Prevention and Early Treatment of Opportunistic Viral Infections in Patients With Leukemia and Allogeneic Stem Cell Transplantation Recipients

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Key Words
Cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, influenza, adenovirus, antiviral agents

Abstract
A leading complication of leukemia therapy and stem cell transplantation is opportunistic viral infections. Infections caused by cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, influenza, adenovirus, and the community respiratory viruses are associated with significant morbidity and mortality in this highly immunosuppressed population. Fortunately, a growing armamentarium is allowing more effective prophylaxis of these pathogens. This article reviews the epidemiology and prophylactic strategies available for these common opportunistic viral pathogens. (JNCCN 2008;6:191–201)

Infections are an important cause of both morbidity and mortality among leukemia patients and patients undergoing hematopoietic stem cell transplantation (HSCT). Common viral infections in this population include cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and community respiratory viruses (influenza, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, rhinovirus, and adenovirus). This article reviews the epidemiology and available preventative strategies for these common viral infections. Table 1 summarizes recommendations for antiviral prophylaxis.

CMV

Epidemiology
CMV is a common viral infection associated with significant morbidity and mortality after HSCT; it is less common among patients with leukemia treated without transplantation. Up to 85% of the population has serologic evidence of latent infection. Clear evidence shows that the competency of the cellular immune system correlates with risk for CMV and clearance of viremia in HSCT recipients.

Among patients with leukemia, CMV reactivation is variable (2.6% to >50%), with the highest risk among those receiving purine analogs (e.g., fludarabine; 4.6%) and T-cell-depleting monoclonal antibodies (e.g., alemtuzumab; 15%–66%). In patients receiving alemtuzumab, reactivation of CMV and other herpes viruses tends to occur approximately between the first and third month after start of therapy, when the greatest degree of CD4 and CD8 cell depletion occurs.

Among HSCT recipients, CMV replication and disease typically occurs after engraftment until approximately 100 days posttransplantation (peak day, +45–60). Late-onset CMV infection (later than 100 days; median day, +160) is increasingly recognized and likely relates to enhanced immune suppression for management and prevention of graft-versus-host disease, prophylaxis, and...
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Table 1 Recommendations for Prophylaxis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Population</th>
<th>Recommended Antiviral Agent</th>
<th>Initiation</th>
<th>Duration</th>
<th>Vaccination</th>
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<tr>
<td>CMV</td>
<td>HSCT</td>
<td>GCV, VGCV, ACV, VACV</td>
<td>PET (weekly monitoring of CMV antigen or CMV) PCR</td>
<td>First 100 days posttransplantation Development or treatment for GVHD Duration of therapy is until CMV no longer detected</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alemtuzumab therapy</td>
<td>GCV, VGCV</td>
<td>2 months after therapy or until CD4 &gt; 100 cells/µL Duration of therapy is until CMV no longer detected</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>HSCT</td>
<td>No evidence for the use of prophylactic therapy at this time</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>HSV-1</td>
<td>HSCT</td>
<td>ACV, VACV, GCV*, VGCV*</td>
<td>Neutropenia</td>
<td>At least 30 days posttransplantation</td>
<td>NA</td>
</tr>
<tr>
<td>HSV-2</td>
<td></td>
<td>Alecmtuzumab therapy</td>
<td>ACV, VACV, GCV*, VGCV*</td>
<td>2 months after therapy or until CD4 &gt; 100 cells/µL</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>ACV, VACV, GCV*, VGCV*</td>
<td>Start of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>HSCT, Leukemia</td>
<td>ACV, VACV, GCV*, VGCV*</td>
<td>Onset of influenza activity in community</td>
<td></td>
<td>LAV is contraindicated</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td>Oseltamivir, Zanamivir</td>
<td>Onset of influenza</td>
<td>Influenza season†</td>
<td>Injected†</td>
</tr>
</tbody>
</table>

*Agents have in vivo and in vitro activity against HSV and VZV but are not recommended first-line agents.
†Not FDA-approved for this indication.
‡Inactivated vaccine is not recommended for the first 6 to 12 months after HSCT given poor antibody response.
Abbreviations: ACV, acyclovir; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GCV, ganciclovir; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; LAV, live attenuated vaccine; NA, not available; PET, preemptive therapy; PCR, polymerase chain reaction; VACV, valacyclovir; VGCV, valganciclovir; VZV, varicella-zoster virus.

Preemptive therapy posttransplantation. Mortality correlates with severity of disease (minimal for asymptomatic viremia; high for CMV pneumonia), degree of immune suppression, and timing of antiviral therapy. Risk factors for CMV disease include recipient and donor CMV serostatus (donor-negative/recipient-positive: 45%–85% with reactivation, 20%–30% with disease); type of transplant (allograft [6%–30%] > autograft [1%–6%]) and mismatched or unrelated (donor > matched); and presence of acute graft-versus-host disease.

CMV can cause a range of manifestations, from asymptomatic viremia to CMV syndrome (CMV replication, fevers, and systemic symptoms) to end-organ disease. Although CMV retinitis, hepatitis, and encephalitis have been described, CMV pneumonia and gastrointestinal disease are more frequent and challenging to manage. The most important and fatal presentation of CMV is pneumonitis, with early reports of mortality as high as 80% to 100%. Even with optimized early therapy, mortality remains high. Gastrointestinal disease frequently occurs concurrently with acute gastrointestinal graft-versus-host disease and is often difficult to differentiate from graft-versus-host disease.

Prophylaxis

Various strategies have been developed to prevent CMV disease in bone marrow recipients. These strategies involve the use of CMV-negative or leukocyte depleted blood products, immunoglobulin, and antiviral therapies.

Minimization of CMV Exposure: Transfusions carry a significant risk for CMV transmission, which can be reduced by transfusing blood products from CMV-seronegative donors or using blood products that have been leukoreduced. Among CMV-seronegative recipients of both CMV positive and negative transplants, CMV-seronegative blood transfusions are associated with a lower rate of infection than unscreened products (18% vs. 38%).
Leukoreduction of blood products is likewise associated with a significantly reduced risk for CMV infection (0% vs. 23% for blood not leukoreduced). CMV-seronegative blood products are associated with a lower risk for CMV transmission than leukoreduced blood products (0% vs. 2.4%). Given the strength of the data, seronegative HSCT recipients should undergo transfusion with CMV-seronegative or leukoreduced blood products.

**Antiviral Prophylaxis:** The main antiviral strategies for preventing CMV disease are prophylaxis and preemptive therapy. Prophylaxis involves administering antiviral therapy for a defined period to all patients at risk. Preemptive therapy involves periodic testing for CMV infection and is defined as the initiation of antiviral therapy against CMV based on the detection of virus in culture, a positive antigenemia assay, or positive molecular assays. The success of this method requires early identification of CMV replication before onset of end-organ disease. Preemptive therapy allows for decreased side effects and infectious complications of prophylactic therapy.

Several agents have been identified that have anti-CMV activity, including ganciclovir and its prodrug valganciclovir;cidofovir; foscarnet; maribavir; and fomiviren. Acyclovir and its produg valacyclovir seem to have prophylactic efficacy in vivo despite high in vitro 50% inhibitory concentrations.

Ganciclovir is available as an intravenous solution, oral pill, and oral produg (valganciclovir). Although studies of intravenous ganciclovir (5 mg/kg twice daily for 5 days, then daily for the first 100 days or 2.5 mg/kg every 8 hours for 1 week, then 6 mg/kg daily Monday through Friday for 100 days) showed a reduction in the incidence of CMV infection (3%–20% vs. 45%–56%) and disease, no improvement in survival was seen and an increased risk for neutropenia with resultant increased risk for infection occurred. Oral therapy, with either ganciclovir (6.9%–7.2% bioavailable) or valganciclovir (61% bioavailable), is an alternative. Oral (3 g 3 times daily from engraftment until day 84 posttransplantation) and intravenous (5 mg/kg 3 times weekly from engraftment until day 84 posttransplantation) ganciclovir have equivalent toxicity, tolerability, and number of CMV infections when used for prophylaxis. Although ganciclovir prophylaxis can be considered for patients at high risk (patients with T-cell–depleted transplants and those undergoing immunosuppression for grant-versus-host disease) for developing CMV infection and disease, alternative prevention strategies are typically preferred.

Although acyclovir does not have significant activity against CMV, high-doses have been shown to prevent CMV without risk for bone marrow toxicity. High-dose intravenous acyclovir (500 mg/m² 3 times daily, from day < 5 until day > 30) followed by oral acyclovir (800 mg 4 times daily for 6 months) has been found to effectively reduce the incidence of CMV disease (52%–59% vs. 61%–75%) and increase overall patient survival. High-dose intravenous acyclovir prophylaxis is most, but not all, studies has equivalent rates of CMV antigenemia and survival but lower rates of neutropenia and bacterial infections than intravenous ganciclovir in allogeneic HSCT recipients. High-dose valacyclovir (2 g 4 times daily) also seems to be as effective in preventing CMV disease compared with intravenous ganciclovir. When using acyclovir or valacyclovir as prophylaxis, the use of CMV viral load monitoring and preemptive therapy is essential.

Maribavir, a novel anti-CMV agent, is being evaluated for prophylaxis against CMV disease in allogeneic stem cell transplant recipients. Maribavir works by inhibiting the UL97 protein kinase and viral DNA synthesis. Initial phase II studies of maribavir show that it effectively reduced the incidence of CMV infection, but its use was associated with taste disturbance (18%–35%), nausea (21%–35%), and diarrhea (8%–21%); no significant cytopenias were noted. These data are preliminary, and a phase III study assessing the safety and efficacy of maribavir for primary prophylaxis in HSCT recipients is currently underway.

Foscarnet is a pyrophosphate analog with in vitro activity against all known human herpes viruses. Although foscarnet does not have the bone marrow toxicity of ganciclovir, it has dose-limiting nephrotoxicity and neurotoxicity. Given the concern for nephrotoxicity, foscarnet is rarely used as prophylaxis, especially with the advent of preemptive therapy. Cidofovir is a nucleotide analog with a wide spectrum of activity and long half-life, allowing for once-weekly dosing. It is effective at preventing CMV viremia, but is associated with renal toxicity ranging from proteinuria to elevations in creatinine and need for dialysis. Renal toxicity occurs less frequently in
patients preemptively treated (12%) than in those receiving longer courses of therapy (35%).

Prophylaxis Among Non-HSCT Patients With Leukemia: Most current guidelines for prophylactic treatment of CMV infection in patients with leukemia focus on individuals who received alemtuzumab or purine analogs. Few studies have evaluated CMV prophylaxis or preemptive therapy in this patient group. Studies using weekly ganciclovir prophylaxis (7.5 mg/kg intravenously, once weekly) and oral ganciclovir (1 g 3 times daily) for preemptive therapy have shown reduced rates of CMV. No studies have evaluated valganciclovir in non-HSCT patients. Weekly screening of CMV-seropositive patients who receive alemtuzumab can be considered.

Immunoglobulin-Based Prophylaxis: Available studies, including multiple meta-analyses of earlier data, suggest that CMV immune globulin decreases incidence of CMV infection, may decrease the risk for symptomatic CMV disease in seronegative transplantation recipients, and reduce the risk for CMV pneumonia in seronegative and seropositive recipients. CMV immune globulin has not been compared with the current practice of antiviral prophylaxis or preemptive treatment. Given the available data and newer agents that seem to be more effective, CMV immune globulin is not widely used.

Preemptive Therapy

Although CMV viremia typically occurs before onset of end-organ disease, viremia may be absent, particularly with central nervous system and gastrointestinal disease. Therefore, selection of assay method, threshold for treating, and frequency of testing will directly affect the success of the intervention. Several assays are currently available to detect CMV in HSCT recipients, including culture, antigenemia, and molecular assays, although only the latter 2 methods have the sensitivity to be used to guide preemptive therapy. CMV antigenemia detects phagocytized CMV within leukocytes, but is limited by reader experience and presence of neutropenia (the assay is unreliable when the absolute neutrophil count < approximately 1000 cells/mL). Several molecular assays to detect CMV DNA in plasma, leukocytes, and whole blood have been developed. Generally, HSCT recipients with antigenemia and a viral load of greater than 400 copies/mL are considered positive for CMV. Although some centers use higher cutoffs, this approach is associated with decreased sensitivity.

Both degree of viremia and viral kinetics predict risk for progression to disease, with higher viral burden and more rapid rise in viral load associated with worse outcomes. Antiviral Strategies: Preemptive therapy requires an agent with clear anti-CMV activity; therefore, high-dose acyclovir or valacyclovir cannot be used for this indication. Ganciclovir is the most widely tested agent for preemptive therapy, although its use is associated with significant risk for neutropenia; up to 40% of patients may develop an absolute neutrophil count of less than 1000 cells/mL. Because it can be given orally, valganciclovir has been studied for preemptive therapy in HSCT recipients. No studies have randomized intravenous ganciclovir to oral valganciclovir, limiting the strength of available data. Two retrospective studies found that valganciclovir (900 mg twice daily for 14 days, then 900 mg daily until 7 days after negative CMV test) was associated with rapid clearance of viremia detected with qualitative polymerase chain reaction (PCR; 93% by 14 days) and well tolerated except for neutropenia. Unfortunately, a high rate (40%) of relapse was seen that required retreatment. In a prospective observational study comparing intravenous ganciclovir (5 mg/kg twice daily) and oral valganciclovir (900 mg twice daily), the rates of CMV clearance (90% for ganciclovir vs. 95% for valganciclovir) and hematologic toxicity (75.9% for ganciclovir vs. 80% for valganciclovir) were similar between the groups. The ganciclovir group required slightly more erythrocyte transfusions (41% for ganciclovir vs. 20% for valganciclovir).

Given the bone marrow toxicity associated with ganciclovir and valganciclovir, foscarnet was also studied for preemptive therapy because its use is not associated with neutropenia. Foscarnet (90 mg/kg intravenously every 12 hours) for preemptive therapy (started from first positive CMV antigenemia detected and continued for 14 days) is associated with slightly faster clearance of CMV and is no different in terms of treatment failures, side effects, or mortality compared with intravenous ganciclovir.

Preemptive therapy monitors for CMV reactivation, allows for targeted therapy, and is the most frequently used method of CMV prevention among HSCT recipients. This approach has less toxicity, less neutropenia, and fewer infectious complications. On detection of CMV, antigenemia, or increased viral load, treatment should be initiated with intravenous...
ganciclovir, 5 mg/kg twice daily; valganciclovir, 900 mg twice daily; or foscarnet, 90 mg/kg every 12 hours (for patients intolerant to ganciclovir or valganciclovir).

**HSV 1 and 2**

**Epidemiology**

Many transplantation recipients will experience reactivation of HSV-1 and -2 secondary to immune system impairment by underlying disease, mucosal damage, neutropenia, lymphopenia, or medical interventions to prevent rejection. Fewer than 2% will develop primary infection. The seroprevalence of HSV-1 and -2 in the United States is estimated to be 62% and 22%, respectively. Seropositive individuals have a 37% to 62% risk for developing symptomatic disease after HSCT without prophylaxis. Reactivation, typically with oral or mucocutaneous lesions, frequently begins within the first few weeks after transplantation. Less-common manifestations include esophagitis, pneumonitis, and, rarely, hepatitis. HSV commonly reactivates in patients with leukemia undergoing conventional chemotherapy, ranging from 3.6% to 33%. The patients at highest risk are those treated with purine analogs or alemtuzumab, and the greatest risk factor in these patients is a CD4 cell count less than 50 cells/mL.

**Prophylaxis**

Acyclovir, valacyclovir, famciclovir, ganciclovir, valganciclovir, cidofovir, and foscarnet have activity against HSV. Seronegative patients should attempt to prevent exposure to HSV. Early studies of intravenous acyclovir in HSCT recipients clearly documented its clinical efficacy: 0% to 2.5% of patients treated with acyclovir versus 50% to 70% of those treated with placebo developed HSV lesions. Various regimens of oral acyclovir have been studied, including 200 mg every 6 hours from day −8 until 35 days posttransplantation and 400 mg 3 times daily until day +14, followed by 200 mg 3 times daily from day −6 until day 90 posttransplantation. Despite the dose, oral acyclovir prophylaxis results in a marked reduction of HSV lesions (0%–7% vs. 85%) with no significant toxicity. Valacyclovir (500 mg twice daily) confers similar protection to oral or intravenous acyclovir (2.7% valacyclovir vs. 2% acyclovir vs. 45% no prophylaxis). Although short courses of antiviral prophylaxis, typically through day +30, have traditionally been recommended, HSV reactivation can occur in as many as 32% of HSCT recipients over the first year posttransplantation. Prolonged prophylaxis is associated with a significant reduction in risk for HSV disease: 3.9% if continued for 1 year and 0% if continued for 2 years. A decrease in the development of acyclovir-resistant HSV also seems to occur. As a result of these data, either acyclovir or valacyclovir is recommended for all seropositive HSCT recipients from the start of conditioning to at least 4 weeks posttransplantation; longer prophylaxis can be considered in patients who continue to undergo enhanced immune suppression.

**Prophylaxis Among Non-HSCT Patients With Leukemia:** Acyclovir prophylaxis in patients with leukemia seems to be safe and effective. An early study of acyclovir use (5 mg/kg intravenously twice daily) showed a reduction in oropharyngeal HSV (0% vs. 50%); however, a high incidence of HSV reactivation occurred once therapy was stopped. Oral acyclovir (800 mg daily) has been found to decrease acute oral infections versus placebo (3% vs. 41%). Oral valacyclovir (500 mg or 250 mg twice daily) is equally effective (3.8% low-dose valacyclovir vs. 16.7% high-dose valacyclovir vs. 7.8% acyclovir) compared with oral acyclovir (400 mg twice daily) at preventing HSV in both patients with leukemia and HSCT recipients. Based on these results, prophylaxis against HSV reactivation is reasonable for HSV-positive patients with leukemia who are at high risk for reactivation, especially those receiving purine analogs or alemtuzumab and during periods of neutropenia.

**VZV**

**Epidemiology**

Most adults have been exposed to VZV; a true primary infection with VZV in adults is rare. In HSCT recipients, reactivation of VZV typically occurs between 2 and 6 months without prophylaxis, although later occurrences are also seen. Although most patients have zoster limited to the skin, disseminated zoster may occur. Complications of herpes zoster include postherpetic neuralgia (25%), scarring (19%), and bacterial superinfection (17%). HSCT recipients may also develop visceral VZV resembling graft-versus-host disease. Without prophylaxis, 28%...
to 40% of HSCT recipients will develop zoster and 15% to 30% will develop disseminated varicella. Without treatment, mortality may be as high as 10%. Although less common, primary infection may also occur and is associated with a progressive course with high mortality. Patients with hematologic malignancies undergoing conventional chemotherapy can experience VZV reactivation at a rate of 3% for patients with chronic myelogenous leukemia to 25% for patients with Hodgkin lymphoma. The greatest risk for reactivation is within the first 12 months posttherapy.

Prophylaxis
Fortunately, VZV can be prevented through minimizing exposure, administering antiviral prophylaxis, and providing passive immunization with varicella immune globulin. The only available vaccine is a live attenuated vaccine, which should not be administered to immunosuppressed patients, including those with indications for HSCT, outside of a clinical study.

Minimization of Exposure: Patients who have undergone HSCT or have leukemia should avoid exposure to individuals with active VZV infection, particularly primary disease, because airborne transmission is common. Additionally, VZV-susceptible family members, contacts, and potential visitors should be vaccinated as soon as the decision to perform HSCT is made. Optimally, the vaccine should be given 4 weeks or more before conditioning. HSCT recipients and candidates should avoid contact with vaccine recipients who develop a rash after vaccination; routine contact with a vaccinee requires no special precautions. For patients with leukemia or HSCT recipients who have any manifestation of VZV, airborne/contact precautions should be instituted if they are admitted to the hospital or seen in an outpatient setting to avoid exposure of other immunosuppressed individuals.

Antiviral Prophylaxis: All available antiviral agents used as prophylaxis against CMV and HSV are also effective against VZV, and therefore most information on preventing VZV is available as secondary outcomes data from other studies. These studies all showed that the prophylactic use of acyclovir, ganciclovir, or their valine prodrugs prevent the development of VZV while the antiviral was being used. Recent data suggest that prolonging prophylaxis for 1 year or more (acyclovir 800 mg twice daily or valacyclovir 500 mg twice daily) reduces the occurrence of VZV reactivation (5% acyclovir vs. 26% placebo at 1 year).

Prophylaxis Among Non-HSCT Patients With Leukemia: The use of antiviral prophylaxis and duration of prophylaxis against VZV are controversial among patients with leukemia who have not undergone HSCT. Most guidelines do not routinely recommend prophylaxis against VZV. Available data show that VZV can reactivate once prophylaxis has been discontinued. With the lack of data, the best approach for prophylaxis is to monitor for VZV reactivation, especially once agents active against HSV or CMV have been discontinued, and treat the reactivation appropriately. Before the start of chemotherapy, VZV serologies should be evaluated and, if negative, exposure should be minimized. The use of antiviral prophylaxis for immunocompromised patients has not been demonstrated in clinical trials in this patient population.

Postexposure Prophylaxis: Varicella zoster immunoglobulin (VZIG) should be strongly considered after exposure to a possible case of chicken pox or herpes zoster in a seronegative patient. The recommended dose for either VZIG or Varizig is 12.5 units/kg up to a maximum of 625 units at once. The dose should be given within 96 hours of exposure. If neither VZIG or Varizig is available within the 96-hour timeframe, standard intravenous immune globulin (400 mg/kg once) can be given. The use of antiviral medications as postexposure prophylaxis to VZV in seronegative patients has not been investigated in HSCT recipients or patients with leukemia. A nonrandomized study in immunocompetent children demonstrated a protective benefit with acyclovir (16% of children treated with acyclovir developed varicella vs. 100% of untreated controls). Experts in the field recommend that seronegative patients exposed to VZV should be given VZIG, followed by acyclovir or valacyclovir prophylaxis. Vaccination: Currently the only commercially available VZV vaccines (Varivax and Zostavax, Merck & Co., Inc., Whitehouse Station, NJ) are live, attenuated vaccines and are therefore contraindicated in immunosuppressed patients. Although the live vaccine has been studied in patients with immune reconstitution more than 24 months posttransplantation, it is not recommended for patients immediately before or less than 24 months after HSCT outside of controlled studies. Two studies of a heat-inactivated varicella vaccine (not yet commercially available) in HSCT recipients showed that patients who received the
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vaccine at 1, 2, and 3 months posttransplantation had reduced incidence of zoster (13% vaccine vs. 30% placebo) and that infection was less severe when it occurred. Further studies are warranted.

**EBV**

Like all other herpes viruses, EBV persists for life in the host. Uncontrolled EBV replication in an HSCT recipient can result in a posttransplant lymphoproliferative disorder (PTLD). PTLDs are a spectrum of disease from polyclonal hyperplasia to monoclonal B-cell hyperplasia to malignancy. The overall incidence for the development of PTLD in stem cell transplant recipients is approximately 1%, with the greatest risk in recipients of human leukocyte antigen-mismatched T-cell–depleted transplants, who have a risk as high as 24%. PTLDs tend to develop around 6 months after transplantation, during the time when cytotoxic T-cells become undetectable in the peripheral blood.

**Prophylaxis**

Although no evidence shows that antiviral prophylaxis decreases the incidence of developing PTLD, it may have benefit in high-risk groups (e.g., children and EBV-negative recipients of a positive transplant). Use of antiviral prophylaxis has not been proven and many patients who develop PTLD have received prophylaxis before the disease develops. Seronegative individuals should undertake behaviors that minimize the likelihood of EBV exposure. Studied approaches to prevent PTLD have focused on EBV DNA monitoring and the use of donor-derived cytotoxic T cells. Although EBV DNA monitoring may be useful in identifying patients at risk for developing PTLD, the correlation between EBV DNA-emia and development of PTLD is not strong. In one study, 68% of pediatric HSCT recipients had detectable EBV DNA-emia, whereas only 7% progressed to PTLD. DNA-emia was highest in those who progressed. Treatment with anti-CD20 monoclonal antibody (rituximab) may resolve PTLD and EBV viremia. Preemptive studies of rituximab (375 mg/m²) in this setting are limited, but use seems to be associated with clearance of viremia and reduced risk for PTLD.

Use of EBV-specific cytotoxic T cells for treating and preventing PTLD have also been studied and are associated with reduced EBV replication and decreased risk for PTLD. Donor-leukocyte infusions have also been studied for treating PTLD, and have shown a significant reduction in EBV viremia and PTLD, but they are also associated with a significant risk for fatal pulmonary reactions and graft-versus-host disease. Widespread use of donor lymphocyte infusions has significant resource and logistic limitations, and this intervention should still be considered experimental.

**Community Respiratory Viruses**

The community respiratory viruses have been increasingly associated with significant morbidity and mortality among patients with leukemia or who have undergone HSCT (Table 2). In general, respiratory viruses occur with the same seasonality in immunocompetent and immunocompromised patients. Clinical differentiation of one virus from another is difficult, and immunosuppressed patients have atypical

<table>
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<th>Virus</th>
<th>Epidemiology in HSCT</th>
<th>Diagnosis</th>
<th>Therapy</th>
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</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>11%–18%</td>
<td>Culture, DFA, EIA, PCR</td>
<td>M2 inhibitors (amantadine and rimantadine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neuraminidase inhibitors (oseltamivir and zanamivir)</td>
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<tr>
<td>Respiratory syncytial virus</td>
<td>35%–49%</td>
<td>Culture, DFA, EIA, PCR</td>
<td>Antibody-based therapy (IgIV, RSV Ig, palivizumab)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Ribavirin*</td>
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<tr>
<td>Parainfluenza virus</td>
<td>9%–30%</td>
<td>Culture, DFA, PCR</td>
<td>None</td>
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<tr>
<td>Adenovirus</td>
<td>3%–47%</td>
<td>Culture, DFA, EIA, PCR</td>
<td>Cidofovir*</td>
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<tr>
<td>Rhinovirus</td>
<td>18%–24%</td>
<td>Culture, DFA, PCR</td>
<td>Pleconaril (investigational)</td>
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</tbody>
</table>

*Not FDA approved for this indication.
Abbreviations: DFA, direct fluorescent antibody; EIA, enzyme immunoassay; HSCT, hematopoietic stem cell transplantation; IgIV, intravenous immunoglobulin; PCR, polymerase chain reaction; RSV Ig, respiratory syncytial virus immune globulin.
In general, viral shedding is prolonged, placing patients at risk for greater complications and increasing the likelihood that resistant viruses will emerge despite therapy. As with other viral infections, lymphopenia is a risk factor for more serious infection, progression, and mortality, and reconstitution of lymphocytes correlates with clinical and virologic improvement.

**Influenza**

**Vaccination:** Prevention of influenza depends on either vaccination or antiviral therapy. Currently 2 FDA-approved formulations of influenza vaccination are available: an inactivated injectable vaccine and a live, attenuated, intranasal vaccine. Because of the concern for progressive influenza infection with the live vaccine, only the inactivated injectable vaccine is routinely recommended for immunocompromised patients. Individuals in close contact with transplant recipients, including family members, should also be vaccinated; inactivated injectable vaccine is preferred. Unfortunately, influenza vaccination is less effective in inducing an antibody response and preventing influenza infections in transplant recipients than vaccination in healthy control subjects; vaccination during the first 6 to 12 months after HSCT is associated with minimal to no response.

**Antiviral Prophylaxis:** To overcome the limitations of vaccination, some experts recommend the use of antiviral agents to prevent influenza. Although both M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir) are approved for this indication, the widespread emergence of resistance to M2 inhibitors has resulted in the loss of this class for preventing or treating influenza. The neuraminidase inhibitors have been documented to be 70% to 93% effective in preventing influenza in immunocompetent adults and children. Limited data on the use of neuraminidase inhibitors in immunosuppressed patients suggest significant protective efficacy. A prospective study in progress will hopefully provide further details about the safety and efficacy of this practice.

**Conclusions**

Overall, viral infections remain a common complication in patients with leukemia and HSCT recipients. Despite a wide range of antiviral agents, high-quality, prospective, randomized studies of prophylactic interventions are limited in this vulnerable population. New antivirals are currently being developed with improved activity and reduced side effects that show promise for antiviral prophylaxis. Additional research is needed to identify safer and more effective options for managing the common viral infections in this population and for clarifying the optimal regimen and duration of prophylaxis.

**References**

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