir and valganciclovir, like that of the other drugs approved for CMV treatment, foscarnet and cidofovir, is through inhibition of viral DNA polymerase activity. Treatment dosing for IV ganciclovir is 5 mg/kg twice daily with a duration of 2 to 4 weeks, but longer therapy may be required, depending on the decline in viremia and resolution of symptoms. Valganciclovir is dosed 900 mg orally twice daily and both ganciclovir and valganciclovir should be dose-adjusted for renal impairment. The equivalence of IV ganciclovir and oral valganciclovir for the treatment of mild-to-moderate CMV infection and disease in SOT recipients has been demonstrated in a multicenter, randomized trial comparing the two therapies in 321 SOT recipients. Valganciclovir demonstrated a rate of viral clearance at 21 days similar to that of IV ganciclovir with comparable side effects. Also, there were no differences in long-term outcomes at 1 year of follow-up. Of note, patients were excluded if they had a life-threatening CMV disease and median initial viral loads were relatively low, <20,000 copies/mL. In this study, most patients in each arm of the trial were viremic for longer than 21 days, demonstrating that treatment of CMV infection may need to be prolonged. Treatment should last at least 2 weeks and continue until viremia has resolved. Low pretreatment CMV viral loads have been correlated with more rapid disease resolution with antiviral treatment. Intravenous ganciclovir is recommended over valganciclovir for patients with impaired Gl absorption, those with questionable compliance, or those with life-threatening disease. Oral ganciclovir can prevent CMV disease, but neither it nor acyclovir is recommended for the treatment of CMV. Because of their toxicities, particularly nephrotoxicity, foscarnet and cidofovir are reserved for failure or intolerance of ganciclovir or valganciclovir. Reduction of immunosuppression should be considered in patients with moderate-to-severe CMV disease.

CMV recurs in 25 to 30% of SOT recipients after treatment, and relapse is associated with longer time to viral clearance. The best predictor of relapse of CMV is detectable
CMV viremia at the time antiviral therapy is discontinued,\textsuperscript{91} so treatment should be continued with weekly monitoring until viremia is resolved.\textsuperscript{27,80} The benefit of intravenous immune globulin (IVIG) or CMV immune globulin as adjuncts to antiviral therapy has not been established, but could be considered, particularly in cases of CMV pneumonia or other severe disease due to CMV.\textsuperscript{27,80,94} A 1 to 3 month course of secondary prophylaxis is often administered to SOT recipients after therapy is complete, but close monitoring of symptoms and viral loads is an acceptable alternative.\textsuperscript{27,80,93}

Ganciclovir-resistant CMV is uncommon, but is more likely to occur among lung transplant recipients and CMV D + /R– transplant recipients with an incidence of 5 to 10%,\textsuperscript{85–98} and in those who have received prolonged low doses of antiviral prophylaxis.\textsuperscript{96} Resistance typically occurs as a result of a mutation in the viral \textit{UL97 kinase} gene, which is required to phosphorylate ganciclovir and make it active.\textsuperscript{97} Resistance is less commonly due to mutation in the \textit{UL54 CMV DNA polymerase} gene, which incorporates ganciclovir triphosphate into the DNA resulting in termination of viral replication.\textsuperscript{27} Foscarnet remains active against UL97 mutants, and cidovirovir may also be a viable treatment option as neither requires phosphorylation by UL97 for activity.\textsuperscript{8,27,97} Certain mutations in UL97 may not result in clinical resistance to ganciclovir, and low-level ganciclovir resistance can sometimes be overcome with increased doses of ganciclovir, up to 10 mg/kg twice daily.\textsuperscript{27,80} Mutations in UL54 are less common, but typically result in cross-resistance to foscarnet, cidovirovir, and ganciclovir.\textsuperscript{8,27,97} Ganciclovir resistance should be suspected if there is not a significant decline in the level of CMV viremia after 2 weeks of appropriate treatment, particularly in patients who have received prolonged antiviral prophylaxis or treatment.\textsuperscript{27,80} Genotypic testing can confirm the presence of mutations that may confer clinical resistance.\textsuperscript{97}

Foscarnet, either alone or in combination with ganciclovir, can be effective in the treatment of ganciclovir-resistant CMV.\textsuperscript{15,99} Foscarnet is very active against CMV, but is considered a second-line agent due to its nephrotoxicity. Cidofovir is another treatment option but is also nephrotoxic. An important adjunctive maneuver in treating CMV is reducing the level of immunosuppression.\textsuperscript{27,80,100} Switching to a mammalian (or mechanistic) target of rapamycin [mTOR] inhibitor such as sirolimus (rapamycin) or everolimus may be helpful, as lower rates of CMV infection have been noted with these agents.\textsuperscript{101} CMV immunoglobulin or IVIG may also be considered as they could bolster host defenses.\textsuperscript{27,80}

Ganciclovir-resistant CMV infections have been associated with high rates of treatment toxicity, relapsed CMV infection, and mortality.\textsuperscript{98} and there is a clear need for novel, nontoxic anti-CMV agents, particularly ones with activity against resistant strains. Medications currently being investigated for treatment of CMV include maribavir, lefunomide, cyclopropavir, synguanol, letemovir (AIC246), and artesunate.\textsuperscript{8,102–108} In addition, brincidofovir is a lipid conjugate derivative prodrug of cidovirovir with broad activity against double-stranded DNA viruses, including CMV, and it has been used in small series to successfully treat refractory or resistant CMV infections.\textsuperscript{109,110} It has enhanced potency compared with cidovirovir and no nephrotoxicity or myelosuppressive effects.\textsuperscript{111} Cytotoxic T-cells active against CMV can be engineered and have been employed to help overcome CMV infection in immunocompromised hosts, although this type of therapy remains under development and is not yet widely available.\textsuperscript{112,113}

**Prevention**

If CMV prophylaxis is not administered to SOT recipients at risk, CMV infection and disease may occur within the first 3 to 4 months after transplant.\textsuperscript{114,115} Antiviral therapy to prevent CMV is therefore recommended for CMV D + /R– and CMV R+ SOT recipients.\textsuperscript{28,80} Prophylaxis can prevent CMV disease\textsuperscript{10,12,20,28,116} and in some studies, protects against rejection, graft dysfunction, and graft loss.\textsuperscript{10,36,45,117} In addition, a study of over 61,000 adult recipients of deceased donor kidney allografts demonstrated that CMV prophylaxis of D + /R– renal transplant recipients was associated with a significant decrease in cardiovascular deaths, particularly in those recipients ≥ 40 years of age.\textsuperscript{118}

The two strategies generally employed for CMV prevention are universal prophylaxis and preemptive treatment.\textsuperscript{114} The former involves administering antiviral medication to all persons at risk (e.g., CMV D + /R– and R +), whereas the latter involves CMV testing at regular intervals (e.g., weekly) and starting antiviral therapy only when CMV is detected. Universal prophylaxis has the advantage of protecting against other herpesviruses, and it has been associated with a decreased risk for opportunistic processes such as PTLD, infection by \textit{Pneumocystis jiroveci}, aspergillosis, and bacterial infections in SOT recipients.\textsuperscript{10,49,119,120} Preemptive therapy avoids the use of potentially toxic and costly medications, and may also allow exposure to CMV so that immunity develops and limits the later development of CMV disease.\textsuperscript{27,80,114}

However, preemptive therapy is logistically difficult and the monitoring expensive, and this approach may not detect CMV infection before the onset of disease, particularly in CMV D + /R– SOT recipients. Most SOT programs internationally and in the United States favor universal prophylaxis\textsuperscript{70,100} although studies vary in outcome differences between the two options. Two meta-analyses have shown reduced CMV disease and allograft rejection with both strategies,\textsuperscript{4,116} with universal prophylaxis associated with fewer opportunistic infections and lower mortality in one study\textsuperscript{4} but similar mortality in the other.\textsuperscript{116} A more recent meta-analysis of 20 studies involving 2,744 SOT recipients showed a similar risk of CMV syndrome with the two approaches, but a higher risk of late-onset CMV for prophylaxis compared with preemptive therapy and no difference in graft loss, acute rejection, other opportunistic infections, or mortality.\textsuperscript{121} The Swiss Transplant Cohort Study of over 1,200 SOT recipients demonstrated similar rates of CMV disease with prophylaxis and preemptive strategies but improved graft survival with prophylaxis.\textsuperscript{122} The available randomized trials that compare universal prophylaxis and preemptive therapy have also shown similar efficacy for CMV disease prevention,\textsuperscript{36,123–125} but improved allograft survival with universal prophylaxis in
some studies. Antiviral resistance has been encountered with each strategy. Current CMV guidelines for SOT recipients recommend universal prophylaxis for D +/- R- SOT recipients and either prophylaxis or preemptive therapy for R- recipients. CMV D -/+ R- SOT recipients do not require CMV prophylaxis. Among HCT recipients, valganciclovir was not proven superior in preventing CMV disease, other infectious complications or death when compared with preemptive therapy in a randomized, double-blind trial, and more patients receiving valganciclovir required hematopoietic growth factors.

Valganciclovir 900 mg/day, oral ganciclovir 3 g/day, or IV ganciclovir 5 mg/kg/day are recommended for CMV prophylaxis in solid organ transplantation based on randomized clinical trials. In addition, valacyclovir 8 g/day may also be used for renal transplant recipients only. Valganciclovir is most commonly used, including in liver and lung transplant recipients despite not being U.S. Food and Drug Administration-approved for prophylaxis in those populations. At some centers, IVIG is used in combination with antiviral therapy for thoracic transplant recipients, though data are sparse. Use of low-dose valganciclovir prophylaxis (450 mg daily) is not recommended as it has been associated with breakthrough CMV infection and may also be associated with ganciclovir-resistant CMV infection. CMV can occur in up to 80% of CMV-seropositive HCT recipients after allogeneic HCT but most HCT centers use preemptive therapy after HCT due to the myelosuppressive effects of ganciclovir and valganciclovir.

Newer agents have been studied for use in CMV prophylaxis. Maribavir at a dose of 100 mg orally twice daily was ineffective compared with oral ganciclovir for CMV prophylaxis in liver transplant recipients. Similarly, maribavir was no more effective than placebo in preventing CMV disease in allogeneic HCT recipients. However, letermovir, which has a novel mechanism of action against CMV, reduced the incidence of CMV infection in allogeneic HCT recipients compared with placebo and was well-tolerated. Brincidofovir, an agent with a prolonged half-life, also appears to be a promising agent for CMV prophylaxis. A randomized trial of brincidofovir versus placebo in allogeneic HCT recipients has shown efficacy of brincidofovir in preventing CMV viremia and disease when dosed only twice weekly. The results of a recently completed multicenter phase 3 trial in HCT recipients examining the efficacy of brincidofovir for CMV prevention have yet to be published.

The duration of antiviral prophylaxis for SOT recipients varies by transplant center and by organ and generally ranges from 3 to 6 months. As noted above, a concern is the development of late-onset CMV after prophylaxis is discontinued. Extended prophylaxis of 200 versus 100 days of valganciclovir in 316 CMV D +/- R- renal transplant recipients showed a significantly lower incidence of CMV disease at 12 months among those receiving 200 days of prophylaxis (16.1 vs. 36.8%, p < 0.0001) and a higher risk of opportunistic infections with 100 days of prophylaxis (27 vs. 13%, p = 0.001) and is recommended for these patients. Twelve versus 3 months of valganciclovir in lung transplant recipients significantly reduced the rate of CMV disease from 32 to 4% (p < 0.001) and CMV infection from 64 to 10% (p < 0.001) and is recommended particularly for CMV D +/- R- lung transplant recipients but may also be used in R+ lung transplant recipients. Some have suggested even longer courses of prophylaxis in CMV D +/- R- lung transplant recipients. However, the toxicities and costs of prolonged prophylaxis need to be considered. Although supportive data are limited, a hybrid approach to prophylaxis is an option, particularly for patients at high risk of late CMV disease or those on augmented immunosuppression.

This approach involves a period of prophylactic antiviral therapy followed by a period of monitoring for CMV viremia. Unfortunately, the sensitivity of monitoring for CMV infection after prophylaxis discontinuation, and its specificity in predicting disease are low. Assays to measure CMV-specific immunity are under study. The QuantiFERON-CMV assay, Cellestis, Valencia, CA) is an enzyme-linked immunosorbent assay-based measurement of interferon-gamma secretion in response to CMV peptides and is the only commercially available test for assessing CMV-specific immunity. Additional study is needed to determine its utility and the test sensitivity is low in patients with lymphopenia, but the assay has been able to predict disease and may help with stratifying patient risks for CMV and guiding prophylaxis or preemptive treatment. Finally, while none is available for clinical use, CMV vaccines are in development, with some in phase II clinical trials and an ongoing phase III DNA vaccine trial.

**Epstein–Barr Virus**

**Epidemiology and Prevalence**

EBV, also known as HHV-4, is a double-stranded DNA gamma herpesvirus that infects more than 90% of adults worldwide, usually causing asymptomatic infection in immunocompetent individuals. Primary EBV infection has been shown to occur with a bimodal distribution. The first peak is between 2 and 4 years of age with a higher incidence among children in day care settings. The second peak occurs in adolescence and may be associated with higher socioeconomic groups that may have avoided early infection. Regardless, the primary route of infection is close salivary contact, although the virus has been detected in male and female genital secretions suggesting that sexual transmission may occur. The manifestations of EBV infection in immunocompromised hosts such as SOT or HCT recipients are wide-ranging, from asymptomatic infection to infectious mononucleosis to malignancy. As discussed further below, EBV is also associated with certain malignancies occurring in immunocompetent individuals.
Given EBV’s widespread prevalence and potentially devastating consequences in immunocompromised hosts, it is an important consideration in transplant medicine. After primary infection occurs, EBV establishes lifelong latency primarily in B lymphocytes (memory B cells), and to a lesser extent in T lymphocytes, and natural killer (NK) cells. The virus is shed in the saliva, hence its spread through close oral contact. EBV may replicate in squamous epithelial cells but not in the absence of B lymphocytes. EBV also has the ability to transform B lymphocytes, and is associated with lymphomas, including Burkitt, Hodgkin, and immunoblastic lymphomas, as well as nonlymphoid malignancies including nasopharyngeal and gastric carcinomas. Among SOT and HCT recipients, PTLD is the most concerning EBV manifestation as it may lead to high-grade monoclonal lymphoma. EBV can exploit normal B lymphocyte biology through complex immunomodulatory effects of EBV proteins, leading to the malignant proliferation of cells. For example, Epstein–Barr nuclear antigen–1 protein binds to viral DNA, allowing the EBV genome to be maintained in the B cell, and additional EBV proteins can function as oncogenes, blocking differentiation and facilitating lymphocyte proliferation. The importance of viral and cellular micro-RNAs in promoting EBV onogenesis has also been recently noted. The immune response to EBV infection is mediated by NK cells and cytotoxic CD4 and CD8 T lymphocytes. With anti-T cell immunosuppression after transplant, EBV-infected B lymphocytes can proliferate with impunity. The polyclonal proliferation may transform to monoclonal proliferation that develops into a lymphoma. In SOT recipients, the source of the EBV is usually reactivation from the recipient, although PTLD that occurs early posttransplant is more likely to be of donor origin. In HCT, the source of EBV is usually from the donor. Among SOT recipients, the highest rate of PTLD is in the first year after transplant, although more recent data suggest that this rate may be decreasing and that the onset of PTLD is getting later post-SOT. Recent data among HCT recipients show a median time to development of PTLD ranging from 2 to 6 months post-HCT.

**Clinical Manifestations**

Initial infection in young children is usually asymptomatic, while acute infection in immunocompetent young adults more often presents as a mononucleosis syndrome, with fever, generalized malaise, lymphadenopathy, sore throat, myalgia, and GI symptoms. In immunocompromised individuals, EBV infection may be asymptomatic or the disease spectrum can range from a mononucleosis syndrome to lymphoid interstitial pneumonitis to PTLD. PTLD is a heterogeneous spectrum of lymphocyte proliferative disorders comprising more than 20% of malignancies after transplant. Although EBV can cause a polymorphic lymphoid hyperplasia, an aggressive monomorphic lymphoma with gene rearrangements may occur. Most PTLD lesions are of B cell origin and are EBV-positive; EBV-negative PTLD more often occurs years after transplant. While potentially any organ can be affected by PTLD, pulmonary or intrathoracic PTLD is common, particularly among lung transplant recipients who develop PTLD early after transplant.

Nonmalignant pulmonary manifestations of EBV primary infection or reactivation are uncommon, but may occur in immunocompromised patients, and asymptomatic pneumonia is seen in 5 to 10% of patients with mononucleosis. Rapidly progressive pneumonia and BOS have been described after SOT in association with EBV infection. In addition, some have reported EBV reactivation in pleural fluid and suggested a role for EBV in the development of idiopathic pleural effusions, particularly in immunosuppressed patients. An additional respiratory tract condition associated with EBV infection in SOT recipients is laryngeal smooth muscle tumors.

**Diagnosis**

In immunocompetent patients, EBV infection is typically diagnosed by detection of anti-EBV antibodies but, as with CMV diagnosis, antibody tests are unreliable for diagnosis of primary EBV infection or PTLD in immunocompromised individuals due to impairment in humoral responses to infection. However, EBV serologic testing is useful in
stratifying a transplant recipient’s risk of EBV infection and PTLD, as discussed further below. QNAT is often used to quantify EBV viral loads in the blood and assist in diagnosing EBV infection and PTLD, although the variation in QNAT assays used by different centers and lack of a universally recognized cutoff to assess the clinical significance can make test results difficult to interpret.179 EBV QNAT assays are sensitive for detecting infection, but have limited specificity in terms of predicting PTLD.187 In addition, as mentioned above, not all PTLD is EBV-related. BAL fluid with EBV detected has been reported as a more sensitive marker for identifying PTLD in pediatric lung and heart–lung transplant recipients than peripheral blood EBV PCR.188

Radiographic imaging of EBV pneumonia resembles that of other viruses on computed tomography. Findings include reticular opacities, small nodules, or consolidation of one or more lobes.181 In cases of PTLD involving the thoracic region, plain radiographs or computed tomography (CT) images typically show single or multiple lung nodules or masses, infiltrates, adenopathy, or pleural effusion (—Fig. 1).189 Positron emission tomography combined with CT may be more sensitive than CT alone in identifying PTLD.190 Excisional biopsy can provide a reliable diagnosis if imaging has indicated a suspicious lesion, particularly in the setting of sustained EBV viremia.

Risk Factors
Several factors increase the likelihood of developing PTLD or reactivation of EBV. The impaired T cell function associated with the use of antirejection medications after transplantation or with HIV infection increases risk, and the degree of immunosuppression has significant impact on the magnitude of risk.158,166,191 Other risk factors include the transplant recipient age, with children at higher risk than adults, EBV serostatus, and type of organ transplanted.158,192 The incidence of PTLD is highest in haploidentical HCT, heart–lung and multivisceral transplantation (up to 20%), followed by liver (4.5%), heart and lung (2.5%), pancreas (2%), kidney (1–1.5%), and matched HCT (0.5–1%).172 Receipt of antithymocyte globulin (ATG) and other T cell depleting therapies increase risk192,193 as well as an HLA mismatch in HCT recipients.194

Prognosis and Therapy
There are no large controlled trials to guide the management of severe EBV infections.158 For PTLD, the most dire manifestation of EBV infection posttransplant, the primary treatment is a reduction in immunosuppression, which carries the risk of graft dysfunction or loss155 and incomplete tumor response.196 Therefore, surgical resection, local radiation, and pharmacologic therapy are other modalities that may be required.158,197,198 The role of antiviral therapy is unclear as there is limited evidence supporting its use, particularly in the absence of other therapeutic maneuvers.158 Most EBV-infected cells within PTLD lesions are not undergoing lytic EBV DNA replication, the target for antiviral activity.199 When antiviral treatment is used, ganciclovir is preferred to acyclovir given the former’s superior in vitro activity against EBV.158,200,201

Among patients with CD20+ PTLD, the use of rituximab, a monoclonal antibody that targets CD20, has been shown to achieve high rates of remission and improved 3- and 5-year survival rates.202–205 Treatment is generally well-tolerated, but the addition of chemotherapy may be required to prevent relapse, depending on specific risk factors.158 Finally, adoptive transfer of EBV-specific cytotoxic T cells has been tried to both treat and prevent PTLD.206–209 The results are most promising for preemptive therapy,206 but this process is complex and few centers have the ability to perform this type of adoptive immunotherapy.

There have been several reports of regression of PTLD after changing immunosuppression to an antiproliferative agent such as sirolimus,210–213 although data are limited as to the relative benefits of reduction of immunosuppression compared with using sirolimus to exploit its potential antitumor activity.211,213 Supporting the use of sirolimus are reports of mTOR inhibitors preventing replication of EBV in cell lines via inhibition of cell cycle progression and interleukin (IL)-10 production, an important stimulator of EBV-related tumors.214

For smooth muscle tumors, surgical resection is an option if there are limited numbers of tumors. However, when there are multiple tumors, surgical resection may be insufficient. In addition, these tumors are usually refractory to chemotherapy, particularly in individuals with AIDS, and mTOR inhibitors might be useful in such cases.185

Prevention
Prophylactic use of antiviral therapy is not recommended for prevention of EBV reactivation or PTLD given the limited data supporting this practice.158,215,216 In a very small study, Höcker et al prospectively compared ganciclovir or valganciclovir prophylaxis (N = 20) to no prophylaxis (N = 8) in EBV-seronegative pediatric renal transplant recipients with EBV-seropositive donors.217 EBV primary infection occurred in 45% of antiviral recipients compared with 100% of controls (p < 0.0001). However, additional data are needed to fully assess the efficacy of this approach. IVIG, including CMV immune globulin, has also been studied as a prophylactic agent for PTLD, but the data are inconclusive for this approach as well.215,218–220

On the other hand, preemptive antiviral therapy may reduce the risk of PTLD, particularly in children.179,217,221–224 Hierro et al demonstrated that among 47 pediatric liver transplant recipients with detectable EBV DNA, an undetectable EBV viral load was achieved among almost half of patients with ganciclovir alone, largely without reduction in immunosuppression, and no new PTLD cases were seen.223 In a similar population, Venturi et al reported partial or complete response to 30 days of ganciclovir in 64% of cases with an inverse correlation between QNAT viral load and ganciclovir serum concentration.224 Among HCT recipients, rituximab has been used preemptively when high levels of EBV are detected by QNAT, and found to prevent approximately 90% of EBV-associated PTLD.209 However, there is no definitive
threshold of EBV viremia identified at which preemptive therapy is optimal. Patients at an increased risk for EBV reactivation and PTLD (e.g., seronegative SOT recipients of organs from seropositive donors and those receiving T cell depleting therapies such as ATG) should be closely monitored for clinical signs and symptoms of PTLD.158

Herpes Simplex Viruses 1 and 2

Epidemiology and Prevalence
Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are common infections worldwide. In the United States, the seroprevalences of HSV-1 and HSV-2 are 58 and 17%, respectively.225 Transmission of these viruses is by direct contact with infected skin or infected secretions. Transmission can occur during periods of subclinical viral shedding, when symptoms are absent.226

Clinical Manifestations
Among immunocompetent adults, both HSV-1 and HSV-2 cause a variety of infections that involve mucocutaneous surfaces. Syndromes overlap, but HSV-1 typically causes orolabial herpes, while HSV-2 causes anogenital disease.227 Both syndromes are characterized by painful, ulcerating vesicles of the skin and mucous membranes of the affected region. After primary infection, HSV-1 and HSV-2 establish latent infection of sensory ganglion neurons.228 Reactivation of latent virus leads to recurrent mucocutaneous disease.229,230 Severe HSV-1 or HSV-2 disease is uncommon in immunocompetent adults. However, important neurologic syndromes, including Bell palsy, meningitis, and encephalitis can occur and are associated with significant morbidity and mortality.231

Immunocompromised patients with HSV disease most commonly develop one of the mucocutaneous syndromes described above. Most infections in immunocompromised patients represent reactivation, and recurrences are often more frequent, more extensive, and of longer duration than in immunocompetent patients.232

The immunocompromised host is also at risk for both local extension of disease (e.g., HSV esophagitis) and disseminated infection. Although HSV is not considered a respiratory virus, the oropharyngeal HSV disease can extend to the lower respiratory tract, either by contiguous spread or by aspiration.233 The lower respiratory tract disease can present as tracheobronchitis or pneumonia and manifest as fever, cough, dyspnea, bronchospasm, and/or chest pain.233–235 Tracheobronchitis may be complicated by airway ulceration and hemorrhage. The most common radiographic findings reported with HSV pneumonia include bilateral symmetric ground glass attenuation, although consolidation has also been described.236 Disseminated HSV infection with involvement of noncontiguous visceral organs is associated with very high mortality, especially with HSV hepatitis.237 HSV hepatitis commonly presents with fever, transaminitis, hyperbilirubinemia, thrombocytopenia, and abdominal pain.237 HSV viremia is associated with visceral involvement and increased mortality. Among a series of intensive care unit patients, HSV viremia had a high incidence of pneumonia (38%), hepatitis (15%), and death within 20 days (27%).238

Diagnosis
Mucocutaneous HSV lesions, including esophageal or tracheobronchial ulcerations viewed endoscopically, are often diagnosed based on their characteristic appearance. Scrapings or biopsies of lesions can be tested for HSV by viral culture or direct immunofluorescence assays (DFA), though a combined approach may have the highest diagnostic yield.239 Sampling early vesicular lesions is optimal; such lesions should be unroofed and scraped for culture or DFA. PCR-based identification of viral genomic material is both more sensitive and rapid than viral culture, and can be performed on blood or cerebrospinal fluid; CSF testing for HSV DNA is the gold standard for suspected herpes encephalitis.239,240

HSV pneumonia is difficult to diagnose due to the lack of specificity of symptoms, radiological features, and detection of HSV in the airway.233 Historically, the diagnosis was often based upon autopsy findings.233 HSV can be detected in clinical respiratory specimens by viral culture or PCR-based techniques, but the isolation of HSV from BAL fluid does not necessarily indicate true disease. Asymptomatic HSV-1 viral shedding in the lower respiratory tract is relatively common, especially in critically ill and immunocompromised patients.241 It is suggested that a higher HSV viral load in BAL fluid is associated with a worse outcome and with pneumonitis,241 but a causative association has not been proven.233 Bronchoscopy does allow direct observation for signs of tracheobronchitis, but bronchoscopic examination can also be normal.233 Overall, HSV is considered to be an uncommon cause of pneumonia, even in immunocompromised patients. In one series of 63 immunocompromised patients diagnosed with pneumonia, HSV was determined to be the leading cause in 2 patients (3%).242

Prognosis and Therapy
For severe HSV infections or when absorption of oral medications may be impaired, intravenous acyclovir should be used for treatment.243,244 Oral valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, exhibit superior oral bioavailability and can be used to treat limited HSV disease with simpler dosing regimens as compared with oral acyclovir.243,245 Acyclovir resistance is uncommon, but can be encountered among immunocompromised patients, and may occur in the setting of multiple courses of acyclovir for recurrent disease.246,247 Such strains are also famciclovir/ penciclovir resistant, but can be treated with foscarnet or cidovir.243,245 Topical cidovir has been used successfully to treat acyclovir-resistant mucocutaneous HSV infection in immunocompromised persons, thus avoiding the nephrotoxicity of systemic therapy.248

Prevention
Chronic suppressive therapy should be considered in patients with a history of HSV infection, particularly if episodes are
recurrent. In addition, HSV-seropositive transplant recipients are given antiviral medication to suppress HSV around the time of transplant (typically for 1 month) even if they have not had symptomatic episodes in the past. Oral acyclovir or valacyclovir can be used, but most SOT recipients are administered valganciclovir for prophylaxis against CMV, and since this drug is also active against HSV, additional suppressive therapy directed at HSV is unnecessary. Immunosuppressed HSV-seronegative persons should be made aware of the risks of acquiring HSV infection and should avoid contact with persons who have active HSV lesions, although, as noted above, infection can also be acquired from asymptomatic persons. Daily antiviral therapy taken by an HSV-infected person is effective at preventing transmission to uninfected partners and is an option for serodiscordant couples.

### Varicella-Zoster Virus

Varicella-zoster virus (VZV) is one of the most common opportunistic infections among hematopoietic stem cell transplant (HSCT) and SOT recipients. Primary varicella infection causes chickenpox, a febrile illness accompanied by a diffuse cutaneous vesicular exanthem. The course is usually self-limited, but immunocompromised hosts can rarely develop severe pneumonia, encephalitis, or visceral disease. Following resolution of the initial infection, VZV establishes latency within sensory ganglia. Reactivation of latent VZV may occur in individuals with impaired immunity and gives rise to stereotypical dermatomal vesicular skin lesions, termed herpes zoster (HZ) or “shingles.” Widespread cutaneous dissemination and visceral involvement can also occur in immunocompromised patients, but respiratory involvement is uncommon.

### Epidemiology and Prevalence

Primary VZV infection in adults is unusual as more than 90% of adults in the United States are seropositive. HZ occurs in more than 1 million patients annually and the lifetime attack rate is 10 to 30%. The incidence of HZ increases with age, rising to 10 cases per 1,000 patient-years by age 75. Patients with impaired cell-mediated immunity are at particularly high risk of HZ. The incidence of HZ (per 1,000 person-years) was 29.4 among HIV-infected individuals compared with 2.0 cases among HIV-seronegative controls. Data from the Veterans Affairs health care system cited an incidence rate among 1,107 SOT recipients of 22.2 per 1,000 patient-years. The risk of VZV infection reflects the intensity of immunosuppression and VZV serological status. Among SOT recipients, incidence rates are as follows: renal 3 to 10%; liver 5.7 to 12%; heart 6 to 16.8%; and lung 12.5 to 20.2%. The highest rates of VZV infections have been reported among HSCT recipients (23–67%). In one study of HSCT recipients, the incidence of HZ was 175 cases per 1,000 person-years, with cumulative incidence rates at 27% at 1 year; 36% at 2 years; and 44% at 3 years.

### Clinical Manifestations

With primary VZV infection, pneumonia is a rare but potentially serious complication, with an estimated incidence of 2.3 in 400 cases. In contrast to HSV, involvement of the lungs occurs via the bloodstream rather than by local extension. Typically, VZV pneumonia presents within 7 days of the onset of rash, but respiratory symptoms may precede rash. Among immunocompromised hosts, pneumonia is more common and may be more severe. Symptoms of VZV pneumonia include diffuse interstitial nodular opacities that are often more severe than expected for the degree of clinical symptoms.

The majority of HZ infections are limited to vesicular cutaneous lesions in a single dermatome, even in immunocompromised patients. Dissemination with the involvement of noncontiguous dermatomes occurs in up to 10% of HSCT recipients. However, visceral involvement, including respiratory tract involvement, and fatalities are rare. Rarely, immunocompromised patients may present with visceral involvement in the absence of cutaneous lesions of HZ.

### Diagnosis

The diagnosis of primary VZV or HZ is often established clinically, but laboratory studies may be confirmatory. Direct detection methods, such as DFA, are more rapid and more sensitive than viral culture. VZV may also be detected by PCR in blood or tissue. PCR testing of serum or blood may be helpful in the immunocompromised patient who has visceral disease before the appearance of cutaneous lesions.

### Prognosis and Therapy

Acyclovir (oral or IV), valacyclovir, or famciclovir are the preferred agents for VZV infections. Ganciclovir and valganciclovir display excellent in vitro activity against VZV and can be used. Acyclovir resistance may occur, particularly with prolonged use. Foscarnet may be effective as salvage therapy for acyclovir-resistant VZV, but resistance to foscarnet may also develop.

### Prevention

Prophylaxis with acyclovir or valacyclovir is effective in high risk immunosuppressed patients. In one study of 263 cases of SOT recipients treated with oral valacyclovir for 1 year posttransplant, no cases of VZV infections were observed. A live attenuated VZV vaccine (Oka strain; Zostavax Merck & Co., Inc., Kenilworth, NJ) has been shown to reduce the frequency and severity of VZV infections and postherpetic neuralgia in elderly adults and at-risk populations. This vaccine was designed to stimulate waning immunity in the elderly and is distinct from the varicella vaccine (Varivax Merck & Co., Inc., Kenilworth, NJ) used to immunize seronegative persons, as the latter contains 10 to 12-fold less virus. However, live
viruses are generally contraindicated in immunosuppressed individuals. Therefore, society guidelines recommend vaccination for varicella or herpes zoster before transplant, as long as there is at least 4 weeks between administration of a live vaccine and the initiation of highly immunosuppressive therapy.

**Human Herpesvirus-6**

**Epidemiology and Prevalence**

HHV-6, first isolated in 1986 from the peripheral blood mononuclear cells (PBMCs) of six adults with lymphoproliferative disorders, is classified in the β-herpesvirus subfamily, genus Roseolovirus, and is closely related to CMV. HHV-6 exhibits tropism for CD4 lymphocytes, endothelial cells, and the central nervous system. HHV-6 is a ubiquitous virus that infects > 80% of children by 3 years of age and > 90% adults are seropositive. HHV-6 accounts for > 98% of HHV-6 infections in the United States, Japan, and Western countries, whereas HHV-6A predominates in sub-Saharan Africa. HHV-6A is more neurotropic than HHV-6B.

HHV-6 is the only HHV known to integrate into the germline. The complete HHV-6 genome may integrate into the telomeres of host cell chromosomes and be vertically transmitted. This condition, chromosomally integrated HHV-6, is present in approximately 1% of the populations of the United States and United Kingdom and results in very high viral loads (exceeding 5.5 log10 copies/mL) which are typically asymptomatic. This condition must be discerned from HHV-6 primary infection or reactivation which may result in the manifestations described below.

**Clinical Manifestations**

**Primary HHV-6 Infection**

In 1988, Yamanishi et al implicated HHV-6 as the cause of roseola (exanthema subitum) or sixth disease in children. In 1989, HHV-6 was isolated from PBMCs from 100% (26/26) of infants with roseola during the first 3 days of fever; the rate of viral isolation fell to 17% by day 5 to 7 and 0 by day 8. Subsequent studies demonstrated that primary infection with HHV-6 is a common cause of acute febrile illness with or without skin rash in infants and young children. In a prospective study of 243 acutely ill children < 2 years old who presented to an emergency department (ED), HHV-6 viremia was detected in 34 (14%). Symptoms of HHV-6 infection included: malaise (82%); fever > 40°C (65%); inflamed tympanic membranes (62%); nasal congestion (57%); rash (18%); seizure (3%). The typical rash of roseola was present in only three children. Only 2 were hospitalized and all 34 recovered, usually after an average of 4 days of fever. In 1994, Hall et al studied 1,653 infants and young children (< 3 years) who presented to an ED with acute febrile illnesses. Overall, 160 (9.7%) had a primary HHV-6 infection, as documented by viremia and seroconversion; 21 (13%) were hospitalized and 21 (13%) had seizures. Often the seizures appeared late and were prolonged or recurrent. Conversely, no primary HHV-6 infections were found among 582 infants and young children with acute nonfebrile illnesses or among 352 controls without acute illness. In another cohort of 81 children 2 years old with primary HHV-6 infections, the following symptoms were present: fever (57%); fussiness (69%); rhinorrhea (65%); diarrhea (26%); rash (31%); roseola (23%); and seizures (0%). A study in the United States followed 227 children born to HIV-seropositive mothers. The cumulative infection rates of HHV-6 DNAemia at 6 and 12 months of age were 28 and 78% in HIV-negative children compared with 11 and 33%, respectively, among HIV-infected children (p < 0.001). There was an association between high CD4 counts and HHV-6 infection, consistent with the tropism of this virus for CD4 lymphocytes. Among HIV-infected children, HHV-6 infection was associated with progression of HIV disease (p < 0.05). HHV-6 is endemic in sub-Saharan Africa in healthy young children. In a study of 371 asymptomatic infants in Zambia, serum HHV-6 DNAemia was present in 15% at 6 months and 19% by 18 months. Two studies from Zambia detected HHV-6 DNA in the blood of 5 to 30% of HIV-negative children admitted to the hospital with febrile illnesses.

**Reactivation of HHV-6 in Immunocompromised Hosts**

Like other herpes viruses, HHV-6 establishes lifelong latency in the host and may reactivate under conditions of impaired immunity. Most severe HHV-6 infections occur in markedly immunocompromised children or adults including HCT or SOT recipients; or those with congenital
or acquired immunodeficiency disorders, HIV, lymphomas or hematological malignancies receiving chemotherapy.

Among HCT recipients, asymptomatic HHV-6 DNAemia is common (30–60%), but the vast majority of infections are self-limited and do not require treatment. In one study, 82 allogeneic HCT recipients had weekly blood tests for HHV-6 PCR; HHV-6 viremia was detected in 46 (56%) at a median of 23 days. In another study of 315 allogeneic HCT recipients, blood was drawn twice weekly for 3 months for HHV-6 PCR; viremia was detected in 111 (35%) at a median of 20 days post-HCT. In a recent study, plasma assays for HHV-6 DNA were performed in 106 pediatric allogeneic HCT recipients; HHV-6 viremia was detected in 48% at a mean of 20 days post-HCT and the onset of viremia coincided with the appearance of lymphocytes and monocytes in the peripheral blood. Among SOT recipients, HHV-6 has been isolated in >20% of subjects when serial samples are obtained, but serious HHV-6 infections are uncommon. Cervera et al prospectively followed 193 SOT recipients for 1 year, 4 of 7 seronegative SOT recipients seroconverted but only 1 developed clinically significant infection (cholestatic jaundice).

Clinically significant complications of reactivation of HHV-6 in transplant recipients (HCT or SOT) include: interstitial pneumonitis, bone marrow suppression, delayed engraftment and graft failure among HCT recipients, GVHD among HCT recipients, gastroenterocolitis, CMV infection, and encephalitis. Encephalitis may result in dementia, memory loss, loss of consciousness, seizures, and even death. Magnetic resonance imaging scans may show signal abnormalities in the limbic system but are often normal.

Among organ transplant recipients, HHV-6 infections have been associated with increased mortality. Among liver transplant recipients, HHV-6 may precipitate graft dysfunction or hepatitis, and may increase the risk of fungal infections and mortality. However, severe hepatic failure has been rare. Among renal transplant recipients, HHV-6 viremia is common (>26%) and is usually asymptomatic but fatal infections have been described. Clinically significant HHV-6 infections rarely complicate heart transplantation, but HHV-6 pericarditis and encephalitis have been reported. In a series of 30 lung or heart-lung transplant recipients, serial clinical specimens (blood, BAL fluid, tissue) were tested for HHV-6 PCR; HHV-6 was detected in 20 (66%) at a median of 18 days posttransplant. Although no clinical disease was linked to HHV-6 infection, mortality was higher in HHV-6-infected patients (7/20 expired) compared with uninfected patients (0/10 expired). Additionally, eight of nine viral or fungal infections were associated with HHV-6. Another series of 26 lung transplant recipients detected no cases of HHV-6 infections in peripheral blood. Costa et al examined 87 transbronchial biopsies from 30 lung transplant recipients by QNAT; HHV-6 DNA was detected in 6.9%, but did not correlate with allograft rejection and the clinical significance was not clear. In another series, 22 lung or heart-lung transplant recipients were followed for 1 year posttransplant; HHV-6 antigenemia was detected in 20 (91%) in blood or BAL. Only two had clinically significant disease (pneumonitis in one; encephalitis in one). Neurohr et al followed 87 consecutive lung transplant recipients for a mean of 3.3 years; HHV-6 was detected in 20 (23%) and was associated with an increased risk of BOS. However, in a subsequent study, Manuel et al followed 93 lung transplant recipients for 3 years, and measured HHV-6 PCR in all BAL specimens. HHV-6 was detected in 20.4% of patients, but was not associated with acute lung allograft rejection or BOS. In summary, HHV-6 is isolated in blood or BAL in >20% of lung transplant recipients but the clinical significance remains unclear. One case of HHV-6 colitis was reported in a lung transplant recipient.

HHV-6 may infect HIV-positive patients, but is often clinically silent. In a study of 32 HIV-infected males, HHV-6 was detected more frequently (100% detection) in subjects with CD4 counts >400 compared with 58% with CD4 counts <400 (58% detection, p<0.06), consistent with the tropism of HHV-6 for CD4 lymphocytes. Falasca et al evaluated the detection rate and viral load of HHV-6 in gastric, duodenal, and colon biopsies from HIV-positive (n=26) and HIV-negative (n=27) subjects. HHV-6 DNA was detected in 88% of HIV-infected individuals compared with 63% of HIV-negative subjects. In a study of 50 HIV-infected children (aged 3–13 years), HHV-6 was detected in oral mucosal cells in 9 (18%). In HIV-infected patients, endogenous reactivation of HHV-6 may occur. Primary HHV-6 infection in children with HIV has been associated with progression of HIV disease.

Diagnosis
Identification of HHV-6 DNA in blood mononuclear cells, serum, or tissue and seroconversion have been the traditional methods to diagnose HHV-6 infection, but QNAT detection of HHV-6 DNA in biological samples by real-time PCR is the most convenient and most often used method currently. Still, the clinical significance of HHV-6 DNAemia is not clear, as most subjects are asymptomatic and do not require treatment. No threshold has been formally recognized to identify infection requiring treatment. The decision to treat should be based on clinical features, viral load, and host features, including severity of immunosuppression.

Prognosis and Therapy
The prognosis of HHV-6 infections is usually excellent; most cases spontaneously resolve without sequelae. The vast majority of patients infected with HHV-6 do not require treatment. However, treatment may be required for selected complications in immunocompetent patients, such as encephalitis, pneumonia, disseminated or life-threatening disease, or for clinically significant disease in immunocompromised hosts. When patients are on immunosuppressive drugs, cessation or minimization of immunosuppression is a key to a favorable outcome.
role of specific antiviral agents is controversial. Randomized therapeutic trials have not been done. However, ganciclovir, valganciclovir, foscarnet, and cidofovir all display in vitro activity against HHV-6, and favorable responses have been cited in anecdotal cases and small series.\textsuperscript{294,300,363–365} Acyclovir is less active and should not be used.\textsuperscript{294} The role of routine surveillance tests for HHV-6 is controversial. In one study of HCT recipients, high-level HHV-6 infection was associated with increased incidence of CMV infection, acute GVHD, and mortality.\textsuperscript{333} By contrast, in another cohort of HHV-6 infected HCT recipients, early survival (3 and 6 months) was similar in patients receiving viral therapy or no treatment.\textsuperscript{335} Adoptive immunotherapy (transfer of HHV-6 specific T cells) may be an option in the future.\textsuperscript{366}

**Human Herpesvirus-7**

**Epidemiology and Prevalence**

HHV-7, another lymphotropic virus that was first identified in 1990,\textsuperscript{367} belongs to the β herpesvirus family and has close homology with HHV-6.\textsuperscript{368} HHV-7 is a ubiquitous virus that is acquired early in life (usually during the first 5 years),\textsuperscript{369} presumably via contact with oropharyngeal secretions.\textsuperscript{370} Like HHV-6, it infects more than 90% of the human population.\textsuperscript{371,372} In a prospective study, 496 children <3 years old seen in the ED or clinic were evaluated for primary infections with HHV-6 and HHV-7; three cohorts were studied: (1) 250 children with fever, signs of sepsis, or seizures, (2) 65 healthy children for well visits, and (3) 161 children with chronic medical illness.\textsuperscript{373} In the first cohort, 29/250 (11.6%) had a primary HHV-6 infection and 8 (3.2%) had a primary HHV-7 infection. Seizures occurred in 75% with HHV-7 compared with 17% with HHV-6 (\(p < 0.04\)). Median age was 23 months in subjects with HHV-7 compared with 9 months for HHV-6. No cases of HHV-7 infections were seen in the other two cohorts.

**Clinical Manifestations**

Importantly, the clinical spectrum of HHV-7 has not been well defined. HHV-7 may cause diseases similar to HHV-6,\textsuperscript{374} including a roseola-like illness,\textsuperscript{375} acute febrile respiratory disease,\textsuperscript{373,374} and seizures in young children.\textsuperscript{372,373} Rare manifestations include encephalitis and Guillain–Barre syndrome.\textsuperscript{376,377} Like HHV-6, HHV-7 establishes latency in lymphocytes for the life of the host. Reactivation of HHV-7 may occur among immunocompromised hosts, but clinically important infections are much less common than with HHV-6.\textsuperscript{3,72,378} A recent study of 105 HCT recipients detected HHV-6 in 60.0% and HHV-7 in 8.6%, with peak detection approximately 21 days posttransplant.\textsuperscript{325}

**Diagnosis**

HHV-7 PCR diagnostic assays are primarily used for research purposes as there is no common clinical scenario warranting HHV-7 diagnostic testing.\textsuperscript{379} Given the rarity of HHV-7, and limited data regarding clinical importance and management, we will not further discuss this agent.

**Human Herpesvirus-8**

**Epidemiology**

HHV-8, first discovered by Chang et al in 1994,\textsuperscript{380} is closely related to EBV and is in the family of gamma herpesviruses.\textsuperscript{381} HHV-8 is also termed Kaposi sarcoma–associated herpesvirus (KSHV). The importance of HHV-8 (KSHV) is its oncogenic properties. HHV-8 is the causative agent for at least three malignancies: (1) Kaposi sarcoma (KS), a lymphatic endothelial cell malignancy,\textsuperscript{326,381,382} (2) multicentric Castleman disease (MCD),\textsuperscript{381,383,384} and (3) primary effusion lymphoma (PEL).\textsuperscript{381,385–388} In addition to these three “hallmark” malignancies, rare cases of hemophagocytic lymphohistiocytosis\textsuperscript{381,382,389–392} have been associated with HHV-8. The pathogenesis of these malignancies likely results from viral and cellular angiogenic and inflammatory factors.\textsuperscript{381} HHV-8 can stimulate cell proliferation and inhibit apoptosis of tumor cells in KS, MCD, and PEL.\textsuperscript{388}

HHV-8 is endemic in sub-Saharan Africa\textsuperscript{393–400} with seroprevalence rates of 50 to 70%.\textsuperscript{313,393–395,397,398,401} In Uganda, the seroprevalence of HHV-8 increases with age as follows: 1.5 to 2 years old, 16%; 10 to 13 years old, 32%; 14 to 19 years old, 37%; adult >50 years old, 49%.\textsuperscript{402} In sub-Saharan Africa, factors that increase seropositivity for HHV-8 include HIV infection and malaria parasitemia.\textsuperscript{403} Seropositivity rates vary considerably among different regions/countries and are as follows: Europe 6 to 30%, with highest prevalence in Mediterranean countries\textsuperscript{404}; Southeast Asia 4.9 to 15.5%\textsuperscript{404}; the Caribbean 4.4%\textsuperscript{404}; Latin America 3 to 16%\textsuperscript{405,406}; and United States 1.5 to 6%.\textsuperscript{388,404,407} High rates of KS and HHV-8 seroprevalence are also found among Amerindians from Brazil and Ecuador.\textsuperscript{405} Several distinct subtypes of HHV-8 have been described, with some subtypes preferentially found in specific geographic regions (e.g., Africa, Asian Pacific, United States, Europe, Middle East, etc.).\textsuperscript{393}

HHV-8 may be transmitted by close contacts (e.g., saliva, bodily fluids)\textsuperscript{382,408–410} or by sexual transmission.\textsuperscript{410,411} Transmission via blood transfusion\textsuperscript{412} and organ transplantation\textsuperscript{413,414} has been described.

Primary infections with HHV-8 in immunocompetent subjects are mild and self-limited within a few days.\textsuperscript{326} Children may develop fever and rash\textsuperscript{400}, in adults, fever, diarrhea, and lymphadenopathy may occur.\textsuperscript{326,415} Like other herpesviruses, following resolution of the primary infection, the virus persists in a latent state in lymphoid cells.\textsuperscript{326} In immunocompetent individuals, pathogen–specific CD8 T cells control HHV-8 replication, preventing progression to neoplastic disease.\textsuperscript{415}

HHV-8 may reactivate in individuals with severe impairment in immune defense,\textsuperscript{416} particularly those infected by HIV\textsuperscript{,388,417} and SOT recipients.\textsuperscript{329,382,395,418,419} and other congenital and acquired immunodeficiency syndromes.\textsuperscript{420} Globally, HIV infection is associated with an increased prevalence of HHV-8 seropositivity compared with HIV-negative persons (odds ratio [OR] = 1.99, 95% confidence interval [CI] = 1.70–2.34).\textsuperscript{417} The association is strongest among HIV-positive men who have sex with men (OR = 3.95, 95% CI = 2.92–5.35) and those with
hemophilia (OR = 3.11, 95% CI = 1.19–8.11). Additionally, HHV-8 is endemic in sub-Saharan Africa in both HIV-negative and HIV-positive individuals.410

Diagnosis
Serology has limited utility in the diagnosis of acute HHV-8 infection and there is no standard serological test for clinical use.388 HHV-8 DNA can be quantified in plasma and PBMCs via PCR. HHV-8 viremia is invariably present with PEL and MCD,421 and is associated with the clinical stage of KS.422 Immunohistochemistry can identify HHV-8 proteins in tissue and is often used adjunctively in the diagnosis of KS, MCD, and PEL.419

Clinical Manifestations
As noted above, HHV-8 has been associated with several distinct clinical manifestations, including KS, MCD, and PEL, and the clinical features of each are discussed separately below.

Kaposi Sarcoma
The disease most often associated with HHV-8 infection is KS, an angioproliferative cancer of endothelial cells.420 Histopathological features of KS include spindle-shaped cells, inflammatory infiltration, and angioproliferation with extravasating erythrocytes.423 Endothelial cell markers (CD31, CD34, factor VIII) and lymphatic endothelial markers may be present.423 HHV-8 latency-associated nuclear antigen (LANA) is present in spindle cells in KS.423

KS is classified as one of four epidemiologic forms: (1) Classic KS which primarily affects elderly Eastern European Jewish or Mediterranean men, (2) endemic KS which occurs in sub-Saharan Africa,439,424 (3) epidemic KS is seen in HIV-infected subjects with AIDS,596,409 and (4) iatrogenic KS from immunosuppressive therapy.381

KS has a variable clinical course ranging from very indolent cutaneous forms to a rapidly progressive multiorgans or disseminated disease. The clinical manifestations vary depending upon the immune status of the patient and organs involved.389,425 In the following sections, clinical features, among the four epidemiological forms will be discussed.

Classic Kaposi Sarcoma in Immunocompetent Subjects
Classic KS primarily affects elderly Eastern European Jewish or Mediterranean men (male/female ratio: 10–15/1), typically presenting with indolent and chronic cutaneous plaques and nodules.388 The KS skin lesions are characterized by purpurnal discoloration, usually first appearing on the extremities.419 Classical KS in immunocompetent patients is usually chronic, persistent over many years and is not life threatening.425 Disseminated disease is uncommon.388 For localized forms, surgical resection, radiotherapy, or intralesional injections may be adequate as therapy.

Endemic Kaposi Sarcoma in Sub-Saharan Africa
The African endemic form of KS, is found in HIV-negative or HIV-positive individuals (children or adults) in countries of East and Central Africa.393,394,398 KS is the most common cancer in sub-Saharan Africa.404,424 Among an estimated 66,200 cases of KS worldwide, 58,800 are believed to have occurred in sub-Saharan Africa.426 The incidence of endemic KS in Africa is more common in males and adults > 35 year old.398

Endemic KS in Africa is more aggressive than classic KS in Europe and Mediterranean Countries.404 Typical cutaneous lesions are purplish/reddish in color, often affecting the lower extremities, and may infiltrate and destroy subcutaneous tissue and even bone.427 In African children and adults with endemic KS, oral manifestations (soft palate, gingiva) are common.428,429 Multicentric involvement of GI tract, lungs or bronchi, spleen, liver, and lymph nodes may occur.427 Males typically have a greater systemic tumor burden and widely disseminated disease is usually fatal within 3 years.427

Epidemic Kaposi Sarcoma in HIV-Infected Persons
Epidemic KS may complicate HIV infection in all areas of the world, with the highest incidence in Africa.381,396 During the pre-antiretroviral therapy (ART) era, KS was the most common malignancy among HIV-infected persons (incidence 1,500–2,500 cases per 100,000 person-years).431,432 The use of ART has resulted in a significant decline in incidence to < 500 cases/per 100,000 person-years in developed, resource rich nations.431,432 By comparison, the incidence of KS in the general population is approximately 1:100,000 person-years.404 The incidence of KS in HIV-positive individuals is approximately 1:20, with even higher rates (up to 30%) among HIV-infected men who have sex with men.404,409,411,430

The radiographic features of pulmonary KS are varied; multiple pulmonary nodules, tumors masses, bronchovascular bundle thickening, and pleural effusions are the most common findings on chest CT scans.433 Endobronchial KS may present as red or purple nodules or lesions at airway bifurcations434, because of the risk of bleeding, endobronchial biopsy is not recommended. Immune reconstitution inflammatory syndrome-associated KS flares have been reported in pulmonary KS.435 Musculoskeletal involvement with HIV-associated KS has rarely been described.436

HHV-8 infection enhances HIV replication. HIV-infected men who are seropositive to HHV-8 have impaired proliferative responses to HHV-8.437 Following ART in HIV-infected individuals with KS, cytotoxic lymphocyte responses to HHV-8 increase.388

Kaposi Sarcoma in Solid Organ Transplant Recipients
Organ transplant recipients are at an increased risk of developing KS, but the incidence varies considerably among different geographic regions. Among adult SOT recipients in the United States, Southeast Asia, and Northern Europe, the cumulative incidence of KS is approximately 0.5% compared with 6 to 28% incidence in regions of the Middle East and some Mediterranean regions.426,419

Multicentric Castleman Disease
MCD, an aggressive lymphoproliferative disorder characterized by generalized lymphadenopathy, constitutional
symptoms, and anemia, has also been linked with HHV-8 in some, but not all cases. MCD associated with HHV-8 is the plasma cell variant. Exacerbations of MCD correlate with increased HHV-8 viral load and increased IL-6 and IL-10 levels, underscoring the importance of viral replication and cellular cytokines in the pathogenesis of this disease. Tumor cells in HIV-positive individuals with MCD are plasmablasts that are scattered in the mantle zone of follicles, express B cell antigens, and are usually MUM1 (+), CD138 (−), and CD138 (+). The HHV-8-infected cells may form small confluent clusters, sometimes coalesced into “microlymphomas” or large sheets of cells thought to represent frank lymphoma. Importantly, these plasma cells harbor latent HHV-8.

MCD most commonly affects HIV-infected patients (> 90% males) but may also occur in HIV-negative immunosuppressed persons, especially SOT recipients. Among HIV-positive subjects, > 99% of cases of MCD are associated with HHV-8, as are > 50% of MCD among HIV-negative subjects. Cardinal features of MCD in HIV-infected patients include fever, constitutional symptoms, lymphadenopathy, splenomegaly, cytopenias, polyclonal hypergammaglobulinemia, and elevated inflammatory markers (e.g., C-reactive protein [CRP] and IL-6). Among HIV-positive patients with MCD, 54 to 72% have coexistent KS. B-cell lymphomas occur 15 times more commonly in HIV-positive individuals with MCD compared with HIV-positive subjects without MCD. MCD is characterized by recurrent flares with systemic symptoms, lymphadenopathy, inflammation, and high HHV-8 viral load. Recently, a new clinical entity characterized by severe systemic infection/reactivation, termed KSHV inflammatory syndrome, has been proposed. Serum IL-6 levels, HHV-8 viral load, and CRP may be useful as markers of disease activity and response to therapy.

Primary Effusion Lymphoma

PEL, a rare form of large B-cell lymphoma first described by in 1989, is caused by HHV-8 and is associated with serous effusions (pleural, peritoneal, ascites) in the absence of lymphadenopathy or organomegaly. Extracavitary or solid variants of PEL have been described but are rare. Most cases of PEL (50–80%) are coinfected with EBV. PEL cells most likely represent postgerminal center B cells with a plasma cell phenotype. In 1995, identified HHV-8 DNA in all patients with PEL underscoring the critical role of HHV-8 in the pathogenesis of this malignancy. The tumor cells of PEL are large, with abundant basophilic cytoplasm, irregular nuclear contours, and prominent nucleoli with plasmablastic, immunoblastic, or anaplastic differentiation. Immunohistochemical stains typically are negative for pan-B cell markers such as CD19, CD20, CD79a, and PAX-5, but the lymphoma cells express plasma cell markers including CD138, VS38c, and MUM1. The tumor cells often express CD30, CD38, CD71, and epithelial membrane antigen. Detecting HHV-8 in the tumor cells by in situ hybridization, PCR, or by immunohistochemistry against LANA is essential to diagnose PEL. Most cases of PEL occur in HIV-infected patients but a few cases have been reported after SOT. PEL represents approximately 1–4% of AIDS-related lymphomas and 0.3% of all aggressive lymphomas in HIV-negative subjects. Cases of PEL have also been reported in older immunocompetent patients from geographic areas where HHV-8 is endemic, such as sub-Saharan Africa and the Mediterranean region.

PEL usually presents as a malignant pleural, peritoneal, and/or pericardial effusion without a detectable solid mass. Rare cases present as tumor masses and are considered to represent an extracavitary or a solid variant of PEL. Unusual sites of involvement include skin, GI tract, lung, central nervous system, and lymph nodes.

Prognosis and Therapy

Kaposi Sarcoma

The course of KS is more aggressive in persons with AIDS, compared with HIV-negative persons. In HIV-infected persons with KS, oral mucosa and craniofacial regions are affected in 30% at initial presentation, and visceral involvement (e.g., GI tract, liver, spleen, lymph nodes) is common. Lung involvement occurs in 15 to 30% of HIV-infected persons and may be associated with hemoptysis which is sometimes fatal. Even in the post-ART era, pulmonary KS has been associated with a worse prognosis. In a single center study of 305 cases of KS in HIV-infected patients from 1996 to 2004, 5-year survival rates were 49% (median survival 1.6 years) in subjects with pulmonary involvement compared with 82% survival among those without pulmonary involvement.

Survival rates for HIV-infected patients with KS are worse compared with HIV-negative subjects, but survival rates have improved in HIV-infected subjects in the post-ART era. In the pre-ART era, staging systems were developed to predict prognosis in HIV-infected patients with KS. In a cohort of 211 HIV-infected patients with KS, Italian investigators cited 3-year survival rates of > 80% among “good risk” subjects compared with 34% survival among “poor risk” patients. The use of ART has markedly reduced the incidence of KS in HIV-infected subjects in resource-rich countries but reductions have not yet been achieved in sub-Saharan Africa.

Treatment of KS depends upon the immune state of the patient and the extent and severity of organ involvement. All patients with AIDS–associated KS should receive ART. Among HIV-negative individuals on immunosuppressive therapy, a reduction in immunosuppression should be performed when feasible. For limited, localized disease, intralesional or topical chemotherapy, laser, cryotherapy, radiation therapy, or surgical resection may be adequate. Multiagent chemotherapy is reserved for patients with severe symptoms, visceral involvement, or multiorgan disease, but relapses are common.
and toxicities may be significant.404,419,425 Optimal treatment is controversial, as no randomized controlled trial data are available. Clinical responses have been cited with a variety of agents, alone or in combination, including doxorubicin, vinca-alkaloids, etoposide, gemcitabine, interferon-α 2, taxanes, and radiation therapy.26,388,419,425,472 In SOT recipients, a switch from calcineurin inhibitor therapy to sirolimus may also be useful based on the latter’s known antiproliferative properties326, changing cyclosporine to sirolimus was associated with regression of KS in all of 15 renal transplant recipients undergoing this modification, with no episodes of acute rejection.438

Ganciclovir, valganciclovir, foscarnet, and cidovirof have in vitro activity against HHV-8.385 Novel strategies incorporating antiangiogenic factors, immunomodulatory agents, cytokines, and virus-activated cytotoxic therapy are being developed.384,404,416,470 Ganciclovir or valganciclovir as prophylactic antiviral therapy may reduce reactivation in high risk individuals.473

Multicentric Castleman Disease
Treatment of MCD is controversial, as randomized trials are lacking. Surgery and antiviral therapies including ART,474 interferon-α, and chemotherapy have proved largely ineffective.443,445,451 In one randomized trial, 79 HIV-negative and HHV-8-negative subjects with MCD were treated with the anti-IL-6 antibody siltuximab (n = 53) or placebo (n = 26); favorable responses were observed with siltuximab in 34% compared with 0% in the placebo group.475 In several studies, prolonged remissions were achieved with the anti-CD20 monoclonal antibody rituximab, at the expense of B cell depletion and flares of KS.445,447,451,476,477 Bower et al reported 49 HIV-positive patients with newly diagnosed MCD who were treated with rituximab with (n = 14) or without (n = 35) etoposide.478 Survival rates were 94% at 2 years and 90% at 5 years compared with 42 and 33%, respectively, in 12 patients treated before the introduction of rituximab (p < 0.001). Eight of 46 patients who achieved clinical remission suffered symptomatic, histologically confirmed relapse of MCD. All were successfully retreated and were alive in remission. The 2- and 5-year progression-free survival rates for all 49 patients treated with rituximab-based therapy were 85 and 61% respectively. In summary, HIV-associated MCD is a remitting-relapsing disease, but the outlook has improved dramatically in recent years with the introduction of rituximab-based therapy.478 Rituximab also reduced by 11-fold the risk of developing lymphoma in HIV-positive patients with MCD.476

Primary Effusion Lymphoma
The prognosis for PEL is poor, with a median survival of less than 6 months.443,456,459 Given the rarity of PEL, optimal therapy has not been elucidated. Anecdotal successes have been cited with chemotherapy and/or antiviral agents, but are rarely durable.386,388,419,460 Responses to intracavitary cidofovir have been cited in case reports.479,480 Sirolimus inhibits growth of PEL in vitro and in animal models481 and has promise for treatment of PEL. Bortezomib exhibited antitumor effects in vitro cultures of PEL cells.482

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