14.1 Human Polyomaviruses, BK Virus, and Hemorrhagic Cystitis: Epidemiology and Virological Characteristics

BK polyomavirus (BKPyV) belongs to the genus *Polyomavirus* of the family *Polyomaviridae* that comprises 13 different species with human host (Calvignac-Spencer et al. 2016). BKPyV virions are small non-enveloped particles of 40–45 nm in diameter, with an icosahedral symmetry, resistant to heat, and environment exposure (Hirsch and Steiger 2003). Structurally, BKPyV consists of a circular 5.1 kb double-stranded DNA genome within a capsid made of proteins Vp1 on the outside and Vp2 and Vp3 on the inside. The BKPyV genome is divided into three regions: the noncoding control region (NCCR); the early viral gene region (EVGR); the late viral gene region (LVGR). The NCCR is responsible for DNA replication and bidirectional viral gene expression; the EVGR encodes the regulatory nonstructural proteins called small tumor antigen (sTag), large tumor antigen (LTag), and spliced variants called truncated Tag; the LVGR contains the genes for the structural proteins Vp1, Vp2, Vp3, and a small accessory protein of unknown function called agnoprotein. The Vp1 capsid protein is the main target of BKPyV-specific antibodies while LTag is used as target for immunohistochemical diagnosis in tissue samples. BKPyV was isolated for the first time in a patient (B.K.) who underwent a kidney transplant and presented in the urine particular epithelial cells with nuclear viral inclusions called “decoy cells” (Gardner et al. 1971). Subsequently, BKPyV has been associated with hemorrhagic cystitis (HC) after hematopoietic stem cell transplantation (HSCT) (Apperley et al. 1987; Arthur et al. 1986), and nephropathy after kidney transplantation (Binet et al. 1999; Randhawa et al. 1999). Serologic studies showed that up to 90% of the adult population has been exposed to BKPyV during infancy and childhood (Egli et al. 2009). The infection can be asymptomatic or causes flu-like symptoms indistinguishable from other causes of viral community respiratory tract infections. The transmission is thought to be by direct person-to-person contact or by exposure to respiratory secretions. After primary infection, the virus remains latent in renal tubular epithelial and urothelial cells and asymptomatic viruria can be detected in 5–10%
of healthy individuals (Hirsch and Steiger 2003; Egli et al. 2009). The urinary shedding increases to 60–80% in patients undergoing HSCT, as well as the BKPyV viruria load increases to less than 3 \( \log_{10} \) to >7 \( \log_{10} \) copies/mL (Cesaro et al. 2018a; Cesaro et al. 2015).

The incidence of BKPyV-HC is 8–25% and 7–54% in pediatric and adult patients, respectively, being higher in allogeneic than autologous HSCT and in haploidentical HSCT with post-transplant exposure to cyclophosphamide as prophylaxis of graft versus host reaction (GVHD) (Cesaro et al. 2018a). The occurrence of BKPyV-HC has a negative impact on duration and quality of hospitalization in the early post-transplant period while its effect on mortality and overall survival is still debated (Cesaro et al. 2015; Gilis et al. 2014).

The pathogenesis of posttransplant HC is multifactorial and the factors implicated are different according to the time of onset. The early-onset HC occurs during the conditioning regimen or by 48 hours from its end, and it is considered to be a consequence of the direct toxicity of drug metabolites or radiotherapy on the urothelial mucosa; its appearance can be facilitated by the presence of coagulopathy and thrombocytopenia. The late-onset HC is usually observed with the start of neutrophil engraftment (around the second week posttransplant) up to the first 2 months after transplant, and it is associated with infection by BKPyV (Apperley et al. 1987; Arthur et al. 1986; Cesaro et al. 2018a; Cesaro et al. 2015; Gaziev et al. 2010).

The current pathogenetic model of BKPyV-HC is based on the occurrence of the following events: (a) Urothelial toxicity due to the conditioning regimen with denudation of bladder mucosa. (b) High level of BKPyV replication due to the severe impairment of the immune system in the early weeks post-HSCT that increases further the damage of urothelial mucosa for the cytopathic effect of the virus. (c) Attraction and infiltration of the mucosa and submucosa by allo-reactive inflammatory cells during the engraftment period that determines the loss of urothelial lining, urinary bleeding, and macroscopic hematuria (Cesaro et al. 2018a).

### 14.1.1 Risk Factors

High-level of BKPyV viruria is found up to 50–80% of HSCT patients in the early months posttransplant, but its specificity is low because only less than 20–25% develop BKPyV-HC. The combination of BKPyV viremia >1 \( \times 10^3 \) genomic copies/mL and viruria >7 \( \times 10^6 \) genomic copies/mL resulted instead a more specific and sensitive predictive factors for late-onset BKPyV-HC in HSCT patients (Cesaro et al. 2015; Gaziev et al. 2010). Several other factors related to the type of transplant or transplant complications and recipient age are associated with a higher risk of BKPyV-HC: The use of cord blood (CB) and peripheral blood (PB) as stem cell source (Gilis et al. 2014; Rorije et al. 2014), unrelated donor transplant (Giraud et al. 2006), grade II–IV acute GvHD alone or combined with high BKPyV load in urine (Gaziev et al. 2010; Rorije et al. 2014; Bogdanovic et al. 2004; Hayden et al. 2015), myeloablative conditioning (MAC) containing anti-thymocyte globulin, cyclophosphamide or high-dose busulfan (Gaziev et al. 2010; Giraud et al. 2008; Peinemann et al. 2000), and in pediatric patients recipient age > 7 years (Laskin et al. 2013).

### 14.1.2 Definition, Clinical Findings, and Diagnostic Considerations

The severity of HC is defined by four grades: microscopic hematuria (grade 1); macroscopic hematuria (grade 2); macroscopic hematuria with clots (grade 3); and macroscopic hematuria with clots and impaired renal function secondary to urinary tract obstruction (grade 4) (Cesaro et al. 2015a). The diagnosis of BKPyV-HC is based on presence of signs of cystitis (dysuria, urinary frequency, lower abdominal pain), hematuria grade 2 or higher and the demonstration of BKPyV-viruria, with viral loads of >7 \( \log_{10} \) genomic copies/mL. Plasma viral loads of >3–4 \( \log_{10} \) copies/mL are seen in more than two thirds of allogeneic HSCT recipients with BKPyV-HC (Cesaro et al. 2015; Laskin et al. 2013; Cesaro et al. 2009;
Erard et al. 2005; Koskenvuo et al. 2013), and declining plasma loads have been found to correlate with clinical recovery. Ultrasound and computed tomography examinations can support the clinical diagnosis showing nonspecific signs of HC such as bladder wall thickness, mural edema, intraluminal clots, urethral obstruction, mucosal enhancement, and perivesical stranding (Schulze et al. 2008). BKPyV-HC generally resolves after 3–5 weeks, but it is associated with prolonged hospital care and significant patient pain or discomfort. Moreover, bleeding together with additional complications such as renal failure and delayed immune recovery may contribute to higher nonrelapse mortality and lower overall survival.

14.1.3 Prevention and Therapy

Apart from the early-onset HC that can be prevented by supportive measures such as hyperhydration, bladder irrigation, and in patients who receive cyclophosphamide in the conditioning regimen, the use of mesna (sodium mercaptopyrano-nesulphonate), there are no effective measures to prevent BKPyV-HC. The use of fluoroquinolones that in vitro reduce BKPyV replication showed in retrospective studies modest or conflicting results (Cesaro et al. 2018a). Moreover, their use is associated with the increased risk of tendinitis and development of antibiotic resistance (Averbuch et al. 2017). Considering BKPyV does not encode classic antiviral targets such as viral nucleoside kinases or DNA polymerase, the current antiviral drugs developed for herpesviruses are ineffective or suboptimal. Cidofovir (CDV), a nucleotide analogue that inhibits DNA replication for a broad range of viruses, is the antiviral more active against BKPyV. Its use has been reported by several authors in retrospective studies. Although there is no agreement on the optimal dose and the modality of administration of CDV, most authors used the dose of 3–5 mg/kg/weekly or every 2 weeks associated with probenecid to decrease nephrotoxicity. Overall, a complete clinical response was found in 74% of patients with a reduction $\geq 1$ log of BKPyV load on urine and in blood in 38% and 84% of patients, respectively. Mild-to-moderate increase of creatinine level was found in 18% of the patients (Cesaro et al. 2018a). In a smaller number of patients treated with a low dose of cidofovir, 0.5–1.5 mg/kg/week, without probenecid, a complete clinical response was observed in 83% of patients with a reduction of BKPyV load in the urine and in blood in 62% and in 67% of patients, respectively. Mild-to-moderate renal toxicity was reported in 20% of patients (Cesaro et al. 2018a). There are anecdotal experiences where cidofovir at the dose of 5 mg/kg/week has been administered intravesically to avoid nephrotoxicity with 43% of complete clinical response and 50% of virological response (Cesaro et al. 2018a). Other drugs that have been associated with some efficacy against BKPyV-HC are leflunomide, an antimetabolite drug with immunomodulatory and antiviral activity, vidarabine, and oral levofloxacin. Brincidofovir, a lipid derivative of cidofovir, has shown in vitro the capacity to inhibit the replication of BKPyV in urothelial cell cultures but clinical data of efficacy and safety are awaited (Tylden et al. 2015). BKPyV-HC may benefit of nonspecific treatment aiming at speeding the repair and regeneration of urothelial mucosa such as hyperbaric oxygen therapy (HOT) or the topical application of fibrin glue by cystoscopy (Zama et al. 2013; Tirindelli et al. 2014). Both procedures depend on local availability. Moreover, HOT also depends on patient tolerance because it can cause earache due to barotrauma and claustrophobia.

In absence of validated medical treatment for BKPyV-HC, the use of adoptive transfer of donor-derived virus-specific T cells (VSTs) is a possible option, especially in patients who undergo haploidentical HSCT with deep ex vivo T-cell depletion. This approach showed to be effective in infections caused by Cytomegalovirus, Epstein-Barr virus, and Adenovirus, although its use is limited by costs, complexity of production, time of preparation, and availability of a seropositive donor (Baugh et al. 2018). To overcome these obstacles, the preparation and banking of VST lines from third-party healthy donors has
been proposed in order to treat timely HSCT recipients with drug-refractory infections. In a “proof of principle” phase II study, the use of pentavalent third-party-donor VSTs (directed against CMV, EBV, ADV, HHV-6, and BKPyV) in 16 HSCT patients with BKPyV disease (14 HC, 2 nephritis) obtained clinical benefit in all patients with a significant reduction of BKPyV viruria load by week 6 post infusion. Thirteen of 14 patients with BKPyV-HC had a complete resolution of macrohematuria, and in seven, increase of circulating BKPyV-VSTs was observed. In contrast, four of five patients with BKPyV-HC, who were screened for the study but not treated, had disease progression (Tzannou et al. 2017). The VST infusions were well tolerated, and none of the patients developed cytokine release syndrome. These results are encouraging and support further studies.

14.1.4 JC Polyomavirus

JC polyomavirus (JCPyV) was described in 1971, and its name derives from the initials of the patient in whom it was isolated for the first time (Padgett et al. 1971). JCPyV is member of the human polyomavirus family and shares with other polyomavirus, such as BKPyV, a common morphology, and structural organization. Seroprevalence studies showed that 40–80% of adult population has contracted JCPyV infection during infancy or adulthood. The infection is asymptomatic, and the route of transmission is supposed to be through fluids or secretions containing virus particles or also contaminated food or water. The contagion is followed by a viremia phase with the exposure of various target organs. JCPyV, as BKPyV, persists latently in the reno-urinary tract and intermittent low-level viruria has been described in healthy individuals who remain asymptomatic without any organ diseases (Dalianis and Hirsch 2013). In patients severely immunocompromised, such as patients affected by HIV/AIDS, patients with multiple sclerosis treated with natalizumab, or hematological patients, JCPyV has been associated with the development of progressive multifocal leukoencephalopathy (PML) (Pavlovic et al. 2015). In hematological patients, PML has been reported in Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, and autologous or allogeneic HSCT (Pelosini et al. 2008; Kharfan-Dabaja et al. 2007). The main risk factors are treatment with purine analogues, male sex, age > 55 years, CD4+ count ≤200 × 10^9/L, treatment with rituximab (Pelosini et al. 2008). The analysis of published data revealed that long-lasting lymphopenia, profound CD4+ and CD8+ deficiency, and reduced interferon-γ response are common findings described across different diseases and treatments associated with PML (Pavlovic et al. 2018). Mortality rates for PML ranges from 62% to 95% (Pelosini et al. 2008).

Retrospective studies on two allogeneic HSCT patients showed that JCPyV viremia preceded the neurological symptoms of PML by 105, and 126 days and that JCPyV viral load in blood strictly correlated with steroid dosage used for GvHD treatment. These observations suggest that the detection of persistent JCPyV viremia may predict the development of PML and that a faster withdrawal of immune suppression is allowed in patients with a good control of GvHD (Avivi et al. 2014). On the other hand, the lack of a clear correlation between the preemptive detection of JCPyV viremia and the development of PML underlines the role of other factors implicated such as neurotropism and virulence activity of a specific virus subtype (Pavlovic et al. 2018).

Currently, PML is still an untreatable disease with poor outcome and both prophylaxis and treatment represent unmet needs. In hematological patients, the main therapeutic measures aim at improving immune response to JCPyV by withdrawing steroids or other immunosuppressive drugs whilst anecdotal benefit has been reported with antivirals (brincidofovir, ganciclovir, and leflunomide), JCPyV cell entry inhibitors (chlorpromazine, citalopram, mirtazapine, risperidone), JCPyV vaccination, and administration of JCPyV or third-party BKPyV-specific cytotoxic T lymphocytes (Pavlovic et al. 2015; Balduzzi et al. 2011; Muftuoglu et al. 2018).
14.2 Adenovirus

14.2.1 Epidemiology and Virological Characteristics

The species of human adenovirus (HAdV) comprises seven subgroups, termed A–G, belonging to the family *Adenoviridae*, genus *Mastadenovirus*, with the species B divided in subspecies B1 and B2. Inside of each species, 51 HAdV were identified by serotyping but, from 2007, many other types were detected by genomic analysis (Lion 2014). The name comes from the initial isolation of HAdV from adenoids of subjects with acute febrile respiratory illness. HAdV species have a large (90–100 nm), icosahedral, non-enveloped structure containing a double-stranded DNA and can infect different mucosal sites. The most common site of entry is *Coxsackie Adenovirus* receptor (CAR) except for subgroup B that uses CD46 cell-surface antigen. The transmission occurs through airborne droplets, human direct contact or through secretions, biological fluids (vomitus, feces, saliva), contaminated water, medical instruments, airflow filters, hospital surfaces, and hands of personnel or caregivers. HAdV indeed is resistant to gastric and biliary secretions or low pH, and maintains its stability for weeks in dry environment. Moreover, the non-enveloped structure makes it resistant to many disinfectants and the inactivation requires the exposure to alcohol solutions for at least 2 min or to sodium hypochlorite solutions for 10 min. After infecting epithelial cells (incubation time of 2 days–2 weeks), the spectrum of clinical symptoms is variable and depends on the HAdV type. In the immunocompetent host, HAdV species cause usually mild-to-moderate, self-limiting diseases such as conjunctivitis, nephritis, upper respiratory tract infection, cystitis, gastroenteritis, and rarely they have been associated to severe form of pneumonia or myocarditis. HAdV species are responsible for 5–10% of febrile episodes during infancy and approximately 10% of pneumonia in infants and young children; moreover, 70–80% of children have serological evidence of a prior HAdV infec-
to HAdV infection is both humoral, by generating protective neutralizing antibodies, and cellular, by induction of specific CD4+ and CD8+ T lymphocytes (Keib et al. 2019). The lack of specific cellular immunity in the first months after transplant is primarily responsible for increasing viral replication in a patient with HAdV latency following a previous exposure (Feuchtinger et al. 2008; Guerin-El Khourouj et al. 2011).

14.2.2 Risk Factors and Outcome

Severe HAdV infection is associated with high load viremia and disseminated disease, in particular pneumonia. The factors associated to post-transplant HAdV viremia are young age, detection of HAdV in stool or nasopharynx before or after the transplant, the use of mismatched or haploidentical donor, the use of a cord blood allograft, T-depletion of the graft by CD34+ cell selection or the use of serotherapy with anti-thymocyte globulin or alemtuzumab, the presence of graft-versus-host disease (GvHD) requiring steroids at the dose of >1 mg/kg of prednisone, and severe lymphopenia (<300 lymphocytes/μL) (Lee et al. 2017). On the basis of the type of transplant and graft, period after transplant, and therapy of GvHD, Lindemans et al. proposed a risk classification for HAdV infection: a high-risk group comprising HSCT recipients within the first month after a cord blood graft, recipients of in vitro T-cell-depleted (CD3 + cell <5 × 10⁹/kg) graft, and/or patients receiving prednisone with a dose >1 mg/kg together with one or more lymphocyte-proliferation inhibitors (e.g., cyclosporine-A and mycophenolate mofetil); an intermediate risk group comprising recipients of cord blood or T-cell-depleted grafts between first month and fourth month after HSCT and/or patients with immunosuppressive therapy consisting of two lymphocyte proliferation inhibitors or one lymphocyte-proliferation inhibitor and prednisone >0.5 and <1 mg/kg for prophylaxis or treatment of acute GvHD; and a low-risk group comprising recipients of all other types of transplant other than cord blood or T-cell-depleted graft, or all transplants after 4 months, irrespective of the type of donor sources, receiving immunosuppressive therapy with one proliferation inhibitor and/or prednisone ≤0.5 mg/kg/d (Lindemans et al. 2010). This classification can help define the type of HAdV monitoring and the timing of intervention. Despite the severity of HAdV infection may vary from a self-limited infection with low viremia to a fatal disease, one of the most important factors influencing the outcome is the recovery of specific cellular immunity. The appearance or the increase of HAdV-specific T cells have been associated with the clearance of infection; therefore, the absence of T-cell recovery (CD3+ <25/μL) or the absence of T-cell response to HAdV viremia (CD3+ <300/μL within 2 weeks) is used as indicator of poor outcome of infection (Feuchtinger et al. 2007; Chakrabarti et al. 2002). HAdV viremia ≥1000 genomic copies/mL is an indicator of disseminated disease, and there is evidence that viral burden, peak of HAdV viremia, duration of HAdV viremia, and log₁₀ reduction of HAdV viremia in response to treatment are independent risk factors for mortality (Mynarek et al. 2014; Zecca et al. 2019). Given the different incidence of HAdV infection, overall mortality is higher in pediatric than in adult patients but in high-risk patients with HAdV viremia ≥1000 genomic copies/mL, the figures are as high as 18–22% in both age groups (Zecca et al. 2019; Lee et al. 2016).

14.2.3 Diagnostic Considerations

The study of previous exposure by serology of the donor/recipient pair has no role in defining measures to prevent HAdV infection after transplant due to the wide diffusion of HAdV in the population, the cross-reactivity of available assays, and the lack of effective drugs for HAdV prophylaxis. It has been shown that the presence or the appearance of a specific T-cell response is associated with protection or rapid recovery from HAdV infection, but its use is limited to experimental studies or selected centers (Feuchtinger et al. 2008; Guerin-El Khourouj et al. 2011).
et al. 2007; Zandvliet et al. 2010). The diagnosis of HAdV infection in HSCT patients is based on the demonstration of viral replication. In the past, this required 1–3 weeks using cell culture method or 2–3 days using the shell vial method, but the turnaround time of both limited their use in clinical practice. A shorter turnaround time of 2–4 hours is possible by direct demonstration of HAdV antigen in clinical specimens of nasopharyngeal swabs or aspirate, bronchoalveolar fluid or tracheal aspirate, stool with agglutination assay, fluorescence-labeled monoclonal antibody, enzyme immuno assay. The most sensitive, specific, and rapid technique is the determination of HAdV DNA with PCR on routine clinical samples of blood, stool, respiratory secretions, urine, cerebrospinal fluid, and tissues (Matthes-Martin et al. 2012). In particular, the presence of a high HAdV load in the blood is a sign of disseminated disease. Therefore, the use of quantitative real-time PCR in blood is useful to initiate early treatment, monitor the response to the treatment, and to predict the outcome of infection. Although low-level of HAdV DNAemia can be found in the early phase of an asymptomatic allogeneic HSCT, especially in pediatric patients, the development of HAdV DNAemia ≥1000 copies/mL is a marker of severe disease and predict dissemination, whereas a HAdV DNAemia ≥10,000 copies/mL is usually associated with disseminated disease, organ involvement, and high mortality. HAdV DNAemia ≥1000 copies/mL has been found in 14% of pediatric HSCT and 2% of adult HSCT, representing 61% and 51% of those viremic within 6 months from transplant, respectively (Sedlacek et al. 2018). Moreover, the peak of viral load, the duration of viremia, and the log reduction of viral load in response to therapy are predictors of mortality in patients with HAdV DNAemia (Lion 2014; Mynarek et al. 2014; Zecca et al. 2019). Based on these findings, the recommendation is to perform an active surveillance of HAdV in patients at risk by at least weekly determination of DNAemia during the first 3–4 months after transplantation (Hiwarkar et al. 2018). In pediatric patients, it is also recommended an active surveillance by PCR of HAdV load on stool because peak levels >10^5–6 copies/g are significantly associated with the subsequent development of HAdV DNAemia in a median time of 8–11 days (Lion et al. 2010; Hum et al. 2018). Quick raising of HAdV stool is proposed as criterion to start a preemptive treatment earlier, before HAdV infection became invasive, especially in patients lacking T-cell recovery. Nasopharyngeal detection of HAdV before HSCT in pediatric patients has been associated with the development of posttransplant and HAdV viremia (de Pagter et al. 2009). This finding has to be considered together with the patient clinical situation to decide whether to proceed or postpone the transplant procedure. For screening purposes, the use of conserved regions of HAdV genome such as the hexon gene and the fiber gene is fundamental to perform a reliable assay with a good sensitivity toward the different (sero) types (Huang et al. 2008). Conversely, typing of HAdV species is limited to epidemiological studies or in case of investigation of nosocomial outbreaks and is not commonly used to decide the antiviral treatment except for the use of ribavirin. In this case, the traditional serological methods have been substituted by molecular techniques based on PCR amplification or genome analysis, which are more rapid and precise (Ebner et al. 2006).

### 14.2.4 Definitions and Clinical Symptoms

In the immunocompetent and immunocompromised subject, the different species of HAdV show a different cell and tissue tropism and cause different diseases (Table 14.1). Indeed, the

| Disease                  | Adenovirus species |
|--------------------------|--------------------|
| Cystitis, nephritis      | B1, B2             |
| Disseminated disease     | A, B2, C, F        |
| Gastroenteritis          | F, G               |
| Hepatitis                | C                  |
| Keratoconjunctivitis     | B1, C, D           |
| Meningoencephalitis      | B1, C              |
| Respiratory tract disease| B1, B2, C, E       |
viruses belonging to the same species have a high DNA homology and usually do not recombine with virus of other species. The terminology proposed by ECIL for the different stages of HAdV infection is shown in Table 14.2 and includes clinical, virological, and histopathological evidence of infection or disease (Matthes-Martin et al. 2012). Disseminated invasive HAdV disease is defined by the involvement of ≥2 organs (pneumonitis, encephalitis, enteritis, retinitis) in the presence of HAdV viremia in peripheral blood or other sites (bronchoalveolar lavage, cerebrospinal fluid, nasopharyngeal or respiratory secretion, urine) and in absence of other identifiable causes (Lion et al. 2010; Lion et al. 2003). HAdV-related death is defined by death occurring with a high-level of HAdV viremia, HAdV detected in multiple sites, and multiple organ involvement or failure. In the HSCT patients, HAdV disease develops typically within the first 100 days after transplant (Lion et al. 2003), and the most frequent symptoms are fever, enteritis, and hepatitis. HAdV is responsible for 5–6% respiratory tract infections in HSCT patients with fever, cough, and sore throat. The involvement of lower respiratory tract is frequent in patients with high viremia or disseminated HAdV disease with a high risk of respiratory failure and lethality of 40–70%. Gastrointestinal involvement is characterized by cramps, diarrhea, or hemorrhagic enterocolitis that is not easily distinguishable by severe gut GVHD. Asymptomatic shedding in the stools of HAdV is frequently observed in pediatric patients during the early phase of HSCT patients but viral loads ≥1 × 10^6 copies/g identify patients at high risk for HAdV viremia and disseminated disease (Lion et al. 2010). Fulminant hepatitis in patients with disseminated disease has been reported, usually the association between HAdV infection and liver disease or the increase of transaminases is rarely observed in the post-HSCT course and its differentiation from severe liver GVHD may require biopsy. HAdV is a cause of hemorrhagic cystitis although less frequently than BKPyV. Bladder involvement determines dysuria, macroscopic hematuria, abdominal pain, and in the more severe cases, urinary obstruction; moreover, in the context of a disseminated disease, HAdV may affect the kidney and determines a tubulo-interstitial nephritis and renal failure. Meningoencephalitis with fever, headache, seizures, and disorder of consciousness is a rare complication of HAdV infection and affects mainly pediatric HSCT patients. Overall, mortality associated with HAdV infection is 6% for pediatric patients and <1% for adult patients but can reach up to 50% in patients with HAdV viremia and 60–80% in patients with disseminated disease (Lion 2014; Lion et al. 2010; La Rosa et al. 2001).

### 14.2.5 Treatment and Prevention

Prophylaxis for HAdV infection with the currently available virustatic drugs is not recommended (Matthes-Martin et al. 2012); moreover, there is no approved antiviral treatment for HAdV infection in immunocompromised patients. The mainstay is based on reduction or suspension of immunosuppression, if feasible, and on the off-label use of antiviral drugs such as cidofovir (CDV) and ribavirin. Ganciclovir is not effective because the lack of the thymidine kinase enzyme gene in HAdV prevents the first step of its phosphorylation into an active compound. Alike, foscarinet is not active against HAdV. In vitro studies

| Virus infection | Evidence of virus infection by detecting a specific immune response, viral antigens, nucleic acids in the host |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| Asymptomatic virus replication | Evidence of viral replication based on increasing viral load, or detection of virus by cell culture or viral antigens in an asymptomatic patient |
| Probable virus disease | Evidence of viral replication in a symptomatic patient in absence of histological evidence of virus organ disease |
| Proven virus disease | Evidence of viral replication in a symptomatic patient with histological evidence of virus organ disease |

Table 14.2 Definitions of infection, replication, and disease for patients who underwent a hematopoietic stem cell transplantation

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showed that CDV is effective against all species of HAdV, whereas ribavirin is effective only against the species belonging to group C. Considering the limited data on its efficacy in vivo, the use of ribavirin is generally not recommended for the preemptive treatment or for therapy of HAdV disease, except for individual cases infected by C species. CDV is a monophosphate nucleotide analogue of cytosine that once phosphorylated intracellularly to diphosphate inhibits viral DNA polymerase and viral replication. The main drawback of CDV is the low bioavailability that determines a low intracellular concentration of the active phosphorylated metabolites, whereas more than 90% of the dose is excreted unchanged in urine. On the other hand, its excessive concentration on the renal tubular cells may cause tubular necrosis and renal insufficiency. Probenecid, an organic acid, is used to reduce the renal tubular cell uptake of CDV and increase its plasma levels because it competes with CDV for the same organic anion transporter at renal tubular cells. Hyperhydration represents another important measure to reduce renal concentration of CDV and its toxicity. CDV has been used for both preemptive and therapeutic purposes (Lion 2014; Lindemans et al. 2010). Usually the starting dose is 5 mg/kg/week for 2 weeks followed by 3–5 mg/kg biweekly, with probenecid. An alternative scheme is 1 mg/kg/day three times per week, with or without probenecid. The treatment is continued until lymphocyte recovery is achieved (lymphocyte >300 μL) or HAdV DNAemia becomes undetectable or stably below the threshold for treatment. In general, CDV has a limited efficacy in the treatment of overt HAdV disease, irrespective of the dose used, especially in patients lacking T-cell reconstitution, and mortality remains high. CDV showed to be more effective in the setting of preemptive treatment, in asymptomatic patients with high or increasing HAdV load to control viral replication and to prevent the progression to disseminated disease until immune recovery occurs (Lion 2014; Lindemans et al. 2010). Brincidofovir (CM001X) is a lipid derivative of CDV that is promising in terms of safety and efficacy compared to CDV. In fact, brincidofovir has a superior oral bioavailability that permits to achieve higher concentration in the infected cells, and not being a substrate of renal cell organic anion transporters, it is not concentrated in renal tubules. In a randomized, phase II study, brincidofovir, 2 mg/kg twice a week, showed a significant virological response, defined reduction of DNAemia load in 2 weeks and clearance of DNAemia in 4 weeks, in two thirds of patients (Grimley et al. 2017). Moreover, no nephrotoxicity or myelotoxicity was reported. The most frequent side effect was diarrhea that affected 38% of patients and may require drug interruption and the start of differential diagnosis procedures for other causes of gastrointestinal disease such as gut GVHD or different infections. A retrospective study comparing pre-emptive therapy with brincidofovir or CDV in pediatric HSCT patients that had a comparable immune-reconstitution and viral burden showed that brincidofovir was associated to higher virological response, 83% versus 9%; moreover, brincidofovir was effective also in 9 of 11 patients not responding to CDV. Importantly, the reduction of DNAemia was observed despite lymphopenia. Only 1 of 18 patients suspended brincidofovir for abdominal cramps and diarrhea, whereas no patient developed nephrotoxicity. Considering the efficacy and the good safety profile, brincidofovir may represent a step forward in the treatment of HAdV infection, but further clinical development is needed (Hiwarkar et al. 2017).

14.2.6 Immunotherapy

The key role of T-cell immunity in HAdV infection is demonstrated by the fact that severe lymphopenia and delayed T-cell reconstitution represent a risk factor for HAdV infection; that the clearance of HAdV infection is associated with appearance of HAdV-specific T cells; and that the survival of patients with HAdV viremia is better in patients who have the recovery of lymphocyte count and HAdV-specific T cells (Zandvliet et al. 2010; Matthes-Martin et al. 2012).

In a recent survey among EBMT centers, the transfer of HAdV-specific T cells is used in 20%
of centers for preemptive or therapeutic purposes (Cesaro et al. 2018b); despite that, this approach is still considered experimental and to be performed in the context of a clinical trial. The advantage of adoptive immunotherapy is that the specific T cells are reactive against all species of HAdV because the immunodominant target antigen is the hexon, a viral capsid component that contains several epitopes conserved among different species of HAdV. The number of specific T cells in a subject previously exposed to HAdV is low, so obtaining an adequate number of cells requires the selection of cells from the peripheral blood of a seropositive donor and in vitro expansion (under GMP conditions); after infusion, a further in vivo expansion occurs under viremia stimulation. Several approaches have been used based on the selection of T cells secreting interferon (IFN)-gamma after stimulation with HAdV antigen (Feuchtinger et al. 2007; Feucht et al. 2015) or the production of cytolytic T-cell lines obtained by antigen-presenting cells transduced with HAdV vectors (Leen et al. 2006). These methods have limitations due to the complexity of the manufacturing process, the costs, the availability of a seropositive donor, and the time of production; in particular, the time of manufacturing could interfere with the “on time” use of the specific HAdV cells as viremia occurs. To overcome these limitations, manufacturing processes using seropositive third-party donors to generate multi-pathogen-specific T cells directed against CMV, EBV, HAdV, HHV-6, and BKV (Bollard and Heslop 2016; Leen et al. 2013) have been assessed. A phase II study in 38 patients using third-party-derived pentavalent CTLs showed an overall efficacy of 92%, with CTLs persisting in circulation for up to 12 weeks after infusion (Tzannou et al. 2017). These studies show that adoptive transfer of HAdV-specific T cells from the stem cell donor or third-party donors is a promising approach for patients not responding to treatment with antivirals and lacking circulating HAdV-specific T cells or for patients with disseminated HAdV infection, although the clinical applicability still depends on the future broader availability and timely access to virus-specific T cells.

### 14.3 Community-Acquired Respiratory Viral Infections

#### 14.3.1 Introduction

Community-acquired respiratory viruses include a variety of RNA viruses such as human orthomyxo-, paramyxo-, picorna-, and coronaviruses, and DNA viruses such as adeno-, boca-, and polyomaviruses (Englund et al. 1999; Whimbey et al. 1996). In patients with hematological malignancies (HM) and recipients of hematopoietic cell transplant (HCT), respiratory viruses have been recognized as a significant cause of morbidity and mortality (Chemaly et al. 2014). Clinical presentation of all respiratory virus infections in patients with HMs or after HCT does not differ from the illness described in the general population. However, immune compromised patients may have atypical presentation with shortness of breath as the only manifestation (Ison 2007). These possibilities highlight the importance of a high index of suspicion. Respiratory virus infections may present with upper respiratory tract infectious disease (RTID) or lower RTID. Upper RTID is defined as the detection of respiratory viruses in upper respiratory tract specimens together with symptoms and/or signs and other causes excluded. Definition of lower RTID is pathological sputum production, hypoxia, or pulmonary infiltrates together with viral identification in respiratory secretions, preferentially in samples taken from the sites of involvement (Hirsch et al. 2013).

Rapid and accurate diagnosis for all community-acquired respiratory viruses is crucial in this patient population to allow prompt introduction of infection control precautions, start of antiviral therapy—if available—and potential deferral of chemotherapy or transplantation.

Patients with HMs or after HCT are at increased risk for progression to lower RTID, respiratory failure, and fatal outcome. This is most probably due to the immunopathology of respiratory virus infection, which reflects a complex interplay involving direct effects by a given virus but also the response of resident respiratory
cells and recruited innate and adaptive immune cells to the lungs. Studies carried out over the last several decades suggest that the host response to respiratory virus infection dictates the type and extent of injury incurred (Newton et al. 2016).

Incidence of each virus can vary seasonally; however, rhinovirus (25–40%) has a higher incidence in HCT recipients than paramyxoviruses including respiratory syncytial virus (RSV) (2–17%), parainfluenza virus (PIV) (4–7%), or human metapneumovirus (hMPV) (3–9%) or influenza (1.3–2.6%), coronavirus (6.7–15.4%), and adenovirus (1–2%). At our institution, we have prospectively collected 1069 nasopharyngeal swabs and bronchoalveolar lavages in HCT recipients collected from January 2010 to December 2014 and found similar distribution as previously published (Martino et al. 2005) (Fig. 14.1). Mortality rates for HCT recipients range from 5% to 80% and seem to be overall higher for RSV (Whimbey et al. 1996; Hirsch et al. 2013; Martino et al. 2005; Chemaly et al. 2006; Nichols et al. 2001a; Peck et al. 2007; Avetisyan et al. 2009; Khanna et al. 2008; Ljungman 2001; Raboni et al. 2003).

### 14.3.2 Respiratory Syncytial Virus

#### 14.3.2.1 Epidemiology

Respiratory syncytial virus (RSV) is a single-stranded RNA virus, member of the *Pneumoviridae* family. The virus is classified into two major antigenic groups, A and B, and infections by subtype A strains appear to be more severe (Walsh et al. 1997). Transmission occurs by contact with virus-containing secretions or fomites and subsequent inoculation of nasopharyngeal or ocular mucous membranes (Hall et al. 1981). The incubation period ranges between 2 and 8 days. RSV is worldwide in distribution, and it causes annual outbreaks: in temperate climates, these occur from late fall to spring, with a peak in January and February that usually precedes that of influenza season (Obando-Pacheco et al. 2018). RSV infections have a higher incidence among immunocompromised patients, especially those with hematologic malignancies submitted to HCT (Chatzis et al. 2018; Englund et al. 1988). The reported incidence in HCT recipients is about 2–17%, and such infections can be acquired through community outbreaks or by nosocomial transmission, generally through health care workers or infected visitors to inpatient units (Martino et al. 2005; Avetisyan et al. 2009; Khanna et al. 2008; Team RSVOI 2014; Shah et al. 2013). Male sex, allogeneic HCT, and pre-engraftment status are some of the factors that increase the risk for RSV acquisition in this population (Schiffer et al. 2009; Nichols et al. 2001b). It is well recognized that RSV infection among patients with HM significantly contribute to raise the burden of morbidity and mortality. These infections may lead to prolonged viral shedding, longer hospital stay, more severe disease with higher risk for progression to lower RTID and respiratory failure (Avetisyan et al. 2009; Khanna et al. 2008; Walsh et al. 2013). Mortality rate is reported up to 80% (Hertz et al. 1989; Harrington et al. 1992), although in more recent reviews, it ranges 10–30%, probably

![Fig. 14.1 Number of episodes of respiratory virus infections in HCT recipients at the University Hospital of Basel from 1/2010 until 12/2014](image-url)
reflecting more sensitive diagnostics and earlier more aggressive treatment (Chatzis et al. 2018; Shah et al. 2013; Seo et al. 2013).

14.3.2.2 Clinical Presentation
RSV may produce a wide range of clinical manifestations, from self-limited upper RTID to severe pneumonia. Although symptoms are not specific, the presence of sinusitis and wheezing can be more suggestive of RSV infection than other pathogens (Hall et al. 2001). The clinical presentation depends upon age, health status, and degree of immunodeficiency. Patients with HM have a greater susceptibility to develop severe disease because of several factors: disruption of mucosal barrier integrity and IgA impairment, decrease in serum antibodies production, and deficient cytotoxic T-cell function increase the risk of infection in the lower airways and reduce the capacity for viral inactivation, resulting in an increase in disease severity and duration (Couch et al. 1997). A large proportion of HCT recipients (80–90%) experience initially upper RTID symptoms, such as cough, rhinorrhea, nasal congestion, sinusitis, otitis media, and subsequently, after an average time of 7 days, 30–40% of them develop a viral pneumonia (Boeckh 2008). The main risk factors for progression to lower RTID are lymphopenia, allogeneic HCT, early posttransplant period, graft-versus-host disease (Hirsch et al. 2013). Hematologic patients with RSV lower RTID usually present with dyspnea and hypoxemia together with new radiographic findings, which include bronchial wall thickening, peribronchial shadowing, air-trapping, multilobar patchy shadowing, or poorly defined nodularity (Gasparetto and Escuissato 2004). Without treatment, a great proportion of these patients develop respiratory failure, with need for ICU admission, mechanical ventilation, and high fatality rate (Chemaly et al. 2014; Shah et al. 2014). Progression to lower RTID, need for supplemental oxygen and higher degree of immunodeficiency are recognized as strong predictors of mortality among hematologic patients (Khanna et al. 2008; Seo et al. 2013). Moreover, RSV infection contributes to the development of respiratory superinfections by bacterial and fungal pathogens (Englund et al. 1988). As late complication, RSV lower RTID may also lead to bronchiolitis obliterans syndrome and to a decline in pulmonary function (Erard et al. 2006).

14.3.2.3 Diagnosis
Laboratory diagnosis has evolved considerably over recent decades. Adequate specimen collection from the site of infection (nasal washes, nasopharyngeal swabs, and bronchoalveolar lavages) and prompt transport to the laboratory are essential for the successful identification of the virus. Viral culture has been traditionally considered the gold standard for RSV detection, but it requires dedicated laboratory expertise and up to 7 days to become positive. Direct immunofluorescence antigen testing is a rapid and inexpensive method, but it has a low sensitivity (Ohm-Smith et al. 2004). Real-time polymerase chain reaction assays have a high sensitivity and specificity and represent currently the preferred method for diagnosing RSV infections. Multiplex PCR viral panels can efficiently test for multiple viruses at the same time and provide results in a short turnaround time (Layman et al. 2013).

14.3.2.4 Treatment
Deferral of chemotherapy or transplantation due to the high risk of fatal outcome needs to be considered (Hirsch et al. 2013). Early initiation of antiviral treatment is crucial to improve the prognosis of immunosuppressed patients with RSV infections. Treatment at the upper respiratory stage has demonstrated to reduce progression to lower RTID and thereby mortality (Chemaly et al. 2014). The therapeutic tools currently available for the treatment of RSV infections are ribavirin, intravenous immunoglobulins (IVIG), and palivizumab.

Ribavirin is a nucleoside analogue with activity against DNA and RNA viruses. Several studies have suggested that it is effective for the therapy of RSV infection in HCT recipients (Chemaly et al. 2006; Shah et al. 2013). Aerosolized ribavirin is the formulation most extensively studied: it allows to reach high concentration in the pulmonary parenchyma without
systemic toxicity; the main disadvantages are the need for special air-flow, room conditions, and the potential teratogenicity for exposed caregivers and the high costs (Chemaly et al. 2014). In a randomized clinical trial, continuous (6 g over 18 hours daily) and intermittent (2 g over 3 hours every 8 hours daily) schedules of aerosolized ribavirin were equally effective in preventing progression to RSV lower RTID (Chemaly et al. 2012a). Systemic formulations (10–30 mg/kg body weight in three divided doses) have also been evaluated and have shown to be effective and well tolerated: intravenous ribavirin could be an alternative in patients with serious infections and/or pulmonary consolidation that prevents distribution of aerosolized medication (Molinos-Quintana et al. 2013); on the other hand, oral formulation is the least expensive form and does not require hospitalization (Khanna et al. 2008). Its bioavailability is around 50% but could be reduced in case of GVHD, thereby limiting its efficacy. In a recent retrospective study, effectiveness of oral and aerosolized ribavirin was compared in 46 patients with RSV infection (20 treated with oral ribavirin vs. 26 with aerosolized ribavirin). There were no differences in clinical outcomes between the two groups with regard to adverse events, progression from upper to lower RTID, escalation of care, or 30-day mortality (Trang et al. 2018).

Polyclonal immunoglobulins are an option for adjunctive therapy to ribavirin, especially in severe RSV infections. IVIG have demonstrated to prevent RSV replication in lung tissues and to induce anti-inflammatory effects that may be beneficial to reduce the airway damage caused by the inflammatory host immune response (Chemaly et al. 2014; Aschermann et al. 2010). RI-001 is a polyclonal IgG prepared from plasma donors with high-titer neutralizing anti-RSV antibody and has shown some promising results: its compassionate use in patients failing with standard of care therapy has shown to be effective and safe (Falsey et al. 2017). This strategy could offer advantages compared to standard IVIG.

Palivizumab is a monoclonal IgG that neutralizes RSV by binding the envelope protein F. It has been shown to reduce viral titers in pulmonary tissues and viral replication in animal models (Shah and Chemaly 2011). Furthermore, palivizumab has proven to have a prophylactic effect in infants at high risk for bronchiolitis, and it is currently registered for this indication (Tomblyn et al. 2009). Nevertheless, there is no strong evidence about its efficacy in adults and HCT recipients with RSV infections. Other limitations are represented by its high cost and the potential risk to select resistant mutants (Zhao and Sullender 2005).

There are no definite criteria for the management of RSV infection in with HM because of the lack of clinical randomized trials. Evidence is limited to few studies, mostly retrospective and from single centers. Despite the uncertainty regarding benefit, the European Conference on Infections in Leukemia (ECIL-4) recommends the treatment of RSV lower RTID and upper RTI at risk for progression to lower RTI with ribavirin and IVIG (0.5 g/kg body weight 1–3 times weekly) (Hirsch et al. 2013).

In view of the unmet clinical need of RSV and other paramyxovirus RTID after HCT and the undocumented efficacy of ribavirin and IVIG, the following key questions remain: who should be treated, and should all paramyxovirus RTID be treated with ribavirin and IVIG? Some studies have suggested classifications that can assist in the risk stratification (Table 14.3). Shah et al. (Shah et al. 2014) identified risk factors for poor outcome of RSV-RTIDs after allogeneic HCT and proposed a scoring index from 0 to 12 to classify patients with low (score 0–2), moderate (score 3–6), and high (7–12) for progression, in order to identify those who would benefit most from (inhaled ribavirin-based) antiviral therapy. At the University Hospital of Basel, we concluded from two retrospective studies that severe immunodeficient (SID) patients, particularly those fulfilling two or more SID criteria, are at high risk for progression to LRTI and poor outcome (Khanna et al. 2008). The proposed criteria of Shah et al. are similar to ours but also introduced age ≥ 40 years, myeloablative conditioning regimen, and use of corticosteroids within the prior 30 days (Shah et al. 2014). Thus, there is a need to further validate such risk strata.
in prospective trials to balance treatment versus overtreatment and adverse events, particularly for HCT patients with low and moderate risk for poor outcome. Even more, their translation to other respiratory viruses needs to be investigated (Khanna et al. 2009; Spahr et al. 2018).

Regarding future perspectives in the therapy of RSV infections, there are currently several compounds being investigated in clinical trials, which can be divided into four different classes: immunoglobulins, nucleoside analogues, small interfering RNAs, and fusion inhibitors (Xing and Proesmans 2019). Among them, presatovir (GS-5806), a novel, orally bioavailable RSV fusion inhibitor targeting the F protein, has been shown to be safe and to decrease the viral load, as well as the disease severity, in a challenge study of healthy adults (DeVincenzo et al. 2014).

14.3.2.5 Prevention

Given the high morbidity and mortality in this subset of patients, preventive measures remain the best approach to reduce the burden of RSV infection and to limit nosocomial transmission. Strict infection control precautions should be implemented, including respiratory isolation of infected patients, hand hygiene, wearing masks and gloves, and educational efforts targeting visitors and health care workers (Dykewicz, and National Center for Infectious Diseases CfDC, Prevention, Infectious Diseases Society of A, American Society for B, Marrow T 2001). These should be screened for signs and symptoms of respiratory illness and restricted from entering the unit if symptomatic. Passive immunoprophylaxis with monoclonal or polyclonal immunoglobulins may be considered in susceptible patients, especially in outbreak situations (Kassis et al. 2010). At present, there is no commercially available vaccine that can prevent RSV infection. Efforts are currently ongoing and focus on live attenuated and recombinant subunit vaccines.

### 14.3.3 Parainfluenza Virus

#### 14.3.3.1 Epidemiology

Parainfluenza virus (PIV) is an enveloped, single-stranded RNA virus belonging to the *Paramyxoviridae* family. PIVs are divided into four types (PIV 1–4) based on their genetic and antigenic characteristics. Similar to in the general population, most clinical infections in HM patients and HCT recipients caused by PIV-3 followed by PIV-1 (Spahr et al. 2018; Fry et al. 2006). PIV infections occur year-round; peak seasonal activity has been reported biennially between late September and December for PIV-1 and during the spring and summer months for PIV-3 (Spahr et al. 2018; Fry et al. 2006; Ustun et al. 2012).
The incidence of parainfluenza infections in HCT recipients is 1–4%. Significantly higher rates can be found in asymptomatic HCT recipients (Chemaly et al. 2014; Peck et al. 2007; Chemaly et al. 2012b). PIV infections can occur early post-transplant, as well as also very late post-HCT, which possibly reflects the high risk of nosocomial transmission, as well as the circulation in the community (Peck et al. 2007; Spahr et al. 2018; Ustun et al. 2012).

14.3.3.2 Clinical Presentation
The clinical presentation of PIV infections in patients with HMs or after HCT does not differ from the illness described in the general population. Importantly, asymptomatic carriage in HCT recipients is frequent and reported in up to 18% (Peck et al. 2007). Upper RTID is the most common presentation in HCT recipients occurring in 56–87% (Spahr et al. 2018; Chartrand et al. 2012; Chemaly et al. 2012c). Clinical presentation of upper RTID may include any combination of symptoms like fever, rhinorrhea, nasal congestion, sinusitis, headache, cough, wheezing, and coryza (Wendt et al. 1992; Johny et al. 2002). Lower RTID is reported in 15–45% (Nichols et al. 2001a; Ljungman 2001; Spahr et al. 2018) with symptoms like dyspnea, hypoxemia, and new or changing pulmonary infiltrates on chest radiography.

Factors associated with progression to lower RTID in patients after HCT include lymphopenia (<0.2 × 10⁹ cells/L) and neutropenia (<0.5 × 10⁹ cells/L), the use of glucocorticoid treatment (≥1 mg/kg bodyweight) (Nichols et al. 2001a; Chemaly et al. 2012b; Seo et al. 2014). Mortality rates range between 4% and 46% (Spahr et al. 2018; Safdar et al. 2010). Risk factors for mortality include presence of lower RTID, receipt of transplants from a mismatched related donor and infection within 3 months after HCT and coinfections (Martino et al. 2005; Nichols et al. 2001a; Schiffer et al. 2009; Ustun et al. 2012; Chemaly et al. 2012b; Safdar et al. 2010; Srinivasan et al. 2011; Marcolini et al. 2003; Hodson et al. 2011).

PIV may activate immunological mechanisms in the lung and has been associated with risk of bronchiolitis obliterans syndrome (BOS) development. BOS belongs in HCT recipients to one of the most frequent late manifestation of noninfectious pulmonary complication (Yoshihara et al. 2007). The diagnosis is based on spirometry measurements, bronchiectasis, and computer tomography (Filipovich et al. 2005). Significant airflow decline was documented in 86% of HCT recipients who developed PIV attributable lower RTID during 100 days after HCT (Erard et al. 2006).

14.3.3.3 Diagnosis
Multiplex NAT by reverse-transcriptase polymerase chain reaction (RT–PCR) is today considered the reference test for diagnosis of PIV because of its sensitivity of 100% and specificity of 95–98%, as well as its rapid turnaround time (Fan and Henrickson 1996). Culture tests are slow and labor-intensive, making it poorly suited to guide the management of acutely ill patients. Antigen detection kits are commercially available. The sensitivity is poor with 28–84%, which limits their widespread use (Bowden et al. 2010).

14.3.3.4 Treatment
There is currently no licensed antiviral agent for the treatment of PIV. Thus, if possible, deferral of high intensity chemotherapy and allogeneic HCT is recommended (Hirsch et al. 2013).

The data on the use of ribavirin remain controversial. It had no effect on viral shedding, symptom duration, hospital stay, progression to lower RTID, or mortality following PIV infections (Nichols et al. 2001a; Boeckh 2008; Chemaly et al. 2012b). Interestingly, in a recent study, ribavirin showed some benefit associated with overall mortality but not with deaths due to respiratory failure or in patients with bronchoalveolar lavage confirmed PIV lower RTID (Seo et al. 2014). On the other hand, a study performed at our institution found that 16 of 19 patients with lower RTID had a beneficial outcome with IVIG alone. Therefore, the use of IVIG is usually recommended at the University Hospital of Basel (Spahr et al. 2018). The impact of IVIG on overall outcome following PIV infection still needs to be determined. Very few novel antiviral drugs
have shown promising results for treating PIV infection in this patient population. DAS181 has shown efficacy against PIV in vitro and in vivo, and in three immunocompromised patients with respiratory infections, including two HCT recipients (Guzman-Suarez et al. 2012; Moscona et al. 2010; Chen et al. 2011). BCX2798 and BCX2855 have been found to have antiviral activity against PIV-3, significantly reducing pulmonary viral titers and mortality in rats when given intranasally within 24 hours of infection (Alymova et al. 2004).

### 14.3.4 Human Metapneumovirus

#### 14.3.4.1 Epidemiology

Human metapneumovirus (HMPV) belongs to the Pneumoviridae family, and it is closely related to RSV. Incidence rates range from 3% to 9% (Martino et al. 2005; Debur et al. 2010; Williams et al. 2005; Oliveira et al. 2008) and did not differ in HM patients from that observed for HCT recipients (Shah et al. 2016). Peak seasonal activity for HMPV infections has been reported yearly between December and May in the Northern hemisphere (Spahr et al. 2018). The importance of HMPV in transplant recipients has not been studied as thoroughly as RSV. Progression from upper to lower RTID has been reported in 21–40% (Williams et al. 2005; Renaud and Campbell 2011) with fatality rates of up to 80% in HCT recipients.

#### 14.3.4.2 Clinical Presentation

Disease manifestation of HMPV is indistinguishable from that of other respiratory viruses including rhinorrhea, sore throat, cough, and fever (Shah et al. 2016). Risk factors for HMPV lower RTID have not been studied in detail. One study examined 118 HCT recipients with HMPV infections and found significant association between steroid use at ≥1 mg/kg within 2 weeks prior to diagnosis, low lymphocyte count, and early onset of HMPV infection after HCT (before day 30 after HCT) and progression to lower RTID (Seo et al. 2016). Another study identified that high viral loads in bronchoalveolar lavage samples and viral RNA from serum samples of HCT recipients with pneumonia have been indicative of severe disease (Campbell et al. 2010).

#### 14.3.4.3 Diagnosis

HMPV infection is commonly diagnosed by NAT, as it is faster and more sensitive than viral culture or antigen detection. Most laboratories currently use commercial multiplex NAT that includes many community-acquired respiratory viruses in parallel.

#### 14.3.4.4 Treatment

No general recommendation for treatment can currently be made. Ribavirin is active in vitro and in vivo against HMPV (Wyde et al. 2003; Hamelin et al. 2006). Some centers consider treating HMPV lower RTID with ribavirin and/or IVIG despite the lack of supporting studies (Spahr et al. 2018; Renaud et al. 2013; Chu et al. 2014).

### 14.3.5 Influenza

#### 14.3.5.1 Epidemiology

The influenza virus belongs to the orthomyxoviridae family and is a segmented, single-stranded RNA virus. Classification of the virus into subtypes is based on its surface hemagglutinins and neuraminidases. Seasonal influenza activity can begin as early as October and continue into May in the Northern hemisphere. The seasonal prevalence of influenza infections in patients with HMs and recipients of HCT closely parallels the community-wide prevalence (Kmeid et al. 2016). The incidence of influenza infections in HCT recipients is 1.3–2.6%, and significantly higher rates may be seen during the peaks of influenza outbreaks in the community (Kmeid et al. 2016). Patients with HMs and HCT recipients have a higher risk of developing severe disease and higher rates of complications such as hospitalizations, prolonged shedding, emergence of resistance, and mortality compared to the general population (Khanna et al. 2009; Minnema et al. 2013; Nichols et al. 2004).
14.3.5.2  Clinical Presentation
Influenza is an acute, usually self-limited, febrile illness. In patients with HMs and HCT recipients up to 35% progress to lower RTID (Chemaly et al. 2006; Nichols et al. 2004).

Identified risk factors for progression to lower RTID or fatal outcome in patients after HCT include lymphopenia (0.1 × 10^9 cells/L and 0.2 × 10^9 cells/L) and neutropenia (< 0.5 × 10^9 cells/L), older age and preexisting lung disease (Khanna et al. 2009; Kmeid et al. 2016; Protheroe et al. 2012; Ljungman et al. 2011; Choi et al. 2011). Influenza-related mortality and all-cause mortality ranges between 4–9.3% and 5–12.4% (Kmeid et al. 2016; Choi et al. 2011).

14.3.5.3  Diagnosis
Rapid and sensitive methods to diagnose influenza are important to initiate early treatment and to reduce the risk of nosocomial transmission. Reliable diagnosis depends on the quality of the collected respiratory sample. Samples should be collected at the site of infections, for upper RTID nasopharyngeal swabs, nasal washings, and for lower RTID preferably bronchoalveolar lavages. Respiratory specimens should be placed in virus transport media and investigated within 24 hours.

Multiplex NAT and reverse-transcriptase polymerase chain reaction (RT–PCR) is today considered the reference test for diagnosis of influenza because of its high sensitivity and specificity, as well as its rapid turnaround time. In contrast, conventional tube culture, shell-vial culture, and rapid antigen detection have multiple limitations. Culture tests are slow and labor-intensive, making it poorly suited to guide the management of acutely ill patients. Numerous rapid antigen detection kits are commercially available that produce test results in <15 min. Although their quick turnaround time is appealing, widespread adoption of these kits in adults has been limited by their poor sensitivity.

14.3.5.4  Treatment
Antiviral treatment should be initiated promptly or empirically in this patient population when influenza infection is suspected. Previous studies have demonstrated that early administration of antiviral therapy has been associated with reduced risk of lower RTID, intensive care unit admission, hospitalization, and death at 6 weeks (Chemaly et al. 2012c; Choi et al. 2011). However, the beneficial effect of antiviral therapy is still observed even with a delayed start from symptom onset (Choi et al. 2011).

The two main groups of antivirals for influenza are the neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir), which are active against influenza A and B and the M2 inhibitors (amantadine and rimantadine), which only act against influenza A. With the increasing resistance against M2 inhibitors, the neuraminidase inhibitors are the most widely used anti-influenza drug in these patients. Oseltamivir is administered orally. In immunocompromised patients, increased doses of oseltamivir (150 mg twice a day, adjusted to the renal function) have been used, as was recommended for patients with the H5N1 avian influenza strain. Reduced absorption due to GVHD, mucositis, and concerns about increased development of resistance due to continued viral replication in these patients (Weinstock et al. 2003; Renaud et al. 2011) motivated higher dosing. However, the benefit on clinical outcomes has not been conclusively demonstrated (Khanna et al. 2009; Casper et al. 2010; Watcharananan et al. 2010). Zanamivir is administered by inhalation or intravenously. In a phase 3, double-blind clinical trial in hospitalized patients with severe influenza, two doses of intravenous zanamivir and oral oseltamivir were compared. The results do not show superiority of intravenous zanamivir compared with oseltamivir to hospitalized patients with influenza (Marty et al. 2017). Similarly, for peramivir significant clinical benefit was not demonstrated compared with placebo in patients hospitalized with suspected influenza infections (de Jong et al. 2014).

Several new agents are currently under investigation including DAS181, favipiravir, nitazoxanide, laninamivir octanoate, pimodivir, and baloxavir for influenza treatment. Studies are needed to evaluate their efficacy in patients with HM or after HCT.

As long as no better studies are available, therapy of uncomplicated influenza infection is based
on expert opinions: most authors use oseltamivir 75 mg twice daily, others suggest higher dosage (150 mg bid), with adjustment to renal function. The intravenous route for antiviral agents is preferred in patients with gastrointestinal GVHD or LRTID, on mechanical ventilation, or requiring bilevel positive airway pressure to circumvent the bioavailability issues. Concerning duration, most experts recommend continuing antiviral therapy until viral replication has ceased, which typically takes longer in this patient population than the 5 days of therapy recommended for immunocompetent patients (Casper et al. 2010).

14.3.5.5 Prevention
The updated guidelines of the American Society of Bone Marrow Transplantation recommend annual inactivated influenza vaccination before the beginning of the influenza season and before transplantation or 4–6 months following transplantation (Tomblyn et al. 2009). The vaccine should be administered prior to the onset of the influenza season to avoid new infections and related complications. The main two contraindications for influenza vaccine are febrile illness and severe allergy to eggs.

During outbreaks, daily chemoprophylaxis with strain-specific anti-influenza antiviral drug has been recommended in HCT recipients (within 24 months after transplant, with GVHD or taking immunosuppressive therapy) by the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (Tomblyn et al. 2009; Fiore et al. 2008). However this strategy may lead to the selection of resistant influenza strains, as seen during the 2009/H1N1 pandemic (Renaud et al. 2011; Baz et al. 2009). At our institution, we perform multiplex PCR in exposed patients, and if negative, we recommend treating HCT recipients for 5 days (75 mg twice daily).

14.3.6 Rhinovirus

14.3.6.1 Epidemiology
Human rhinoviruses (HRV) are members of the *Picornaviridae* family and are classified into three species, HRV-A, -B, and -C encompassing more than 160 serotypes. There are several biologic characteristics of HRV-C that differentiate it from HRV-A and -B. HRV-C readily infects upper and lower RTI, whereas HRV-A and -B species seem to be more limited to the upper RTI (Ashraf et al. 2013; Bochkov and Gern 2012). HRV infections circulate throughout the year (Turner 2010).

Due to the development of PCR assays for viral detection, HRV have become the most frequent virus detected from respiratory specimens in HCT recipients and can account for 25–40% of cases of respiratory viral infections in this patient population (Bowden 1997; Hassan et al. 2003; Milano et al. 2010).

14.3.6.2 Clinical Presentation
HRV is the most common cause of upper RTID in immunocompetent, as well as immune suppressed patients, presenting with afebrile, self-limited syndrome characterized by rhinorrhea, malaise, mild cough, and hoarseness (Arruda et al. 1997; Johnston 1995). The incubation period has been estimated as 1.9 days (95% CI, 1.4–2.4) (Lessler et al. 2009). Asymptomatic carriage in 13% in HCT recipients and prolonged shedding over 4 weeks are frequent (Parody et al. 2007).

HRV may also be associated with exacerbations of sinusitis, bronchitis, asthma, and pneumonia (Gern et al. 1997; Jain et al. 2015). In a prospective 5-year study at the MD Anderson Cancer Center, significant morbidity and mortality was reported (Ghosh et al. 1999). All patients with pneumonia had a fatal outcome. Lung biopsies/autopsies revealed findings consistent with interstitial pneumonitis and/or acute respiratory distress syndrome. It remains unclear if pneumonia is a direct cause of viral invasion of the lung tissue or by host responses in the lung. In a recent study by Seo and colleagues, overall mortality 90 days after HCT was significantly higher for patients with lower RTID than upper RTID (41% vs. 6%). The survival rate after lower RTID was not affected by the presence of co-pathogens. Moreover, lower RTID associated with HRV led to mortality rate comparable to that of RSV, PIV, and influenza (Seo et al. 2017).

Risk factors for mortality following HRV lower RTID included bone marrow stem cell source, low monocyte count, oxygen requirement at time of diagnosis, and steroid use >1 mg/kg prior to diagnosis (Seo et al. 2017).
14.3.6.3 Diagnosis
Diagnosis largely depends on multiplex NAT by RT-PCR. There are no antigen detection kits commercially available. Culture tests are labor-intensive and therefore only performed in specialized laboratories.

14.3.6.4 Treatment
There is currently no licensed antiviral agent for the treatment of HRV. Some agents have been evaluated in immunocompetent individuals including protease inhibitors and RNA synthesis inhibitors (Rollinger and Schmidtke 2011). Given the high prevalence and the severe course of this infection, there is a great need to develop drugs for prevention and treatment of lower RTID.

14.3.7 Coronavirus
14.3.7.1 Epidemiology
Coronavirus (CoV) are divided into group 1–like (CoV-229E and -NL63) and group 2–like (CoV-OC43 and -HKU1) agents that are molecularly distinct. Two additional CoVs associated with outbreaks are the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses (Self et al. 2016). A previous study has demonstrated that CoV is now the second most common virus identified from the upper respiratory tract in HCT recipients detected in 6.7–15.4%, but asymptomatic shedding may be as high as 41% (Milano et al. 2010). Cases of fatal pneumonia related to CoV without co-pathogens have also been reported mainly in HCT populations (Uhlenhaut et al. 2012; Pene et al. 2003; Oosterhof et al. 2010). CoVs occur year-round with a slight predominance in winter. Novel coronavirus (SARS-CoV-2) that causes atypical pneumonia (COVID-19) has raged in China since mid-December 2019 and spread rapidly worldwide. It has developed to be a Public Health Emergency of international concern. The genome of SARS-CoV-2 is similar to that of other coronaviruses and has four genes that encode the following structural proteins—the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins (Wu 2020). SARS-CoV-2 is a zoonotic virus, same as SARS-COV, the etiologic agent of the 2003 SARS outbreak with likely origin in bats, and likely involvement of another (intermediate) host animal such as the pangolin (Ye et al. 2020). Human-to-human transmission of SARS-CoV-2 is primarily via respiratory droplets and by direct contact with infected people and indirect contact with contaminated surfaces and objects. The mean incubation period of SARS-CoV-2 infection varies from 5 to 6 days and the range 1–14 days (WHO 2020). All age groups of humans are susceptible to SARS-CoV-2 infection but at particularly higher risk are the aged, immunocompromised individuals, and people with chronic underlying diseases. The case fatality rate of COVID-19 has been widely variable by country—from less than 0.1% to over 25% (WHO 2020).

During the preparation of this book chapter, very limited data on disease manifestation and course were available on SARS-CoV-2 in hematological-oncological patients and stem cell recipients. In adult patients with cancer or a hematological malignancy, COVID-19 resulted a risk factor for mortality together with age, sex, comorbidities, and tumor type (Liang et al. 2020; Lee et al. 2020). Noteworthy, a retrospective observational study during the pandemic months in Italy showed that adult hematological patients had a worse outcome than both the general population with COVID-19 and the patients with hematological malignancies but without COVID-19 (Passamonti et al. 2020). This dismal outcome was not confirmed in the pediatric population observed during pandemic in Italy and Spain where incidence, morbidity, and mortality were far lower (Bisogno et al. 2020; Faura et al. 2020). A prospective observational study conducted by Infectious Disease Working Party of European Society for Blood and Marrow Transplantation found that patients who underwent stem cell transplantation with COVID-19 were at increased risk for respiratory complication, admission to ICU, and mortality, this last being significantly associated with older age and performance status (Ljungman, personal communication).
### 14.3.7.2 Clinical Presentation

Upper RTID with rhinitis, pharyngitis, and laryngitis is the most common manifestation. Lower RTID is uncommon: patients rarely present with bronchiolitis, bronchitis, or pneumonia. A recent study analyzed 30 HCT recipients and 7 patients with HMs with lower RTID identified over a ten-year period. Twenty-one patients (60%) required oxygen therapy at diagnosis and 19 (54%) died within 90 days of diagnosis. Respiratory co-pathogens were detected in 21 episodes (57%). Mortality rates were not different between patients with and without co-pathogens (Ogimi et al. 2017).

Symptoms and signs of SARS-CoV-2 infection appear after an incubation period of 3–9 days. Importantly, during this period the patient is contagious, and it is estimated that 44% of transmissions occur before the symptoms arises (He et al. 2020). The clinical presentation can vary from an asymptomatic status to fever, fatigue, sore throat, myalgia, dry cough, dyspnea, nausea, dizziness, and less frequently, headache, diarrhea, vomiting, abdominal cramps. Interestingly, among minor symptoms, olfactory or taste disorders are reported up to 34% of patients, and in 91% of patient with taste disorder, this was present before hospitalization (Giacomelli et al. 2020). In pediatric patients, a milder course of infection is observed with a higher rate of asymptomatic cases, but up to 9% of patients may present a Kawasaki-like syndrome (Abrams et al. 2020). The most frequent abnormalities of laboratory parameters are lymphopenia, eosinopenia, thrombocytopenia, elevated AST/ALT, LDH, D-Dimer, C-reactive protein, and troponin (Siordia 2020). Pneumonia and acute respiratory distress syndrome are the most frequent complications, progression to dyspnea, hypoxemia, and/or mechanical ventilation being of 8–10 days from the beginning of symptoms. Although lung X-ray abnormalities are present in 30–60% of patients, lung CT scan resulted more sensitive and specific (Bai et al. 2020). The initial radiologic signs are groundglass opacities distributed to lower lobes followed by their bilateral diffusion and the appearance of patchy consolidation in two or more lobes (Pan et al. 2020). Other severe complications are myocardial injuries (acute coronary syndrome, myocarditis, heart failure, severe hypotension or shock, arrhythmias, pulmonary hypertension), acute kidney injury, and coinfections (RSV, Influenza A-B, Mycoplasma, Legionella, Pseudomonas, Haemophilus, Aspergillus) (Siordia 2020; Lansbury et al. 2020). Particularly SARS-CoV-2 associated pulmonary aspergillosis has emerged as an important co-infection associated with high mortality rates (Arastehfar 2020; Hoenigl 2020; Koehler 2020). Outcome of infection is dependent on the severity of COVID-19.

Severe COVID-19 disease is defined by symptomatic infection with respiratory rate >30 min and SaO2 saturation <95%. The overall mortality of severe COVID-19 is 5.6%, but it may vary according to the country (depending on local health and economical resources) and the phase of pandemic. It is associated with a rate of intensive care admission of 11% and a need of mechanical ventilation of 7%. The main risk factors for severe COVID-19 disease are preexisting factors related to the patient such as immunosuppression, malignancy, diabetes, vascular disease or hypertension and factors related to the severity or type of the clinical manifestations such as abdominal pain, nausea, vomiting, shortness of breath, and chest pain (Li et al. 2020a, b). The case fatality rate was higher for older patients, 8% for patients aged 70–79 years, 14% or more for patients aged >80 years, while it is 1% or less for patients aged <40 years, especially for pediatric and adolescent patients where death is episodic (Siordia 2020).

### 14.3.7.3 Diagnosis

Diagnosis largely depends on multiplex NAT by (RT-PCR). There are no antigen detection kits commercially available. Culture tests are labor-intensive and therefore only performed in specialized laboratories.

### 14.3.7.4 Treatment

There is currently no licensed antiviral agent for the treatment of CoV. Oral ribavirin was evaluated in retrospective studies for the treatment of MERS-CoV in immunocompetent individuals and decreased survival was observed in one study when compared to matched controls (Omrani et al. 2014; Al-Tawfiq et al. 2014).
The treatment of COVID-19 has changed rapidly from the beginning of pandemic because no specific drug was initially available, and the pathogenesis of tissue damage was not really understood. Supportive therapy has a key role to treat symptoms, to prevent respiratory or other organ failures, pulmonary thromboembolism, and coinfections, and it is based on the use of oxygen, noninvasive ventilation, mechanical ventilation, fluids, diuretics, inotropes, anticoagulants, and antibiotics. No specific antivirals are available for SARS-CoV-2. Remdesivir, an adenosine analog drug studied for Ebola, reduced the time to recovery and mortality, this last in a nonsignificant way, in a preliminary report from a double-blind randomized controlled trial although (Beigel et al. 2020). To reduce the inflammatory response and the tissue damage by a dysregulated cytokine secretion, corticosteroids, especially dexamethasone, IL-6 receptor antagonists, and IL-beta antagonists have been used (Lan et al 2020). The best evidence has been demonstrated for dexamethasone resulting in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support (Recovery 2020 https://www.nejm.org/doi/full/10.1056/NEJMoa2021436, https://www.recoverytrial.net/; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al. 2020). The use of convalescent plasma collected from SARS-CoV-2-recovered patients and administered early after the start of clinical symptoms has showed promising results (Li et al. 2020a, b; Farhat et al. 2020), and it is under investigation in several clinical trials.

At the time of publication of this book, no vaccine was available, but several types of vaccine were rapidly developing and assessed in phase I studies on volunteers (Marian 2020) as well as phase II and III studies and expected to become available to the public in 2021.

Current recommendation for prevention of spread of SARS-CoV-2 in HM and patients after HCT are based on guidelines, policies, and procedures decided by national authorities as well as local and institutional policies since the COVID-19 situation varies substantially between and within countries. Avoiding exposure by adhering to recommended hygiene procedures, isolation of SARS-CoV-2-infected individuals, and social or physical distancing especially for risk groups are currently the main prevention strategies utilized in most European countries (Ljungman et al. 2020).

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