Viral infections account for a great majority of acute infections in humans, resulting in significant morbidity and greatly contributing to permanent disability and mortality in many immunocompromised patients, including those receiving treatments for hematological disorders, such as patients diagnosed with acute and chronic leukemia, lymphoma, and myeloma. However, within the hematology population, recipients of hematopoietic cell transplantation (HCT) appear to have the greatest risk. In this latter group, some viral infections are more phase-dependent, whereas other infections may be encountered in all transplant phases. For instance, infections with adenovirus and respiratory viruses are diagnosed in all phases after HCT, whereas manifestations of herpes simplex virus 1 and 2 are mostly seen during the pre-engraftment period, infections due to cytomegalovirus and human herpes virus-6 in the early post-engraftment phase, and infections by Epstein–Barr virus and varicella-zoster virus often after day 100 post-transplant.

To date, pharmacological prophylaxis is only tested and approved for a small fraction of these viral pathogens. For most viruses, such as the respiratory viruses, antiviral prophylaxis is not available and/or not recommended (Table 4.1). In these latter settings, infection control measures and vaccination strategies, and adequate donor selection policies remain the first lines of prevention. However, addressing these topics is beyond the scope of this chapter, which focuses exclusively on the use of pharmacological antiviral prophylaxis in adult hematology patients.

### 4.1 Herpes Viruses

Seven of eight herpes viruses are well known for causing clinical syndromes in hematology patients: herpes simplex virus (HSV) type 1 and 2, varicella-zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV)-6, and HHV-8. HHV-7 is an uncommon cause of morbidity in these patients. Primary infection (usually preceding the diagnosis of the hematological disorder) is normally resolved by the host’s innate immune system, whereafter these viruses establish latency in specific host cells. However, during episodes of disrupted host immunity (resulting from disease or its treatment), these organisms can re-establish...
Table 4.1  Antiviral prophylaxis in adult hematology patients: based on recommendations of European Conference on Infections in leukemia (ECIL) and European Blood and Marrow Transplantation (EBMT) handbook

| Viral pathogen                        | Recommended antiviral prophylaxis                                                                 | Comments                                                                 |
|---------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Herpes simplex virus type 1 and 2     | • Oral acyclovir 3 × 200 mg to 2 × 800 mg/day.<br>• Intravenous acyclovir 250 mg/m² or 5 mg/kg every 12 h. | Oral valacyclovir 2 × 500 mg/day or famciclovir 2 × 500 mg/day are lower recommended alternatives |
| Varicella-zoster virus                 | • Oral acyclovir 800 mg bid or valacyclovir 500 mg once or twice daily.                          | Post-exposure prophylaxis with acyclovir 800 mg five times daily, valacyclovir 1000 mg three times daily, or famciclovir 500 mg three times daily |
| Epstein–Barr virus                    | No prophylaxis recommended                                                                      |                                                                         |
| Cytomegalovirus                       | Letermovir 480 mg (or 240 mg if co-administered with cyclosporine)/day                         |                                                                         |
| Human herpes virus type 6             | No prophylaxis recommended/available                                                            | Foscarnet has been used with non-conclusive results                      |
| Human herpes virus type 7             | No prophylaxis recommended/available                                                            |                                                                         |
| Human herpes virus type 8             | No prophylaxis recommended/available                                                            |                                                                         |
| Influenza virus                       | No prophylaxis recommended                                                                      | • Post-exposure prophylaxis with oseltamivir 75 mg twice daily for 10 days.  <br>• Isolation and infection control measures to prevent horizontal transmission. <br>• Annual vaccination. |
| Respiratory syncytial virus           | No prophylaxis recommended                                                                      | Infection control measures                                              |
| Parainfluenza virus                   | No prophylaxis recommended                                                                      | Infection control measures                                              |
| Human metapneumovirus                 | No prophylaxis recommended                                                                      | Infection control measures                                              |
| Rhinovirus                            | No prophylaxis recommended/available                                                             |                                                                         |
| Human coronavirus                     | No prophylaxis recommended/available                                                             |                                                                         |
| Enterovirus                           | No prophylaxis recommended/available                                                             |                                                                         |
| Adenovirus                            | No prophylaxis recommended                                                                      | Infection control measures                                              |
| Human bocavirus                       | No prophylaxis recommended/available                                                             |                                                                         |
| Polymyx JC virus                      | No prophylaxis recommended/available                                                             |                                                                         |
| BK virus                              | No prophylaxis recommended                                                                      |                                                                         |
| Parvovirus B19                        | No prophylaxis recommended                                                                      |                                                                         |
| Human papillomavirus                  | No prophylaxis recommended                                                                      |                                                                         |
| Hepatitis A virus                     | No prophylaxis recommended/available                                                             | Vaccination of HAV-seronegative patients                                 |
| Hepatitis B virus                     | Tenofovir or entecavir once daily                                                               | For at-risk patients: see chapter on vaccination                         |
| Hepatitis C virus                     | No prophylaxis recommended                                                                      |                                                                         |
| Hepatitis D virus                     | No prophylaxis recommended                                                                      |                                                                         |
| Hepatitis E virus                     | No prophylaxis available                                                                        |                                                                         |
| Norovirus                             | No prophylaxis recommended/available                                                             |                                                                         |
| Zika virus                            | No prophylaxis recommended/available                                                             | Testing of blood products and grafts for the presence of Zika virus      |

lytic viral replication and disease, whereas HHV-8 and EBV are also able to induce malignant proliferations of latency-infected cells.

Although HHV-6, HHV-7, HHV-8, and EBV can cause life-threatening complications, including encephalitis, myelitis, and the development of malignant tumors, antiviral chemoprophylaxis is not recommended (Ljungman et al. 2008). Herein, we will review aspects of infection and reactivation of the four remaining herpes viruses
and the role of chemoprophylaxis in hematology patients. Of note, antiviral drugs that rely on viral kinases for their activation (such as acyclovir and ganciclovir) are only effective during the lytic phases (primary infection or reactivation) as these kinases are not expressed during latency.

### 4.1.1 Herpes Simplex Virus (HSV)

Up to 80% of adult patients with hematological diseases are HSV-seropositive. Following primary infection, the virus establishes latency in the neuronal cells of sensory nerve ganglia, waiting to reactivate during periods of immunosuppression. HSV type 1, and to a lesser extent HSV type 2, are common causes of mucocutaneous lesions. They usually result from viral reactivation, whereas primary infection is unusual. Most lesions are localized in the orofacial region and less frequently in the esophageal and anogenital area. In patients with concurrent chemotherapy-induced or radiation therapy-associated mucosal damage, diagnosis can be suspected on clinical grounds but should ideally be confirmed by appropriate diagnostic techniques such as viral culture and/or detection of HSV DNA by PCR. Although more severe disease manifestations such as hepatitis, pneumonitis, meningitis, and encephalitis have all been reported, these appear to be rare (Levin et al. 2016).

Reactivation of HSV is very frequent following intensive chemotherapy for acute leukemia and in HSV-seropositive stem cell transplant recipients, both autologous and allogeneic. Rates as high as 60% and 80%, respectively, have been reported, especially during the first month after transplantation (Bustamante and Wade 1991; Meyers et al. 1980). These exceptional high rates of reactivation and their associated morbidity justify the use of prophylaxis in HSV-seropositive patients; conversely, antiviral prophylaxis is not recommended in HSV-seronegative patients.

Following a number of successful prophylaxis studies, acyclovir has become a drug of choice for many immunocompromised patients at risk of HSV reactivation (Saral et al. 1981; Gluckman et al. 1983; Hann et al. 1983; Shepp et al. 1987; Bergmann et al. 1995). When given intravenously or orally, this nucleoside analog requires the first activation by triphosphorylation whereby the conversion to acyclovir monophosphate involves a thymidine kinase encoded by HSV (or varicella-zoster virus: see below). Newer antiviral compounds (such as valaciclovir and famciclovir) with greatly improved oral bioavailability compared to that of oral acyclovir are also commonly used, although less studied (Balfour 1999; Orlowski et al. 2004). The European Conference on Infections in Leukemia (ECIL) recommends the following dosing regimens: oral acyclovir 3 × 200 mg to 2 × 800 mg/day, oral valaciclovir 2 × 500 mg/day, or famciclovir 2 × 500 mg/day. Obviously, in patients with severe mucositis, the intravenous route is preferred using acyclovir 250 mg/m² or 5 mg/kg every 12 h. Prophylaxis is continued for 3–5 weeks after the start of chemotherapy or after transplantation but may be significantly prolonged in the setting of graft-versus-host disease and/or corticosteroid treatment (Styczynski et al. 2009).

Resistance to acyclovir, although emerging (e.g., following T-cell-depleted allogeneic transplants), remains a rare event and is associated with viral thymidine kinase deficiency (Chen et al. 2000). These resistant strains remain, however, susceptible to antiviral drugs that do not require viral thymidine kinase for activation, including foscarnet or cidofovir (Styczynski et al. 2009; Chen et al. 2000; Blot et al. 2000).

### 4.1.2 Varicella-Zoster Virus (VZV)

Primary infection with VZV, usually during childhood and early adulthood years, causes varicella (or “chickenpox”), a highly contagious disease that is—unlike other herpes viruses—transmissible via the respiratory route. Hereafter, the virus establishes latency in the dorsal root and cranial ganglia. In VZV-seropositive immunocompromised patients, reactivation usually manifests as painful herpes zoster (or “shingles”), frequently involving multiple dermatomes. In addition, VZV-seronegative hematology patients who are exposed to individuals with VZV manifestations
are at increased risk of developing varicella, especially when receiving corticosteroids at the same time. These varicella cases may present as a generalized, vesicular rash, with or without visceral dissemination (Dowell and Bresee 1993; Hill et al. 2005).

The incidence of VZV disease among hematology patients varies widely and depends largely on factors that affect the cell-mediated immune competence, such as patient’s age, underlying tumor type, and antineoplastic treatment. Especially patients with underlying lymphoproliferative disorders and VZV-seropositive cell transplant recipients (autologous as well as allogeneic) carry a high risk for VZV disease and severe complications. In the absence of adequate prophylaxis, up to 25% of adult patients with acute lymphoblastic leukemia or Hodgkin’s lymphoma develop VZV disease (Novelli et al. 1988). Even higher rates have been reported in seropositive transplant recipients. These infections typically occur at a median of 5–6 months post-engraftment, but may appear years later, especially in patients suffering from chronic graft-versus-host disease (Atkinson et al. 1980).

More recently, the risk of VZV infection has also significantly increased in other patient populations due to the introduction of therapies that profoundly impact on cellular immunity: purine analogs (fludarabine, pentostatin, and cladribine), alemtuzumab, temozolomide, and the proteasome inhibitor bortezomib.

Specific measures for minimizing the risk of transmission (e.g., airborne and contact isolation) and vaccination guidelines are reviewed elsewhere. Epidemiological studies are needed to discern the effect of new VZV vaccines on the risk of VZV reactivation in cancer patients (Winston et al. 2018). Meanwhile, there is a firm recommendation for the use of chemoprophylaxis in VZV-seronegative patients at high-risk following exposure to varicella or herpes zoster: uncontrolled data suggest that post-exposure prophylaxis with therapeutic doses of acyclovir (800 mg five times daily), valacyclovir (1000 mg three times daily), or famiciclovir (500 mg three times daily) reduces both the incidence and severity of VZV manifestations. Post-exposure prophylaxis should commence as soon as possible and be given until 21 days after exposure. In VZV-seropositive patients, post-exposure prophylaxis remains optional (Styczynski et al. 2009).

Several retrospective and three prospective randomized placebo-controlled studies have examined the role of acyclovir prophylaxis primarily in cell transplant recipients (Ljungman et al. 1986; Perren et al. 1988; Boeckh et al. 2006). While acyclovir effectively prevents herpes zoster infection during the treatment period (when given for up to 12 months), late reactivations after discontinuation of prophylaxis are frequent, especially in chronically immunosuppressed patients. Presumably, prolonged antiviral prophylaxis prevents VZV-specific immune reconstitution, resulting in a rebound phenomenon. The EBMT recommends prophylaxis with oral acyclovir (800 mg twice daily) or oral valacyclovir (500 mg twice daily) for at least one year (and longer in the presence of graft-versus-host disease and immunosuppressive therapy) in VZV-seropositive allogeneic transplant recipients (Erard et al. 2007; www.ebmt.org/education/ebmt-handbook n.d.). However, the optimal duration of chemoprophylaxis is a matter of ongoing debate and may be better guided by measuring specific T-cell immune responses. The role of prophylaxis in the autologous setting is unclear.

### 4.1.3 Cytomegalovirus (CMV)

Human cytomegalovirus is a common opportunistic infection after HCT but is encountered less frequently among patients undergoing cytotoxic therapy. Notable exceptions are the combined use of fludarabine and high-dose cyclophosphamide, following alemtuzumab therapy, and more recently the use of idelalisib for chronic lymphocytic leukemia. CMV is transmitted through infected body fluids such as saliva, blood, urine, semen, tears, and breast milk. Seroprevalence rates in adults range from 30–40% in most industrialized countries to almost 100% in the developing world.
An acute CMV infection in an immunocompetent host often remains unnoticed, although prolonged fever, pharyngitis, and/or mild hepatitis can occur. Primo-infections are self-limiting in most cases. The immune system effectively eliminates the virus from the infected tissues, but the viral genome remains latent within the host cells whereby reactivation can occur at any time. Uncontrolled viral replication gives rise to CMV infection and subsequent disease in patients with severely compromised T-cell immunity such as HIV-infected patients, cancer patients, and transplant recipients.

CMV infection is defined as the isolation of virions or detection of nucleic acids or viral proteins (antigens such as pp65) in any body fluid or tissue specimen. The infection is called symptomatic in case of fever and/or bone marrow suppression. CMV disease is defined by the presence of organ involvement (lung, digestive tract, liver, retina, and central nervous system) (Ljungman et al. 2017). CMV primo-infection or reactivation can result in substantial morbidity and mortality in the immunocompromised host. Moreover, CMV reactivation is associated with an increased risk of other opportunistic infections, graft failure, and possibly also graft-versus-host disease in HCT recipients because of the indirect effects on the immune system (Boeckh and Geballe 2011). The risk of CMV reactivation depends on the serological status of recipient and donor (highest risk for seropositive recipients with a seronegative donor), the degree of T-cell depletion, and the intensity of immunosuppression.

The nucleoside analog ganciclovir (GCV), its oral prodrug valganciclovir (VGCV), the nucleotide analog cidofovir (CDV), and the anion pyrophosphate analog foscarnet (PFA) are all approved for CMV treatment. Unfortunately, these drugs are myelosuppressive (GCV and VGCV), nephrotoxic (CDV and PFA), and causes of electrolyte disturbances (PFA) (Griffiths and Lumley 2014). The risk of these side effects increased with concomitant administration of other myelosuppressive or nephrotoxic drugs that are often used in at-risk patients. For these reasons, these drugs, although proven effective to prevent reactivation in clinical studies, have not gained major popularity as prophylactic agents in the vulnerable hematology population.

The nucleosides GCV and VGCV are first activated by triphosphorylation; the active product acts as a competitive substrate for CMV DNA polymerase during viral DNA synthesis. The first step of the phosphorylation process is catalyzed by the viral kinase UL97, the subsequent second step and third step are catalyzed by host cellular kinases. Mutations in UL97 are a major cause of resistance against the first-line agents GCV and VGCV. CDV also inhibits CMV DNA polymerase following phosphorylation by cellular kinases. CDV competitively inhibits the incorporation of deoxycytidine triphosphate by viral DNA polymerase during viral DNA replication, whereas PFA (does not require phosphorylation) directly inhibits polymerase function by blocking the pyrophosphate binding site. The viral DNA polymerase is encoded by UL54. Mutations of UL54 result in varying degrees of cross-resistance among GCV, CDV, and PFA (Hecke et al. 2019).

There are two accepted strategies to prevent CMV manifestations in immunocompromised patients: a preemptive and a prophylactic approach (Maertens and Lyon 2017). The main goal of the preemptive approach is to prevent CMV disease in patients with documented CMV infection, while prophylaxis focuses on the prevention of CMV reactivation/infection. Both strategies are used in concert with general measures regarding optimal donor selection and transfusion of blood products aiming to prevent CMV transmission from one person to another.

Following HSCT, preemptive management is nowadays standard practice of care in most transplant centers and is also recommended by international guidelines. Patients are monitored at least weekly for CMV reactivation using quantitative PCR for the detection of viral DNA (Ljungman et al. 2008). Treatment with antiviral drugs (usually oral valganciclovir or intravenous ganciclovir) is initiated as soon as (mostly asymptomatic) CMV reactivation is confirmed to prevent progression to clinical disease. Preemptive anti-CMV therapy has proven to be very successful; overall, the incidence of tissue-invasive CMV disease has been reduced to less than 3% in recent large clini-
cal trials and to around 10% in daily clinical practice (Green et al. 2016).

Although a preemptive approach successfully prevents CMV end-organ disease, this surveillance-based strategy still allows for CMV reactivation (Green et al. 2016). However, a retrospective analysis of the Fred Hutchinson Cancer Research Center (Seattle) database suggests a negative effect of any degree of reactivation, especially during the first 2 months after transplant (Green et al. 2016). In addition, in a large CIBMTR analysis, CMV reactivation remains associated with increased non-relapse mortality rates, even in the current era of preemptive therapy (Teira et al. 2016). So, despite the proven effectiveness of preemptive therapy in preventing life-threatening CMV disease, allowing low-level CMV reactivation still comes with negative long-term effects, which could potentially be prevented by a prophylactic approach.

On the other hand, routine prophylaxis would expose many patients to the toxic effects of the available antiviral armamentarium, while only 40–80% of these patients may actually need preemptive therapy. Especially the prophylactic use of ganciclovir is problematic in this setting because of the high rates of neutropenia, the increased risk for bacterial and fungal infections, and the occurrence of late-onset CMV disease. Hence, the unmet need for an efficacious anti-CMV drug without dose-limiting toxicities such as bone marrow suppression and renal toxicity. Fortunately, several new antiviral drugs have been developed in recent years.

Brincidofovir is an oral, lipid-conjugated formulation of cidofovir, which is dosed twice weekly. It displays broad antiviral activity beyond CMV and is less nephrotoxic compared to cidofovir (Marty et al. 2013). Contrary to the initial positive results of a dosed-ranging phase 2 trial, the subsequent phase 3 trial failed to meet its primary endpoint of preventing clinically significant CMV infections within 24 weeks after HSCT (Marty et al. 2016). Brincidofovir causes GI toxicity, histologically characterized by epithelial apoptosis and crypt injury (Detweiler et al. 2018). These features mimic those seen in acute intestinal graft versus host disease and mycophenolate mofetil toxicity and may result in an increased use of corticosteroids, thereby further increasing the risk of CMV reactivation.

Maribavir is an oral drug with specific activity against CMV by competitively inhibiting the CMV protein kinase UL97, thereby preventing nuclear egress of virions. The results of the dose-escalating phase 2 study were promising (Winston et al. 2008), but a placebo-controlled phase 3 study did not meet its primary endpoint of preventing CMV disease following HSC allograft. The tolerability was good with dysgeusia being the most common side effect (Marty et al. 2011).

Letermovir demonstrates potent, selective, and reversible inhibition of CMV replication by targeting the pUL56, pUL51, or both subunits of the viral terminase complex, a mechanism of action, which differs from that of currently marketed anti-CMV drugs (Razonable and Melendez 2015). This enzyme plays an important role in the cleavage of viral DNA concatamers into unit-length genome and packaging into procapsids to form mature virions. Mechanism-based side effects are unlikely due to the lack of a mammalian counterpart to the viral terminase complex. Letermovir is highly specific for human CMV and lacks inhibitory activity against other pathogenic viruses.

Letermovir can be given both orally (480 mg [240 mg when co-administered with cyclosporine] once daily) and intravenously. The drug is a weak-to-moderate inhibitor of CYP3A (resulting in increased serum levels of, e.g., sirolimus, tacrolimus), a weak–to-moderate inducer of CYP2C9/19 (decreasing levels of, e.g., voriconazole), and an inhibitor of organic anion transporting polypeptide (OATP)1B1/3. There is no significant interaction with mycophenolate or posaconazole. However, letervimov is contraindicated in patients taking pimozide or ergot alkaloids and in patients receiving simvastatin plus cyclosporine (Kim 2018).

The potential benefit of letervimov was first shown in a double-blind, placebo-controlled, dose-ranging phase 2 study in allogeneic HCT recipients. The incidence of CMV prophylaxis failure (defined as CMV viremia and/or CMV end-organ disease or study drug discontinuation prior to day 84 due to any reason) decreased across increasing letervimov dose groups (60 mg
QD, 120 mg QD, or 240 mg QD) and was highest in the placebo group (Chemaly et al. 2014a). Based on further analysis of the exposure–response curves and the favorable safety profile, the dose selected for the pivotal phase 3 registration study was 240 mg QD with concomitant cyclosporine administration and 480 mg QD without cyclosporine. Adult CMV seropositive patients undergoing allogeneic HCT were randomized 1:1 to letermovir or placebo within a median of 9 days (range, 0–28) after transplantation. At baseline, one-third of patients had engrafted. Patients who had undetectable plasma CMV DNA within 5 days of randomization received letermovir or placebo, for up to 14 weeks after transplantation. Overall, a significantly lower risk of clinically significant CMV infection (disease as well as pre-emptive therapy) among letermovir recipients than among placebo recipients by week 24 after transplantation (37.5% vs. 60.6%, P < 0.001) was noticed. Of these, 1.5% of letermovir subjects and 1.8% of placebo subjects were diagnosed with CMV end-organ disease, mainly gastrointestinal. In addition, all-cause mortality at week 24 after transplantation was significantly lower in the letermovir group compared to the placebo group (10.2% vs. 15.9%, P = 0.03), although the significance was not sustained at week 48 (p = 0.12). In general, the beneficial effect of letermovir was more pronounced in the high-risk stratum, including patients undergoing haploidentical or HLA-mismatched transplantation, cord blood recipients, and transplantations with ex-vivo T-cell-depleted grafts (Marty et al. 2017).

Letermovir is generally well tolerated, with gastrointestinal side effects being the most common ones. There was no evidence of increased myelotoxicity or nephrotoxicity (Marty et al. 2017). However, it has also become clear that extended prophylaxis (beyond week 14) may be needed, especially in patients with delayed recovery of CMV-specific T-cell immunity; many of these patients belong to the higher risk stratum including recipients of T-cell-depleted grafts, cord blood graft transplants or patients on augmented immunosuppression to treat GvHD. As for VZV, the optimal duration of prophylaxis might be better guided by functional assessments of CMV-specific cell-mediated immunity (e.g., by QuantiFERON-CMV or T-Track-CMV assays). Such approaches might even prove to be cost-effective compared to routine prophylaxis (Westall et al. 2019).

4.2 Respiratory Viruses

Community-acquired respiratory viruses are now recognized as common causes of acute respiratory illness in immunocompromised cancer patients. Contrary to immunocompetent individuals, hematology patients (in particular leukemia patients and HCT recipients) usually present with prolonged viral shedding and high rates of disease progression to the lower respiratory tract with clinico-radiological signs of pneumonia, resulting in mortality rates between 10 and 50% (Green 2017; Chemaly et al. 2014b; Hirsch et al. 2013). These viral infections often precede bacterial and fungal infections. The most common human pathogenic viruses causing respiratory infection in hematology patients include influenza viruses, respiratory syncytial virus (RSV), and parainfluenza viruses (PIV) (Wade 2006). However, all respiratory viruses can cause infections, including rhinoviruses, coronaviruses, human metapneumovirus (hMPV), adenovirus, human bocavirus, and enteroviruses. Some of these viruses show seasonality in temperate climates (e.g., influenza and RSV) whereas others remain a threat throughout the year (e.g., PIV). Although not generally considered respiratory viruses, also CMV, HSV, and VZV can present as lower respiratory tract infections.

For most of these community respiratory viruses, specific antiviral therapy is not (yet) available. Notable exceptions are influenza A and B infections, which can preferentially be treated with the oral neuraminidase inhibitor oseltamivir (75 to 150 mg bid for 10 days, mainly to prevent complications), and adenovirus infections, which may respond to cidofovir. For RSV, hMPV, and PIV, ribavirin (intravenous, aerosolized, or oral) with or without the concomitant administration of intravenous immunoglobulins has been used with variable success. No specific therapy is available for rhinovirus, coronavirus, and enterov-
virus infections, but most patients respond well to supportive measures.

Primary antiviral chemoprophylaxis is not recommended for any of these respiratory pathogens. Annual inactivated influenza vaccination of at-risk patients, their health care workers, and household contacts remains the mainstay of influenza prevention in immunocompromised persons (Hirsch et al. 2013). For all other respiratory viruses, no licensed vaccines are available. However, ECIL-4 experts recommend post-exposure prophylaxis for 10 days with oseltamivir for HCT recipients who are less than 1 year after transplant and for leukemia patients undergoing chemotherapy after exposure to a confirmed or probable case of influenza, regardless of their vaccination status (Hirsch et al. 2013).

These infections are transmitted from person-to-person through small-particle aerosols, large droplets, or direct or indirect contact with virus-containing secretions. Autoinoculation of mucosal surfaces following contamination of hands is a very common route of transmission. Routine infection control measures play a key role in containing the spread of the infection and preventing nosocomial outbreaks. Hand hygiene is of utmost importance. In addition, the use of surgical masks might be beneficial. Patients with documented infection should be isolated and strict protection measurements should be applied to visitors and health care workers (including wearing gloves, gowns, masks, and eye protection) (Hirsch et al. 2013). Finally, reducing the dose of corticosteroids (if applicable) should be attempted, since corticosteroids have been identified as an independent risk factor for disease progression and overall mortality for most respiratory viruses (except for influenza virus).

### 4.3 Hepatotropic Viruses

Increasing numbers of patients with hematological conditions and recipients (as well as donors) of HCT have evidence of resolved or active hepatitis B (HBV) or hepatitis C (HCV) viral infection. In addition, hepatitis E virus (HEV) is becoming more prevalent (von Felden et al. 2019). HBV reactivation during immunosuppressive therapy is common, not only in HBV surface antigen (HBsAg)-positive patients, but even in case of resolved infection, and may result in hepatitis flares and even liver failure. HBsAg-positive individuals are at high risk of reactivation during most immunosuppressive therapies with a clear dose/duration–risk association. HBsAg-negative/anti-HB core antibody-positive patients are at lower risk except for allogeneic HCT recipients (frequently showing delayed reactivation) and patients receiving anti-CD20 monoclonal antibodies (such as rituximab and ofatumumab). In these two particular high-risk settings, guidelines strongly recommend antiviral prophylaxis with nucleoside or nucleotide analogs from the start of immunosuppressive therapy until at least 1 year after cessation of therapy. ECIL-5 and other guidelines recommend the once daily oral administration of the third-generation agent tenofovir or entecavir as drugs of choice (Mallet et al. 2016). These drugs are preferred to lamivudine because of their higher genetic barrier to antiviral resistance.

Patients who have successfully eliminated HCV are not at risk for reactivation during immunosuppressive therapy. However, those with chronic HCV infection (presence of HCV RNA) should receive antiviral therapy as soon as feasible (if possible even postponing the transplant/therapy till completion of the antiviral course), following the advice of a hepatologist (Mallet et al. 2016). Expert advice is also needed for patients with chronic HEV, in whom therapy with ribavirin can be considered, and for patients with hepatitis D virus co-infection. Vaccination should be considered for HAV-negative hematology patients undergoing immunosuppressive therapies.

### 4.4 Polyomaviruses

Reactivation of the neurotropic John Cunningham polyomavirus may cause progressive multifocal leukoencephalopathy. Cases have occasionally been described following HCT and after the use of immunomodulatory drugs such as rituximab,
Reactivation of the polyomavirus BK plays a key role in the development of post-transplant hemorrhagic cystitis (HC) and renal dysfunction. The incidence of HC is clearly on the rise since the introduction of un-manipulated haplo-HCT followed by high-dose cyclophosphamide to prevent graft-versus-host disease. Antiviral prophylaxis is not recommended.

4.5 Other Viruses

Norovirus can cause severe and complicated gastroenteritis. Unfortunately, no antiviral prophylaxis can be given. Strict isolation and general infection control measures (hand hygiene) are mandatory.

Finally, more and more patients infected with human immunodeficiency virus (HIV) are diagnosed with hematologic cancer or undergo hematopoietic cell transplantation procedures (Kwon et al. 2019). Specific follow-up and decisions about antiviral prophylaxis should include the advice of an HIV expert.

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