against the different forms of latent EBV infection. Diminishing lytic replication and virion production in these patients would theoretically produce a statistical decrease in the frequency of latent disease by decreasing the number of virions available to cause additional infection. In case reports and animal studies, ganciclovir and/or high-dose zidovudine, together with other agents, has been used to eradicate EBV-LPD and CNS lymphomas, another EBV-associated complication of transplantation. Both interferon and retinoic acid have been employed in the treatment of EBV-LPD, as has IVIg, but no large-scale prospective studies have assessed the efficacy of any of these agents. Several additional drugs are undergoing preclinical evaluation. Standard chemotherapeutic regimens are used if disease persists after reduction of immunosuppressive agents and administration of antibodies. EBV-specific T cells generated from the donor have been used experimentally to prevent and treat EBV-LPD in allogeneic recipients, and efforts are under way to increase the activity and specificity of ex vivo–generated T cells. **For further discussion, see Chap. 218.**

Human Herpesvirus 8 (KSHV) The EBV-related gammaherpesvirus KSHV, which is causally associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease, has rarely resulted in disease in HSC transplant recipients, although some cases of virus-associated marrow aplasia have been reported in the peritransplantation period. The relatively low seroprevalence of KSHV in the population and the limited duration of profound T cell suppression after HSC transplantation provide a plausible explanation for the currently low incidence of KSHV disease compared with that in recipients of solid organ transplants and patients with HIV infection. **For further discussion, see Chap. 219.**

Other (Non-Herpes) Viruses The diagnosis of pneumonia in HSC transplant recipients poses special problems. Because patients have undergone treatment with multiple chemotherapeutic agents and sometimes irradiation, their differential diagnosis should include—in addition to bacterial and fungal pneumonia—CMV pneumonitis, pneumonia of other viral etiologies, parasitic pneumonia, diffuse alveolar hemorrhage, and chemical- or radiation-associated pneumonitis. Since fungi and viruses (e.g., influenza A and B viruses, respiratory syncytial virus [RSV], parainfluenza virus [types 1–4], adenovirus, enterovirus, bocavirus, human metapneumovirus, coronavirus, and rhinovirus [increasingly detected by multiplex PCR]) also can cause pneumonia in this setting, it is important to obtain a specific diagnosis. Diagnostic modalities include Gram's stain, microbiologic culture, antigen testing, and—increasingly—multipathogen PCR and mass spectrometry assays. *M. tuberculosis* has been an uncommon cause of pneumonia among HSC transplant recipients in Western countries (accounting for <0.1–0.2% of cases) but is common in Hong Kong (5.5%) and in countries where the prevalence of tuberculosis is high. The recipient's exposure history is clearly critical in an assessment of posttransplantation infections.

Both RSV and parainfluenza viruses, particularly type 3, can cause severe or even fatal pneumonia in HSC transplant recipients. Infections with both of these agents sometimes occur as disastrous nosocomial epidemics. Therapy with palivizumab or ribavirin for RSV infection remains controversial. New agents, some host-directed, are under study. Influenza also occurs in HSC transplant recipients and generally mirrors the presence of infection in the community. Progression to pneumonia is more common when infection occurs early after transplantation and when the recipient is lymphopenic. The neuraminidase inhibitors oseltamivir (oral) and zanamivir (aerosolized) are active against both influenza A virus and influenza B virus and are a reasonable treatment option. Parenteral forms of neuraminidase inhibitors such as peramivir (intravenous) and several new oral agents remain in trial status. An important preventive measure is immunization of household members, hospital staff members, and other frequent contacts. Adenoviruses can be isolated from HSC transplant recipients at rates varying from 5% to ≥18%. Like CMV infection, adenovirus infection usually occurs in the first to third month after transplantation and is often asymptomatic, although pneumonia, hemorrhagic cystitis/nephritis, severe gastroenteritis with hemorrhage, and fatal disseminated infection have been reported and may be strain-specific. A role for cidofovir therapy has been suggested, but the efficacy of this agent in adenovirus infection remains to be determined. Banked virus-specific T cell therapy is under study for adenovirus infection (as well as for CMV and EBV infections).

Although diverse respiratory viruses can sometimes cause severe pneumonia and respiratory failure in HSC transplant recipients, mild or even asymptomatic infection may be more common. For example, rhinoviruses and coronaviruses are frequent co-pathogens in HSC transplant recipients; however, whether they independently contribute to significant pulmonary infection is not known. At present, the overall contribution of these viral respiratory pathogens to the burden of lower respiratory tract disease in HSC transplant recipients requires further study. Infections with parvovirus B19 (presenting as anemia or occasionally as pancytopenia) and disseminated enteroviruses (sometimes fatal) can occur. Parvovirus B19 infection can be treated with IVIg **(Chap. 221)**.

Rotaviruses are a cause of gastroenteritis in HSC transplant recipients, more frequently in children. Norovirus is a common cause of vomiting and diarrhea, and symptoms can be prolonged in HSC recipients. The polyomavirus BK virus is found at high titers in the urine of patients who are profoundly immunosuppressed. BK viruria may be associated with hemorrhagic cystitis in these patients. In contrast to its incidence among patients with impaired T cell function due to AIDS (4–5%), progressive multifocal leukoencephalopathy caused by the related JC virus is relatively rare among HSC transplant recipients **(Chap. 164)**. When transmitted by mosquitoes or by blood transfusion, WNV can cause encephalitis and death after HSC transplantation.

INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Rates of morbidity and mortality among recipients of solid organ transplants (SOTs) are reduced by the use of effective antibiotics. The organisms that cause acute infections in recipients of SOTs are different from those that infect HSC transplant recipients because SOT recipients do not go through a period of neutropenia. As the transplantation procedure involves major surgery, however, SOT recipients are subject to infections at anastomotic sites and to wound infections. Compared with HSC transplant recipients, SOT patients are immunosuppressed for longer periods (often permanently). Thus they are susceptible to many of the same organisms as patients with chronically impaired T cell immunity **(Chap. 104, especially Table 104-1)**. Moreover, the persistent HLA mismatch between recipient immune cells (e.g., effector T cells) and the donor organ (allograft) places the organ at permanently increased risk of infection.

During the early period (<1 month after transplantation; **Table 169-4**), infections are most commonly caused by extracellular bacteria (staphylococci, streptococci, enterococci, and *E. coli* and other gram-negative organisms, including nosocomial organisms with broad antibiotic resistance), which often originate in surgical wound or anastomotic sites. The type of transplant largely determines the spectrum of infection. In subsequent weeks, the consequences of the administration of agents that suppress cell-mediated immunity become apparent, and acquisition—or, more commonly, reactivation—of viruses, mycobacteria, endemic fungi, and parasites (from the recipient or from the transplanted organ) can occur. CMV infection is often a problem, particularly in the first 6 months after transplantation, and may present as severe systemic disease or as infection of the transplanted organ. HHV-6 reactivation (assessed by plasma PCR) occurs within the first 2–4 weeks after transplantation and may be associated with fever, leukopenia, and very rare cases of encephalitis. Data suggest that replication of HHV-6 and HHV-7 may exacerbate CMV-induced disease. CMV is associated not only with generalized immunosuppression but also with organ-specific, rejection-related syndromes: glomerulopathy in kidney transplant recipients, bronchiolitis obliterans in lung transplant recipients, vasculopathy in heart transplant recipients, and the vanishing bile duct syndrome in liver transplant recipients. A complex interplay between increased CMV