Patients undergoing solid-organ transplantation (SOT) or allogeneic hematopoietic cell transplantation (HCT) are at increased risk for infectious complications. Community-acquired respiratory viruses (CARVs) pose a particular challenge due to the frequent exposure pre-, peri-, and posttransplantation. Although influenza A and B viruses have a top priority regarding prevention and treatment, recent molecular diagnostic tests detecting an array of other CARVs in real time have dramatically expanded our knowledge about the epidemiology, diversity, and impact of CARV infections in the general population and in allogeneic HCT and SOT patients. These data have demonstrated that non-influenza CARVs independently contribute to morbidity and mortality of transplant patients. However, effective vaccination and antiviral treatment is only emerging for non-influenza CARVs, placing emphasis on infection control and supportive measures. Here, we review the current knowledge about CARVs in SOT and allogeneic HCT patients to better define the magnitude of this unmet clinical need and to discuss some of the lessons learned from human influenza virus, respiratory syncytial virus, parainfluenza viruses.
enzavirus, rhinovirus, coronavirus, adenovirus, and bocavirus regarding diagnosis, prevention, and treatment.

**KEYWORDS** bone marrow transplantation, diagnosis, respiratory viruses, solid-organ transplantation, treatment, vaccination

**INTRODUCTION**

Patients undergoing allogeneic hematopoietic cell transplantation (HCT) or solid-organ transplantation (SOT) are at increased risk for infectious complications (1), among which community-acquired respiratory viruses (CARVs) are unique due to the frequent exposure pre-, peri-, and posttransplantation (2–5). Since, following successful transplantation, return to a normal life situation is among the key goals, the avoidance of CARV exposure becomes a challenging task.

Only a decade ago, the seasonal increase in patients presenting with symptoms and signs of respiratory tract infectious disease (RTID) was the main parameter defining “influenza-like illness” (ILI). The epidemiology of ILI was complemented by parallel increases of influenza virus A and B (IV-A and IV-B) detection in the population using classic techniques, such as direct antigen detection (DAD) or virus isolation in cell culture (VIC), for subtyping and vaccine prediction of IV-A and IV-B strains (6). Even though such sentinel testing was also available for human respiratory syncytial virus (HRSV) and human parainfluenzaviruses (HPIV) (7, 8), CARV-specific diagnostics in individual patients presenting with RTID were largely limited to academic medical centers (9) to serve patients at high risk for complications, such as neonates, patients with chronic heart and lung diseases, and transplant patients (10–13). The general landscape has fundamentally changed following the IV-A/H1N1/pdm09 pandemic in 2009 (14), rendering molecular detection of influenza and other CARVs by nucleic acid testing (NAT) widely available in general health care in resource-rich parts of the world (15). Moreover, multiplex NAT and (semi)quantitative NAT (QNAT) now provide comprehensive information about the diversity, dynamics, and impact of CARVs in the general pediatric and adult population (15–18). Apart from classical ILI, CARVs, including IV-A/B, HRSV, HPIV, human rhinovirus (HRV), human metapneumovirus (HMPV), human coronaviruses (HCoV), human bocavirus (HBoV), and human adenovirus (HAdV), are now known to cause overlapping manifestations of other RTIDs, including exacerbations of wheezing/asthma, croup, bronchiolitis, and pneumonitis/pneumonia (18).

For example, a large study of 6,073 children analyzed CARV-attributed symptoms and signs and compared the results with data obtained from a literature meta-analysis covering 49,858 patients (19). The authors concluded that although there were significant associations of, for instance, IV-A/B with fever or headache or of HRSV with cough, dyspnea, and wheezing, none of the RTID presentations were pathognomonic or even unique for a specific CARV. As no clinical algorithm exists that reliably predicts the etiology of CARV-RTID (19), laboratory testing has become essential for both timely diagnosis and intervention. A practical guidance document has recently been published outlining preanalytical and analytical considerations with recommendations regarding specimen collection and preferred laboratory testing for diagnosis of CARV causing acute RTID (20). The intelligent use of clinical and laboratory resources in real time will undoubtedly improve the management of CARV, which includes restricting empirical antibiotic administration, improving infection control and patient cohorting, as well as delivering specific antiviral treatment for CARVs, if available. Moreover, careful review of the data will serve to define patient populations that potentially benefit from future antiviral drug and vaccine development.

While the global impact of CARVs among lower RTIDs has been estimated to have increased in recent years (21) and the clinical impact of specific CARVs in the routine care of RTID is being addressed in ongoing investigations (22–24), the widespread availability of multiplex NAT results already raises questions about CARV prevention and treatment in transplant patients.

It has become clear that classic definitions of ILI and severe acute respiratory
infection (SARI) (25) are not helpful for CARV-mediated RTID in transplant patients (26–30). This is not only due to altered, often mitigated and delayed clinical presentation requiring more appropriately adapted case definitions (Table 1) but also reflects the overlapping epidemiology of CARVs, as summarized elsewhere (5).

Conventionally, upper RTID is defined as CARVs affecting anatomic sites above and including the larynx (and virus is detectable in samples from nose, pharynx, larynx, conjunctivae, or sinuses), whereas lower RTID includes trachea, bronchus, and bronchoalveolar sites. A frequently used definition of lower RTID uses a combination of detecting CARVs in respiratory fluids obtained from the lower respiratory tract by bronchoalveolar lavage (BAL) fluid (presumptive) or biopsy specimens (proven) together with a lowered oxygen saturation and new pulmonary infiltrates (5). Recently, detailed definitions for lower RTID by HPIV in allogeneic HCT patients have been proposed (31), which could be adapted for other CARVs, except that proven (histological evidence) and presumptive (laboratory detection in BAL fluid) lower RTID have been combined. Although this approach seems reasonable for retrospective studies and cohorts, it is clear that the level of evidence is not equivalent in the two situations. Moreover, highly sensitive NAT detection is faced with the potential for contamination of respiratory fluids from the lower respiratory tract by viruses replicating at high level in the upper respiratory tract, which require a thorough understanding of semiquantitative levels and relevant diagnostic thresholds (32, 33). Here, we review the current knowledge on diversity and impact of CARVs in SOT and allogeneic HCT patients to better define the magnitude of this unmet clinical need and to discuss some of the lessons learned from IV-A/B, HRSV, HPIV, and other CARVs regarding prevention and antiviral treatment.

### TABLE 1 Case definitions of CARV-RTID

| Case definition | Case classification |
|-----------------|---------------------|
| Case types      |                     |
| - Possible case: meeting the clinical criteria of RTID |
| - Probable case: meeting the clinical criteria of RTID and having an epidemiological link |
| - Presumptive case: meeting the clinical criteria of RTID and the laboratory criteria (laboratory confirmed) |
| - Proven case: histological evidence of CARV pathology |
| Clinical criteria |                     |
| - New onset of 1 of the following systemic symptoms/signs in the previous 5 days |
| - Fever |
| - Feverishness |
| - Myalgia |
| - Nausea |
| AND |                     |
| - At least 1 of the following 4 respiratory symptoms |
| - Cough |
| - Sore throat |
| - Shortness of breath |
| - Coryza |
| AND |                     |
| - Clinician’s judgment that the illness is due to an infectious agent |
| Epidemiological criteria |                     |
| - An epidemiological link to human-to-human transmission, such as |
| - CARV activity in the community |
| - Contact with visitor, another patient, or healthcare worker |
| Laboratory criteria |                     |
| - Detection of CARV in a clinical specimen, preferably from the site of clinical involvement, by at least 1 of the following |
| - Nucleic acid amplification testing (NAT) |
| - Virus isolation by cell culture (VIC) |
| - Direct virus antigen detection (DAD) |
| AND |                     |
| - Exclusion of a major role of other etiologies (another infectious agent or disease) |

*Modified from reference 5.*
Large comprehensive studies using multiplex NAT for symptomatic children and adults have linked a multitude of CARVs to partly overlapping clinical presentations of RTID (18, 19). In a cross-sectional study including nasopharyngeal swabs (71%) and BAL fluid (27%) from 116 symptomatic children and 155 adults attending tertiary care centers, the most frequently detected pathogen was HRV, followed by HRSV, IV-A/B, and HPIV (34). In a comprehensive longitudinal Swiss study of a total of 11,446 samples from 5,135 symptomatic children (N = 5,135) and adults (N = 6,316) tested by multiplex NAT from 2010 to 2015, HRVs (38%) predominated in both populations during the summer months (Fig. 1) and were seasonally replaced during autumn and winter by HRSV (17%), IV-A/B (11%), HCoVs (11%), HPIVs (9%), HPMV (5%), and, rarely, HAdV (4%) (35). However, the detection rates in children were around 70%, significantly higher than the 30% found in adults, despite the higher rates of underlying morbidities, including being immunocompromised, and the use of BAL fluid in the latter (35). Interestingly, similar CARV rates have been recently reported among mostly very young pediatric SARI cases in a resource-limited setting in Uganda, where the initial molecular IV-A/B testing of 8% was complemented by metagenomic deep sequencing (36, 37). Notably, little new information is available for human polyomaviruses, such as WU and KI, originally discovered in CARV-negative respiratory fluids (for a review, see reference 38), which may be due to the fact that they are not part of current multiplex NAT panels.

A study of adult patients admitted for ILI during the 2009–2011 season in Hong Kong indicated that HRSV was the cause of severe lower RTID in older adults, resulting in respiratory failure, prolonged hospitalization, and high mortality similar to that of seasonal influenza (22). The clinical impact of HPIV and the respective subtypes 1 to 4 was recently described in a 7-year retrospective U.S. study from Chicago covering 550 adults with a mean age of 60.4 years (23). Admission to intensive care units (ICUs) and death were seen in 129 and 28 patients, respectively, and there was no significant difference between patients above or below 65 years of age or those who were or were not immunocompromised (23). In a multicenter Italian study of 414 patients with community-acquired pneumonia requiring admission to intensive care, 226 (55%) had evidence of CARV-RTID, where IV-A was the most common virus in 140 patients (62%), followed by HRV (15%), HRSV (6%), IV-B (4%), HCoV (4%), cytomegalovirus (CMV; 4%), and HMPV (0.4%) (39). The underlying risk factors were similar to those known to contribute to excess mortality during influenza season, namely, older age and chronic
organ failures, especially heart and lung diseases (22). In a Dutch study of patients older than 65 years, IV-A and HRSV were associated with excess mortality, whereas IV-B and HPIV particularly affected those aged 75 years and older (40). In hospital-acquired pneumonia of nonventilated patients, CARVs were detected in 22.4%, a rate similar to that for bacterial pathogens, where the most common viruses were HRV, IV-A/B, and HPIV. A French and Belgian collaborative study reported that detection of CARVs by multiplex NAT was associated with higher ICU mortality, and this association was strongest for IV-A/B, HPIV, and HRSV (41). CARV detection independently predicted ICU mortality in patients with acute respiratory failure (41), an observation shared by other studies (42, 43). Together, the currently available evidence suggests that influenza and non-influenza CARVs represent recurrent, often seasonally exacerbating causes of RTID morbidity in the general population around the globe, requiring significant health care resources and causing excess mortality in the very young, in the very old, and in patients with chronic medical conditions of heart, lung, kidney, diabetes mellitus, and transplantation (21, 44, 45). Indeed, among 747 critically ill hematology patients, CARV-RTID was identified by multiplex NAT in 21.3%, occurring particularly in patients with malignancy and HCT and increasing the risk of ICU mortality by an odds ratio (OR) of 2.07 (95% confidence interval [CI], 1.22 to 3.50) (41).

**GENERAL ASPECTS OF CARVs IN THE TRANSPLANT POPULATION**

The impact of CARVs in transplant recipients depends on diverse factors, including the susceptibility of the host, the overall number (quantity) and effector functions (quality) of immune responses, and also the inoculum size and intrinsic pathogenicity of the specific infectious agent. Obviously, an allogeneic constellation between virus-infected cells and immune effectors contributes to impaired immune control while at the same time enhancing inflammatory (allo-)immune responses necessitating prophylactic and therapeutic immunosuppressive treatment (46). Not unexpectedly, CARVs have their highest impact in lung transplantation and allogeneic HCT (46). In addition, CARV epidemiology and transplantation intersect, seasonally exposing transplant patients to different CARVs in different periods of vulnerability (Fig. 2). For both SOT and allogeneic HCT, the underlying disease and other preexisting medical conditions and their treatments prior to transplantation may already cause significant impairment of the innate and adaptive immune defense, thereby increasing their vulnerability pre- and peritransplant, an aspect that is often underestimated (Fig. 2). Importantly, deferral of transplantation remains an option to be considered in patients with RTID pretransplant, particularly for those patients who are considered to be at higher risk of significant morbidity and mortality, e.g., after allogeneic HCT, if the underlying disease permits (5, 47). These considerations deserve explicit attention for pretransplant infections with IV-A/B, HRSV, HPIV, and HMPV in patients scheduled for allogeneic HCT. For SOT recipients, especially for lung transplant recipients, these issues are equally challenging and need to be balanced against the risk of transplant deferral, particularly in view of the organ donor shortage, the transplanted organ, and the availability of antiviral treatment (48, 49).

After allogeneic HCT, infectious disease (ID) events unfold their impact in three conceptual periods of vulnerability, defined first by conditioning and neutropenia (period I), followed by engraftment and immune reconstitution, e.g., from day +30 to day +100 (period II), and period III, beyond day +100 (Fig. 2). In clinical practice, these periods represent a continuum whereby the second and third period frequently overlap, and this needs to be integrated in the individual patient assessment. Key variables influencing the net state of immunodeficiency are the intensity and toxicity of conditioning (myeloablative versus nonmyeloablative; total body irradiation), the graft source (bone marrow, peripheral stem cells, and cord blood), the quantity and quality (CD34 count, related versus unrelated donor, and HLA mismatching), the transplanted donor immunity, and the desired and undesired immunologic consequences of graft versus malignancy and graft versus host, where the latter extends the vulnerable period due to immunosuppressive prophylaxis or therapy. However, neutropenia may be short
or missing in some protocols of nonmyeloablative conditioning, reduced intensity, and reduced toxicity conditioning (50–52).

After SOT, ID events can also be attributed to 3 periods (53), where nosocomial, surgical, donor-derived, and early herpesvirus infections predominate in the first 4 weeks posttransplant (period I), followed by reactivating latent, opportunistic, and environmental infectious agents during the subsequent periods II and III of 3 to 6 and up to 12 months posttransplant, respectively (Fig. 2). During the first 3 months after SOT, immunosuppression is generally highest and may be even more intense if lymphocyte-depleting induction, higher maintenance immunosuppression, and antirejection treatments are necessary for countering pronounced antidonor/graft immunity, e.g., as defined by panel-reactive antibodies and/or acute cell- or antibody-mediated rejection episodes. Therefore, antimicrobial immune responses may be significantly compromised in proliferation and effector functions that may extend far beyond the first 3 to 12 months posttransplant.

In SOT, the epidemiology of CARVs follows the local seasonal pattern seen in the general population, for example, in the Northern Hemisphere (Fig. 1), but differs in tropical and subtropical countries (36, 54). However, most SOT data are available from lung transplant patients due to the increased surveillance and clinical impact (33, 55–58). IV-A/B and HRSV occur predominantly in the winter months, HRV and HCoV predominate in spring and fall together with peaks of HPIV, while HAdV is detected year-round (55). Clinical disease is generally mild and self-limited in non-lung transplant recipients, although severe and progressive illness can be seen in any transplant patient. Young children, because of limited preexisting immunity and heavy exposure, are at greater risk for severe RTID and their complications (57). This also applies to patients that are more profoundly immunosuppressed due to the type of transplant and/or the receipt of lymphocyte-depleting agents within the past 3 to 6 months. Lastly, patients with severe hypogammaglobulinemia of <4.5 g/liter or lymphopenia of

**FIG 2** Timetable of infectious disease events after allogeneic hematopoietic cell transplantation and solid-organ transplantation. BKPyV, BK polyomavirus; C. *difficile*, Clostridium difficile; CARV, community-acquired respiratory viruses; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G+, Gram-positive; G−, Gram negative; HAdV, human adenovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HHV-6, human herpesvirus-6; HSV, herpes simplex virus; JCPyV, JC polyomavirus; PTLD, posttransplant lymphoproliferative disorder.
CARVs appear to be at heightened risk of severe and progressive CARV-RTID. However, initial signs and symptoms are less prevalent and are not specific to one particular CARV (59). Among IV-A/B-infected SOT recipients, for instance, only 64% had fever, 35% had sore throat, and 40% had myalgias (60). Notably, CARVs are associated with long-term consequences, particularly in lung transplant recipients (55, 61).

While there is concern that CARVs can trigger local alloimmune responses, i.e., acute rejection (62), other recent studies suggest that the inflammatory infiltrates noted on biopsy specimens during acute rejection are mostly antiviral responses helping to clear the infection (63). Following the viral cytopathic insult and the resulting impairment of the mucociliary clearance (Fig. 3), an increased risk of bacterial superinfection ensues, which extends to fungal complications in immunocompromised patients, mandating an increased index of suspicion in clinical care (22, 64). Furthermore, through the elicited innate and adaptive immune responses, CARVs have been discussed as a trigger of acute and chronic rejection, bronchiolitis obliterans syndrome (BOS), and chronic
lung allograft dysfunction (CLAD) (Fig. 3). The historic and current definitions of CLAD have been recently reviewed (65). Thus, a reduced forced expiratory volume in the first second of expiration (FEV1) or forced vital capacity (FVC) of less than or equal to 90% for 3 weeks or more raises the suspicion of CLAD. Subsequently, restrictive CLAD (restrictive allograft syndrome) is diagnosed when FVC is ≤80% for ≥3 weeks and can be distinguished from obstructive CLAD-BOS (FEV1 of ≥80%) for ≥3 weeks and mixed forms. These different terms are still used in the relevant CARV literature and will be presented as used in the original works.

With respect to the pathogenesis, it remains to be demonstrated by randomized specific antiviral, anti-inflammatory, and/or antifibrogenic interventions whether or not CARVs are causal or just a cytopathic inducer of an aberrant immune response and how these responses are aggravated in transplant patients across allogeneic immune barriers in lung and allogeneic HCT patients (Fig. 3). Most likely due to small sample sizes and study heterogeneities, a review and meta-analysis did not identify a significant association of CARVs with acute rejection but possibly with CLAD in lung transplant recipients (63). However, in a more recent large single-center retrospective study of 250 lung transplantations performed from 2007 to 2012, 50 (20%) developed CLAD during the median follow-up of 143 weeks, consisting of BOS in 33 (66%) and restrictive CLAD in 17 (34%). No surveillance testing was done, but 117 episodes of upper and lower CARV-RTID were identified by multiplex NAT in 79 (31.6%) patients, where the first episode occurred at a median of 133 days posttransplant (interquartile range [IQR], 63 to 441 days). In multivariate models, CLAD was independently associated with prior acute rejection (adjusted hazard ratio [HR], 2.16; 95% CI, 1.18 to 3.93; P = 0.01) and CARV-RTID (adjusted HR, 1.92; 95% CI, 1.07 to 3.45; P = 0.03). In a prospective cohort study from 2009 to 2014 enrolling 98 lung transplant recipients, CLAD was diagnosed in 38% at a median time of 20.4 months (IQR, 12 to 30.4) (61). In the time-controlled multivariate analysis, CLAD was associated with CARV-LRTID (HR, 3.00; 95% CI, 1.52 to 5.91; P = 0.002), acute rejection (HR, 2.97; 95% CI, 1.51 to 5.83; P = 0.002), and CMV pneumonitis (HR, 3.76; 95% CI, 1.23 to 11.49; P = 0.02) (61).

In allogeneic HCT, CARV exposure also follows the local epidemiology, placing significant emphasis on infection control measures inside and outside the hospital, particularly for neutropenic and lymphopenic patients during the winter months. In a seminal study of 122 HCT patients using the complete set of clinical and laboratory assessments, including DAD, VIC, and NAT, 30% developed CARV infections up to day +100 (26). HPIV were detected in approximately two-thirds of patients, followed by IV-A/B, HRSV, and HMPV in less than 10% each. Cough, rhinorrhea, or nasal congestion were leading clinical presentations and somewhat unspecific across all the different CARVs, but they were significantly more frequent among virus-positive than virus-negative patients. Fever above 38°C and myalgia only occurred in a third of HCT patients with IV-A/B or HRSV, emphasizing that standard ILI definitions cannot be applied (5). Interestingly, CARV loads were lower in patients without or with only one symptom/sign, suggesting that (semi)quantitative viral loads are of interest for clinical and virological follow-up (27, 66). Conversely, prolonged asymptomatic shedding of HRSV and HPIV has been shown to give rise to nosocomial outbreaks among in- and outpatients (26, 67–71). In a Spanish report, 36% of CARVs in lower RTID occurred between day +100 and 12 months posttransplant, and the mean time from HCT to HRSV infection was +466 days (IQR, 163 to 1,028) in a recent U.S. study (72). In a Swiss study of symptomatic allogeneic HCT recipients between 2010 and 2014 using comprehensive multiplex NAT, 419 (39%) CARV ID events were detected in 1,069 tests, where the leading pathogens were HRV in 21%, occurring year-round but peaking during summer, followed by Paramyxovirus and Pneumoviridae (14% HPIV, HRSV, and HMPV) and IV-A/B (3%) (73). Notably, RTID caused by HRSV, HMPV, and HPIV occurred during the cold seasons at a median time of days +382, +504, and +628 after allogeneic HCT (73), respectively. A large retrospective multicenter study of 1,560 cases of pediatric HCT identified at least one CARV infection in 259 patients (16.6%) occurring until 1 year posttransplant and typically affected younger children (4.8 versus 7.1 years;
Importantly, 48% required some respiratory support, 14% suffered significant pulmonary sequelae, and all-cause and attributable case fatality rates within 3 months were 11% and 5.4%, respectively. Independent risk factors for morbidity and mortality were CARV infection within 60 days of HCT, need for respiratory support, and steroid administration within 1 week of RTID. Together, various factors reflecting impaired immune control were linked to progression to lower RTID and mortality, in line with the notion that vulnerability to CARVs extends beyond day +100 and may be approximated by clinical and laboratory parameters attempting to capture the degree of vulnerability as either immunodeficiency grading (moderate, severe, and very severe) or as immunodeficiency score index (27, 66, 75–78) (Table 2). A few studies have compared both tools (73, 77, 78) and found a significant overlap in predicting progression to HRSV lower RTID and mortality despite the fact that only portions of the parameters were identical. Similar grading tools have not been proposed for lung transplant recipients.

### CARV-SPECIFIC ASPECTS IN TRANSPLANT PATIENTS

#### Influenza Viruses

According to the current taxonomy, the Orthomyxoviridae family contains the genus Influenzavirus and four species, named A, B, C, and D, with the proposed acronyms IV-A, -B, -C, and -D (https://talk.ictvonline.org/taxonomy/). IVs are enveloped virions in helical capsids of approximately 100-nm diameter that contain 7 to 8 single-stranded RNA segments of negative polarity in a nucleoprotein complex, each carrying an RNA-dependent RNA polymerase. IV-A and -B cause the bulk of the seasonal RTID outbreaks during the respiratory virus seasons, typically from November to May in the Northern Hemisphere (Fig. 1) and May to October in the Southern Hemisphere (25). Rates of infection among transplant patients vary depending on the specific population, type of immunosuppression used, and the circulating influenza strain. Likewise, seasonal variability in vaccine efficacy contributes to the respective rates in the transplant population. Influenza can be complicated by progressive disease, including viral pneumonia, secondary bacterial and fungal pneumonia, and extrapulmonary complications. Such severe and progressive complications are more common among allogeneic HCT and lung transplant recipients. To prevent IV-A/B infections, current guidelines recommend respiratory hygiene, influenza vaccination of recipients and their close contacts, and contact and droplet precautions in the health care setting for potentially infected patients (79–81). The vaccine immunogenicity is reduced in SOT and HCT patients, particularly when administered within periods I and II posttransplant (60, 82–85). Early antiviral therapy with one of the neuraminidase inhibitors (oseltamivir, peramivir, or zanamivir) has been associated with reduced risk of hospitalization, reduced progression to pneumonia, reduced need for ICU-level care, and reduced mortality (60) (Fig. 4).

### TABLE 2 Clinical criteria proposed to identify patients undergoing allo-HCT at risk for complicated CARV lower RTID caused by HRSV, HPIV, or IV-A/B

| University Hospital Basel immunodeficiency grading system | MD Anderson Cancer Center immunodeficiency scoring index |
|---------------------------------------------------------|--------------------------------------------------------|
| **Criterion or parameter**                             | **Score**                                               | **Criterion or parameter**                             | **Score** |
| Neutropenia, <0.5 × 10⁹/liter                          | 1                                                      | Neutropenia, <0.5 × 10⁹/liter                          | 3         |
| Lymphopenia, <0.1 × 10⁹/liter                          | 1                                                      | Lymphopenia, <0.2 × 10⁹/liter                          | 3         |
| Allo-HCT <6 months ago                                 | 1                                                      | Preengraftment or allo-HCT <1 months                   | 1         |
| GVHD of ≥2 or requiring treatment                      | 1                                                      | GVHD (acute/chronic)                                   | 1         |
| T-cell depletion <3 months prior to CARV Dx            | 1                                                      | Corticosteroids                                         | 1         |
| B-cell depletion <3 months prior to CARV Dx            | 1                                                      | Myeloablative conditioning                              | 1         |
| Hypo-globulinemia, <4.5 g/liter                        | 1                                                      | Age, >40 yr                                            | 2         |
| Maximal                                                | 7                                                      | Maximal                                                | 12        |
| Moderate (MID)                                         | 0                                                      | Low risk                                               | 0–2       |
| Severe (SID)                                           | 1                                                      | Moderate risk                                           | 3–6       |
| Very severe (verySID)                                  | 2–7                                                    | High risk                                              | 7–12      |

*Allo-HCT, allogeneic hematopoietic cell transplantation; CARV, community-acquired respiratory virus; Dx, diagnosis; GVHD, graft-versus-host disease; HRSV, human respiratory syncytial virus; HPIV, human parainfluenzavirus; IV-A/B, influenza virus A or B; RTID, respiratory tract infectious disease.
In a phase 3 trial, the recently FDA-approved IV-A/B polymerase PB2 inhibitor baloxavir caused faster reductions in IV-A/B loads and alleviated symptoms 1 day earlier than placebo in uncomplicated influenza (86), but data on high-risk and transplant patients are not available so far. Seasonal antiviral prophylaxis can be considered for those patients who are expected not to respond to influenza vaccine or where vaccine is not available (87). While postexposure prophylaxis is discussed for those at high risk of complications, the risk of resistance emergence during the incubation phase and during presymptomatic replication typically favors the use of the higher treatment dose or monitoring the patient for the onset of symptoms to start early therapy (88).

**Specific aspects of influenza in SOT.** Presentation of influenza in the SOT population in those coming to clinical attention in a recent study is associated with reduced incidence of classic symptoms: 64% had fever, 35% had a sore throat, and 40% had myalgias, while about 85% had cough (60). Radiologic evidence of pneumonia is present in 22%, and bacterial coinfections were rare at this early stage. Most will require hospital admission within a median of 6 days, suggesting that hospitalization is generally needed for more than just observation early in the clinical course. Very severe infection, requiring ICU-level care (11%) or mechanical ventilation (8%), can occur in the minority of patients, but mortality in SOT recipients remains sizable (2% to 4%) (29, 60).

**Prevention and management of influenza in SOT patients.** The primary approach to prevention of influenza is through the use of inactivated vaccines covering IV-A/H1N1 or -A/H3N2 combined with one IV-B strain (trivalent) or with two IV-B strains.
(quadrivalent) of the circulating IV-A/H1N1, -A/H3N2, -B/Victoria, and -B/Yamagata viruses. The impact of the quadrivalent IV-A/B vaccine became evident during the 2017/2018 season, when the dominant subtype in Europe was -B/Yamagata, which was not present in the trivalent vaccine. Hence, the quadrivalent IV-A/B vaccine should be preferred, although there are no head-to-head comparisons in the transplant setting. Adjuvanted IV-A/B vaccines appear to be safe in transplant patients, and some studies report a similar response to unadjuvanted vaccines (89, 90). However, compared to results in healthy controls, influenza vaccines result in lower antibody responses (geometric mean) in transplant recipients (91). Since the peak antibody titer is assumed to correlate with the longevity of IV-A/B protection, transplant recipients may have waning protection later in the season, particularly if the vaccine is given early (51, 52). As such, optimal vaccine timing would be as late as possible before the start of the season, for example, in late October to early November in the Northern Hemisphere. Recent clinical data suggest that IV-A/B vaccines not only reduced the frequency of infection and the respiratory viral loads but also protected against progression to more severe disease (60). Intradermal IV-A/B vaccine does not appear to result in improved protection responses in lung transplant recipients and is therefore not preferred over standard injectable vaccine (92). Use of high-dose vaccines has been associated with improved seroconversion and higher postimmunization geometric mean titers (93, 94). Whether or not high-dose vaccines should indeed be preferred requires larger, preferably multicenter studies. Alternatively, a secondary booster dose of IV-A/B vaccine was shown in some studies to improve vaccine responses (51). While head-to-head studies between high-dose and booster vaccines have not been conducted, interpretation of the limited data would favor the high-dose approach.

For patients who would be predicted to have a poor IV-A/B vaccine response (i.e., recent transplant, intense immunosuppression, and use of lymphocyte-depleting therapy), seasonal antiviral prophylaxis can be considered. This approach was associated with reduced incidence of NAT (1.7% versus 8.4%)- and VIC (<1% versus 3.8%)-defined viral breakthrough infections yet without evidence for dominant NAI resistance mutations (95). While generally well tolerated, clinical experience demonstrates challenges in getting the prescription approved by health insurance and a low incidence of discontinuation because of intolerance. Postexposure prophylaxis using the lower prophylactic dose is not recommended, since transmission may have already occurred and the risk of clinical and virological influenza breakthrough should be clearly avoided, especially in immunocompromised patients. Instead, empirical treatment using the therapeutic dosing (i.e., 10 days of twice daily [BID] oseltamivir) should be considered for high-risk patients (i.e., lung transplant or recent transplant or rejection treatment) and close observation of low-risk patients with early treatment when they develop symptoms.

Most of the currently available experience for the treatment of influenza in transplant patients stems from NAIIs, since all circulating IV-A/B strains show adamantane (M2-inhibitor) resistance. Prospective studies have not been performed in the transplant setting to define the optimal dose, route, or duration of antiviral NAI therapy or the role of combination therapies. NAI therapy is associated with reduced mortality, reduced progression to pneumonia, reduced duration of shedding, and, among lung transplant recipients, reduced risk of development of chronic lung allograft dysfunction (60, 96). Early therapy, defined as initiation in less than 24 to 48 h after symptom onset, is associated with the best outcomes in uncomplicated influenza infection of healthy nonimmunosuppressed patients as well as transplant patients (29, 97, 98). Nonetheless, therapy appears to be beneficial in this population beyond 48 h, most likely due to the higher and more prolonged viral replication load (Fig. 2), and all symptomatic transplant patients should be treated (28, 29, 97, 98). Given the atypical and mild degree of symptoms, IV-A/B should remain in the differential diagnosis for any patient with fever or any respiratory or systemic symptoms consistent with influenza. Antivirals should be initiated as soon as IV-A/B is considered in the differential diagnosis (Table 1, possible or probable case) and should not wait for confirmation of infection with diagnostic
testing, especially when there is documented local activity in the community (Table 1, probable or presumptive case). In this setting, molecular point-of-care testing with high sensitivity and specificity and turn-around times of less than 20 min become of interest (99–101). If testing is negative by sensitive validated NAT, antivirals can be discontinued; in lung transplant recipients or patients with evidence of lower RTID or outright pneumonia, testing of lower airway specimens should be performed before stopping therapy, since discordant viral and clinical activity in the upper and lower airways has been documented (32). Similar to HCT recipients (27), influenza replication in SOT recipients tends to be prolonged compared to that in healthy adults, particularly among those with severe illness requiring ICU-level care (60), which requires appropriate testing and infection control measures. Given prolonged shedding, most experts recommend at least 10 days of therapy. Higher-than-usual doses (i.e., oseltamivir 150 mg per os BID) may be associated with reduced risk of resistance emergence and should also be considered in immunocompromised patients with influenza B due to the higher inhibitory concentration of IV-B and slower viral load decline (28, 102, 103).

Donor-derived influenza is a rare complication in SOT. Generally, IV-A/B replication is restricted to the respiratory tract except in rare cases where viral RNA is detected in blood, as viremia is present in patients with very severe seasonal influenza or possibly in patients infected with novel or avian viral strains (104). Viremia typically declines by several orders of magnitude to undetectable levels with the use of antiviral therapy. If the donor has detectable IV-A/B, current guidelines recommend that the lungs should not be used until completion of antiviral therapy. For donors infected with novel or avian influenza, intestinal transplants should be avoided (104). Other organs generally can be used from IV-A/B-infected donors, conferring practically zero risk of transmission. If non-lung recipients experience donor-derived influenza, atypical presentation may be more common, since systemic symptoms may predate respiratory symptoms; hence, testing of blood and respiratory secretions should be considered (56).

**Specific aspects of influenza in allogeneic HCT.** Clinical presentation of influenza in allogeneic HCT and SOT patients is similar to that demonstrated in a recent prospective study, in which cough was the leading symptom in 90% of patients, whereas only 70% had fever, 55% rhinorrhea, 40% sore throat and gastrointestinal symptoms, and 30% myalgia or headache (60). As pointed out earlier, the onset of symptoms and signs appears to be significantly less overt in HCT patients shortly after transplantation (26, 27, 105). Most patients typically will be symptomatic for 10 days, followed by a period of prolonged asymptomatic shedding. Absolute lymphocyte count (ALC) at diagnosis correlated inversely with viral shedding (P < 0.001) (27). Similar to observations in children (106), consecutive infections of IV-A followed by IV-B have been observed in approximately 10% of patients, and one-third of cases occurred despite prior vaccination (27). However, data from two prospective observational studies indicate that vaccination was associated with lower viral loads and lower risk of progression to lower RTID (60, 107). About a quarter of high-risk HCT (i.e., those with infection early posttransplant, profound lymphopenia, and/or therapy for acute or chronic graft-versus-host disease [GVHD]) progress to pneumonia typically after a week of symptomatic upper RTID (Fig. 3). Mortality rates of up to 25% have been reported in HCT patients with lower RTID (108). Retrospective comparative studies suggest more severe outcomes of the pandemic influenza A/H1N1/pdm09 than previous seasonal IV-A, with more patients suffering from lower RTID, hypoxemia, and mortality, where these outcomes were predicted by profound lymphopenia and delayed antiviral therapy (109, 110). However, another large retrospective analysis of influenza A/H1N1/pdm09 diagnosed in 286 HCT patients (222 allogeneic, 64 autologous) at 18 months posttransplant reported cough, fever, and rhinorrhea in 85%, 81%, and 49%, respectively (30). Lower RTID was seen in 33% of patients and correlated with lymphopenia, defined as <200 per μl (OR, 2.5; P < 0.001), and older age (OR, 1.025; P = 0.002). A death rate of 6.3% was noted, which was associated with neutropenia (P = 0.03) and older age (P = 0.04) (30). Clinical criteria have been proposed to identify allogeneic HCT patients at increased risk of IV-A/B progression to lower RTID and mortality using the Basel immu-
node deficiency grading (27, 73) or the MD Anderson immunodeficiency score index (ISI) (76, 77, 107, 111) (Table 2).

**Prevention and management of influenza in allogeneic HCT patients.** The primary approach to prevention of influenza is through the use of inactivated vaccines. Patients in the first 6 months following myeloablative stem cell transplants or within 7 days of receipt of conventional chemotherapy are unlikely to respond to current influenza vaccines. However, earlier vaccination is still considered if allogeneic HCT takes place in an outbreak situation or within the ongoing season (85). Independently, vaccination of close contacts should be strongly considered, and careful infection prevention through the use of contact and droplet precautions in the health care setting should be utilized (81). High-dose influenza vaccine appears to result in improved vaccine responses in pediatric HCT patients (112) and can be considered in adults (113). A study is currently ongoing to assess the efficacy of high-dose vaccine in adult HCT recipients (ClinicalTrials registration number NCT03179761) and in pediatric HCT recipients (ClinicalTrials registration number NCT02860039). As described above, seasonal antiviral prophylaxis can be considered for patients who would be predicted to have a poor vaccine response, whereas postexposure prophylaxis should use therapeutic doses (95).

Prospective studies have not been performed in the transplant setting to define the optimal duration of antiviral therapy, the optimal dose or route of therapy, or the role of combination therapies. Influenza replication tends to be prolonged compared to that in healthy adults, particularly among those with pneumonia or severe illness requiring ICU-level care (27). Antiviral therapy is associated with reduced mortality, reduced progression to pneumonia, and reduced duration of shedding (108, 109). Among allogeneic HCT patients, especially those with poor T-cell reconstitution having received alternative donor transplants, T-cell depletion, and GVHD, antivirals should be initiated as soon as influenza is considered in the differential diagnosis and should not wait for diagnostic IV-A/B testing, but a rapid test of sufficient sensitivity and specificity should be sought (20). If positive, antiviral therapy should be continued for at least 10 days or longer if patients have prolonged viral shedding along with clinical symptoms.

Although neuraminidase inhibitor therapy begun <48 h of symptom start was shown to be clinically effective during a short course of 5 days in immunocompetent adults, drug resistance variants can be detected as minority species by the time the immune system is able to start clearing the virus. Recently, the Committee for Medicinal Products for Human Use of the European Medicines Agency has recommended the marketing of intravenous zanamivir for patients with severe influenza for compassionate use (114). Further studies of IV-A enumerated oseltamivir resistance on day +1 of treatment in 3.6% of patients, which reached 11.8% in 1- to 5-year-old children (115, 116). Resistant IV-A/B showed delayed clearance of 8 versus 11 days but had little effect on symptom resolution. The expected synergy of NAI and immune control or vaccination in immunocompetent patients (Fig. 3 and 4) was experimentally confirmed in the well-established influenza ferret model, an issue also relevant in the care of transplant patients (117). Similarly, experimental ferret models supported a therapeutic effect of ribavirin when administered early with respect to viral loads and clinical symptomatology (118). Although the effect of ribavirin for prophylaxis and treatment of IV-A/B RTID is not well documented, combination therapy with amantadine, NAI, and ribavirin has demonstrated a more rapid decline in viral titers, which has not translated into clinical benefit in immunocompetent patients (119, 120), most likely because of innate and adaptive inflammatory components. This may be different in the HCT setting showing prolonged viral shedding (27), where anecdotal success of combination therapy has been reported for NAI-resistant cases (121). Thus, combinations of NAI and ribavirin cannot be generally recommended but would be considered in otherwise desperate single cases. Reliable data regarding the combination therapy of NAI with the novel cap-snatching inhibitor baloxavir are pending, but preliminary data suggest that this is a viable and potent combination (122, 123). Monotherapy with baloxavir in immuno-
compromised patients may not be preferred at the present time of limited clinical
evidence because of the potential risk of resistance emergence.

Approved therapies that are currently recommended for the treatment of influenza
A and B include the neuraminidase inhibitors zanamivir (inhalation approved globally;
intravenous administration approved only in Europe), oseltamivir (globally approved),
peramivir (widely approved), and laninamivir (approved in Japan and South Korea). Novel
antiviral therapies for the treatment of influenza include three polymerase-targeted
inhibitors, favipiravir (approved with limited indication in Japan), pimodivir (not ap-
proved), and baloxavir (approved in Japan and the United States, pending in Europe)
(Table 3). Some of the new drugs appear to have the potential for greater reduction in
viral titers and show synergy when combined with neuraminidase inhibitors, which
may not translate into clinical benefit in immunocompetent patients (124), as discussed
above, but may do so in SOT or HCT populations, though study results are currently
lacking. Presumably, they may provide benefit in combination with neuraminidase
inhibitors, in preventing resistance emergence or reducing viral shedding. Further, they
may provide an alternative for the treatment of resistant variants. However, the rate of
resistance emergence of the newer drugs in otherwise healthy adults and children may
also challenge their use in immunocompromised populations (86). A number of mono-
clonal antibodies are in early stages of clinical development and may also prove to be
beneficial if they advance further with regulatory approval. Plasma and immunoglob-
ulin products with high influenza titers have been studied in patients with severe
influenza pneumonia and are associated with reduced mortality and the need for
ventilators (125). As such, these approaches may be considered adjunctive therapy in
critically ill transplant patients.

**Human Pneumo- and Paramyxoviridae**

Although previously grouped together as Paramyxoviridae, an increasing number of
viral genome sequences have led to the taxonomic separation of the Pneumoviridae
and Paramyxoviridae families (https://viralzone.expasy.org/). Whereas the former in-
cludes the genus of human Pneumovirus with the species HRSV and HMPV, the latter
includes the respiroviruses HPIV-1, -2, -3, and -4. The virions of both families are
enveloped helical particles of 150-nm diameter containing a single-stranded 15-kb-long
RNA genome of negative polarity in a nucleoprotein-polymerase complex. The different
families are morphologically similar and cannot be distinguished by transmission
electron microscopy (https://viralzone.expasy.org/). Measles and mumps virus are not
considered CARVs, despite similar virology and transmission modalities, including
severe lower RTID/pneumonia as a feared short-term complication, especially among
adults. However, measles and mumps are examples of the protective potential of
vaccination, and vaccines are under current development for HRSV and HPIV. At the
same time, they illustrate the principle limitation of live-attenuated vaccines being
contraindicated in transplant patients. Modeling studies suggest that the epidemi-
logic dynamics of HRSVs, HMPV, and HPIV involve limited cross-immunity (126), and human-derived monoclonal antibodies directed against the prefusion conformation of the F-protein cross-neutralizing HRSV and HMPV have been characterized molecularly, in cell culture, and in murine models (127).

Human respiratory syncytial virus. There are two antigenic types, called HRSV-A and -B, which Cocirculate in the community but may differ locally in their relative abundance. Children <5 years of age are key drivers of transmission and disease, putting immunocompromised contacts in families and institutions at high risk for infection (5, 45). In SOT, HRSV infection has the highest impact in the first year posttransplant, except in lung transplant recipients, where the detection rates remain similar over time posttransplant (55, 128). Among HCT recipients, between 2% and 17% of recipients are diagnosed with HRSV infections (12, 26, 73, 129, 130). Progression to lower-tract infection occurs relatively quickly after onset of upper-tract symptoms and is more common among lung transplant recipients and allogeneic or cord blood transplant recipients, and increased risk of progression has been noted for infections occurring early posttransplant subsequent to lymphocyte-depleting antibody therapy or in patients with pronounced lymphocytopenia (5). Mortality is greatest among HCT recipients, with lower RTID showing average rates of about 25%, although lower mortality rates have been reported more recently (66, 73, 129).

Currently, there are no vaccines available for the prevention of HRSV, but several candidate vaccines are in advanced clinical development. Prevention is based on rigorous infection control and contact precautions. Several reports have described the devastating impact of nosocomial HRSV transmission, particularly in hematology and HCT centers (69). Palivizumab is a monoclonal antibody directed at the abundant postfusion F-protein of HRSV. Palivizumab should be considered for infants that are born at <or= 28 weeks 6 days gestational age and <12 months at the start of HRSV season, who have chronic lung disease of prematurity, and who have hemodynamically significant chronic heart or premature lung disease necessitating medical therapy within 6 months prior to the beginning of the HRSV season (131). Palivizumab prophylaxis can be considered in children <24 months who are immunocompromised or have undergone cardiac transplantation for the HRSV season (131). Earlier studies suggested that many transplant centers were using palivizumab for the prevention of HRSV in children at risk, but more recent data suggest that there is little increase in disease incidence when palivizumab use is more restricted (132).

(i) Specific aspects of HRSV in SOT. No specific antivirals are licensed for prevention or treatment of HRSV infection. In the lung transplant setting, ribavirin has become the standard of care, typically in addition to steroids, despite the lack of randomized trials demonstrating efficacy (133). Early studies administered systemic ribavirin intravenously (33 mg/kg of body weight on day 1 and then 20 mg/kg/day in 3 divided doses until resolution of symptoms) (134). As the intravenous formulation of ribavirin has been difficult to obtain and aerosolized ribavirin is associated with high costs and safety issues for pregnant health care staff, many centers have begun using systemic ribavirin perorally for treatment of HRSV in SOT. A retrospective analysis compared the outcomes of oral ribavirin versus the best supportive care for paramyxovirus infections in lung/heart-lung transplant recipients. Oral ribavirin treatment (15 to 20 mg/kg/day in 2 divided doses for 14 days) was associated with better recovery of graft function at 30 days postinfection (84% versus 59%; P = 0.02) and reduced development of new-onset BOS within 6 months (5% versus 24%; P = 0.02) (135). Thus, oral ribavirin was adopted as a presumed standard of care, often combined with intravenous immunoglobulin (IVIG), as it was found to be a well-tolerated alternative to intravenous or inhaled ribavirin (136, 137). However, appropriately sized randomized controlled trial data are needed to document safety and efficacy of systemic ribavirin (oral and/or intravenous) in SOT and in lung transplant recipients in particular.

(ii) Specific aspects of HRSV in allogeneic HCT. To date, there have not been large, prospective, randomized trials establishing a specific HRSV therapy in HCT patients. Nonetheless, there is a large body of case reports, case series, and retrospective...
analyses investigating aerosolized or systemic (oral or intravenous) ribavirin, antibody-based therapy (standard IVIG, high-titer HRSV Ig, or palivizumab), or combinations thereof. A summary compilation of outcome data suggested that any treatment was associated with less progression to lower RTID ($P < 0.001$) and less mortality ($P < 0.001$) (129). However, there was no significant difference between individual approaches of aerosolized ribavirin, aerosolized ribavirin plus immunoglobulins, or systemic ribavirin plus immunoglobulins with respect to progression to lower RTID, whereas mortality rates were significantly higher for aerosolized ribavirin alone or systemic ribavirin than for aerosolized ribavirin plus an antibody-based therapy (129). This analysis is faced with uncertainties regarding patient bias, time point of diagnosis, late decisions regarding treatment initiation, and the underlying medical conditions, e.g., preferential treatment of sicker cases with more advanced HRSV lower RTID, whose outcome cannot be significantly modified (Fig. 3). Given the absence of better evidence, the principle approach of administering oral ribavirin plus immunoglobulins at an early stage of HRSV upper RTID in severely immunodeficient (SID) patients was introduced in some centers more than 10 years ago (138, 139) in order to reduce HRSV-associated mortality compared to rates seen in historic controls and earlier reports (66). Compared to those of HCT patients with moderate immunodeficiency (MID), patients with SID and very severe immunodeficiency (verySID) (Table 2) showed more prolonged symptoms and HRSV shedding (66). Subsequently, some limited but dramatic evidence was obtained during an HRSV outbreak in the winter season of 2010/2011 in a hematology and transplant unit affecting, in a short time, 56 patients, including 16 allogeneic HCT patients, of whom 40 developed HRSV lower RTID and 14 died. In line with the SID criteria, fatal outcome was associated with hypogammaglobulinemia (OR, 11.8; $P = 0.007$), whereas rapid delivery of systemic ribavirin was protective (OR, 0.14; $P = 0.02$) (69). In a large retrospective analysis of 280 allogeneic HCT patients in a single center over 2 decades (140), aerosolized ribavirin (91 with and 66 without adjuvant immunoglobulin) administered to 157 patients at the stage of upper RTID was associated with reduced progression to lower RTID ($<0.001$) and all-cause mortality ($P = 0.013$) compared to levels for 123 patients not receiving this treatment. Based on the risk factor profile in a subgroup of 237 patients, a weighted ISI was developed to identify patients at high risk for progression to lower RTID and all-cause mortality and to potentially guide treatment (Table 2 and Fig. 5). An advantage of the SID grading is the simplicity of use, where the critical parameters are equally weighted and, if coexisting, can readily shift patients into the verySID group. Advantages of the ISI are a fine gradation over several rank scores and independent validation data for HRSV, but its use is complicated by the different weights, some of which cannot be generalized, e.g., the threshold of 40 years of age.

Importantly, a number of studies have now investigated the association of Basel immunodeficiency grades and MD Anderson ISI scores in HCT and hematologic malignancy patients not only for HRSV but also for IV-A/B, HPIV, and other CARV infections (27, 73, 76, 77, 107, 111). Some of these studies include side-by-side comparisons (77, 78). Indeed, many of the parameters present in the SID grades and ISI overlap and permit separation of patients into groups of similar clinical outcomes regarding progression from upper to lower RTID or mortality (Fig. 5), despite an apparently moderate Cohen's kappa coefficient (78).

Because of the high costs and required logistics for long daily administration and teratogenicity concerns when administering aerosolized ribavirin, many centers have adopted the use of oral ribavirin plus an antibody-based therapy (141). A recent retrospective study of 124 adult HCT patients comparing aerosolized ($n = 70$) and systemic (oral) ribavirin ($n = 54$) reported that all-cause mortality was not significantly different between both groups at day 30 (10% versus 9%; $P = 1.0$) and day 90 (23% versus 11%; $P = 0.10$) postdiagnosis (72). The optimal dose and duration of therapy has been poorly studied, but therapy is generally continued until symptoms have markedly improved or resolved. Dosing of oral ribavirin should be aggressive, as the 50% inhibitory concentration for ribavirin is relatively high and may be challenging to
achieve in the alveolar fluid. As discussed previously (66, 140), optimal therapy should be initiated early, before the development of lower RTID, as this preemptive approach is associated with the best outcomes. Such early therapy should be considered for any HCT recipient within 90 days of transplant, those requiring steroids chronically, those undergoing treatment for GVHD, or those who are severely lymphopenic (ALC of < 100 cells per microliter). Although different dosing schemes of systemic ribavirin have been reported, the guidelines of the fourth European Conference on Infections in Leukaemia (ECIL-4) (5) recommend starting with a loading dose of 600 mg followed by 400 mg every 8 h in order to reach 10 mg/kg body weight every 8 h by day 3 (Table 4).

(iii) New options in the prevention and management of HRSV. There are currently four drugs undergoing development for the treatment of HRSV. ALN-RSV01 is a small interfering RNA (siRNA) that was studied in the treatment of HRSV in lung transplant recipients (142, 143). The drug was studied in two phase 2 studies and demonstrated a reduced risk of development of BOS (13.6% versus 30.3%) in treated patients compared to placebo. Treatment effect was enhanced when ALN-RSV01 was started 5 days from symptom onset and was observed even without ribavirin treatment (142). Despite these promising results, the drug is no longer undergoing clinical development. MEDI8897, a recombinant human IgG1 kappa monoclonal antibody that targets the prefusion conformation of the HRSV F-protein, shows excellent safety and

![Image](image_url)

**FIG 5** Immunodeficiency and probability of survival in allogeneic HCT patients presenting with lower RTID caused by human respiratory syncytial virus. Immunodeficiency scoring index (left) and immunodeficiency grading (right) were calculated as indicated in Table 2 for 85 allogeneic HCT recipients diagnosed with HRSV lower RTID and compared for mortality. High-risk individuals, as identified by a high immunodeficiency scoring index (left, score of 7 to 12; red line), had a higher risk for mortality than those having a moderate index (left, score of 3 to 6; green line) or low index (left, score of 0 to 2; blue line) (OR, 10.5; 95% CI, 1.9 to 56.6; \( P = 0.01 \)). Similarly, individuals with very severe immunodeficiency (right, 2 to 7 criteria; red line) had a higher risk for mortality than those with moderate immunodeficiency (right, 1 criterion, green line) or moderate risk (right, 0 criteria; blue line) (OR, 11.1; 95% CI, 2.8 to 45.1; \( P < 0.001 \)). Both grading approaches predicted time to mortality, as demonstrated by Kaplan-Meier survival curves. (Reproduced from reference 78 with permission of John Wiley and Sons.)

| **TABLE 4** Use of systemic ribavirin for RTID with HRSV, HPIV, and HMPV* |
|-----------------------------|--------------------------------------------------|
| **Treatment course**        | **Description**                                  |
| Oral or intravenous ribavirin | Day 1: start with 600 mg loading dose, then 200 mg every 8 h |
| maximal dosing at 10 mg/kg body weight | Day 2: 400 mg every 8 h |
| every 8 h for adults        | Day 3: increase the dose to a maximum of 10 mg/kg body weight every 8 h |
|                            | In case of adverse events, decrease dose or discontinue ribavirin |
| Oral or intravenous administration | Dose for a creatinine clearance of 30 to 50 ml/min: a maximum of 200 mg every 8 h |
| according renal function    | For a creatinine clearance of 10 to 30 ml/min, no dose recommendation can be givenb |

*aModified from reference 5 on the basis of data from reference 73.

bSome experts use 200 mg once daily under close clinical and laboratory monitoring.
pharmacokinetics in adults and infants (144, 145). Currently, no studies are planned with this compound in immunocompromised patients, but initial studies in otherwise healthy patients are ongoing.

Two direct-acting antivirals are undergoing clinical development for HRSV (presatovir [GS-5806] and lumicitabine [ALS-8176]). Presatovir is a novel oral small molecule that inhibits HRSV entry at low-nanomolar concentrations by blocking viral envelope fusion with the host cell membrane. In experimental infection studies in healthy adults, presatovir was associated with reduction in viral load and severity of clinical disease (146). The drug was studied in four phase 2 studies: one in hospitalized adults with HRSV, one in lung transplant recipients with HRSV, and one in HCT recipients with upper RTID and one with lower RTID, and it was well tolerated in all of these studies. In the lung transplant study, 40 patients were given presatovir and 20 were given placebo. Despite achieving plasma trough levels that were 4-fold higher than the protein binding-adjusted 95% effective concentration of HRSV for at least 21 days, the drug had no effect on clinical symptoms, FEV1, or the viral load kinetics in upper respiratory secretions (147). In the HCT trials, 96 patients after allogeneic or autologous transplantation with upper HRSV RTID received presatovir and 93 received placebo. The coprimary endpoints were not met regarding a faster average decline in upper HRSV load from day 1 to day 9 or progression to lower RTID relative to placebo (148). In a post hoc analysis, patients on presatovir were less likely to progress to lower RTID when having lymphopenia of <200/μl (P = 0.02), when being treated in fewer than 4 days from symptom onset (P = 0.07), or when being in the hospital at the first dose (P = 0.02). In the HCT lower RTID study, 31 patients received presatovir and 29 received placebo, and no difference in virologic or clinical endpoints was observed. Although presatovir was well tolerated, there was no difference in the median number of supplemental oxygen-free days, proportion of patients developing respiratory failure, or all-cause mortality compared to levels for the placebo (149). However, the exploratory small sample size did not permit a meaningful interpretation of the results.

Lumicitabine is an orally bioavailable prodrug of the novel HRSV replication inhibitor ALS-008112, a cytidine nucleoside analogue. The nucleoside triphosphate analogue inhibits HRSV replication by means of chain termination. In experimental infection studies in healthy adults, lumicitabine was associated with more rapid HRSV clearance, a greater reduction of viral load, and more rapid improvements in the severity of clinical disease than placebo (150). A planned clinical trial in hospitalized adults (ClinicalTrials registration number NCT02935673) was recently discontinued, and no studies in transplant populations are currently planned.

**Human metapneumovirus.** HMPV has been detected in SOT and HCT recipients, and rates of 4% (range, 1% to 10%) have been reported when using comprehensive CARV-multiplex NAT in the high-risk population of lung transplantation or allogeneic HCT (32, 55, 56, 73). Like HRSV and HPIV, HMPV has a higher propensity for lower RTID than HRV and for acute and chronic lung dysfunction (Fig. 3), and it has been associated with increased mortality. Only limited data are available for SOT, which stem largely from lung transplant recipients and are usually of small size. In a 5-year prospective study of 98 patients, HMPV was detected by multiplex-NAT in 7.7%, half of which were symptomatic, and two-thirds presented with lower RTID with tracheobronchitis (55). Given the intrinsic propensity for lower RTID, a systematic literature search reviewed all available reports on HMPV infection and attempted to exclude other confounding infections and lung transplant rejection within 6 months. Among a total of 1,007 patients, sole HMPV infection was identified in 57 cases, of which 35% were associated with acute rejection within 3 months, followed by CLAD/BOS (151). However, in other studies, reactivation of cytomegalovirus has been identified as an important cofactor that is not exclusive to HMPV (61).

In allogeneic HCT, a 1-year single-center study of 93 patients tested with CARV-multiplex NAT reported eight (8.6%) patients, seven of which had lower RTID and ground-glass patterns on computer tomography imaging of the chest, six received IVIG
combined with oral ribavirin, and one patient died (12.5%) (152). In a systematic review of the literature, the overall incidence of HPMV was 7% in HCT patients (103 of 1,504) and was not different from that for patients with hematological malignancies (153). Progression to lower RTID occurred in approximately 15% and HMPV-associated mortality was 6%, corresponding to 27% among those with lower RTID (153). In a retrospective study of 118 HCT, 30 had lower RTID, which was associated with steroid use (>1 mg/kg), low lymphocyte counts, and diagnosis less than day +30 posttransplant (154). No clear benefit from antiviral intervention using aerosolized or systemic ribavirin has been documented, and even the role of IVIG is controversial (154). The uncertainty of antiviral treatments may have multiple confounding reasons besides low or limited efficacy and may include patient characteristics, with undefined rates of spontaneous recovery being best documented among patients with upper RTID, severity of immunodeficiency, the underlying disease, and the rates of advanced lower RTID, the course of which can no longer be modified by treatment, as well as the potential role of coexisting cytomegalovirus reactivation. However, some centers use systemic ribavirin, as summarized in Table 4. Clearly, large prospective multicenter studies are needed to define risk factors and clinical impact of HMPV.

Human parainfluenzaviruses. HPIVs cause significant morbidity and mortality in HCT recipients, in patients with leukemia, and in SOT, particularly among lung transplant recipients (155, 156). The incidence of HPIV is about 2 to 7% in HCT recipients and about 5% in lung transplant recipients. Asymptomatic shedding has been documented in SOT and HCT recipients and can give rise to nosocomial outbreaks and a high fatality rate (157–159). Prospective data from Spain from 98 lung transplant recipients identified HPIV in 7.7%, only half of which are symptomatic with mostly lower RTID (55). A systematic review of the literature of 1,196 HPIV infections in 31,730 patients identified an incidence of 5% and 3% HPIV detection rates among allogeneic and autologous HCT patients, which was approximately 2-fold higher than the 2% reported in patients with hematological malignancies (156). Traditional diagnostics covered only HPIV-1, -2, and -3, whereas consistent HPIV-4 data were obtained in the clinical stage only following the use of CARV-multiplex NAT. Indeed, in a comprehensive study of 1,069 CARV-multiplex NAT of allogeneic HCT patients, HPIV-1 and HPIV-2 were detected in 1%, HPIV-4 in 2%, and HPIV-3 in 4%, together amounting to 18% of the CARV-positive samples (73). Most cases of severe RTID have been linked to HPIV-3 (5, 160). Literature data suggest a progression rate to lower RTID in HCT patients of 30% and to HPIV-associated mortality of 12% overall and 27% of those with HPIV lower RTID (156). Similar outcomes were noted in a study of 200 patients, including 120 HCT recipients, where relevant risk factors were neutropenia, steroid use, and refractory underlying malignancy (161). In a recent comparative study, progression to lower RTID and death was only 6% and not different from that for HRSV or HPMV, but it was clearly linked to verySID grading (73). Similarly, in a large single-center study of more than 500 HCT patients, the mean progression rate from upper to lower RTID was 7 days and was associated with monocyte counts of <200/µl, high-dose steroids (1 mg/kg), and HPIV-3 detection (162). An earlier study from the same group reported the 90-day mortality of HPIV lower RTID as being 37%, whereby risk factors were low monocyte counts, being <1 years after HCT, use of high-dose steroids (>2 mg/kg), and oxygen requirement at diagnosis, where no impact of ribavirin and/or IVIG was noted (31).

In addition to the immediate direct effects of the virus, HPIV has been associated with longer-term pulmonary dysfunction in HCT and lung transplant patients. Lung transplant recipients with lower-tract HPIV infections are associated with a high rate of development of BOS or chronic rejection (163). Among HCT recipients, there is an 18-fold increased risk of developing severe late-onset airflow obstruction (164). Unfortunately, this appears to be associated with a frequently progressive and potentially fatal course.

There are no vaccines currently available for the prevention of parainfluenza, so prevention is focused on pulmonary hygiene and contact precautions in the health care setting. There are no approved drugs that have been demonstrated to be active against
HPIV clinically. While most studies have failed to demonstrate a clinical benefit, especially for advanced stages (31, 162), many clinicians will administer IVIG and, less frequently, oral or aerosolized ribavirin for high-risk patients (5, 73) (Table 4) despite lack of evidence for efficacy, especially for lower RTID.

(i) Prevention and new option in management of HPIV. DAS181 is a novel host-directed antiviral with enzymatic activity that is delivered by inhalation. DAS181 is a recombinant protein composed of a sialidase catalytic domain derived from Actinomyces viscosus and is linked to a glycosaminoglycan-binding domain derived from human amphiregulin (Table 5). Similar to other virally encoded neuraminidases, DAS181 destroys sialic acid receptors on epithelial cells of the respiratory tract, which are used by IV-A/B and HPIV for attaching to the host cell. Due to the large size of this novel protein, immunogenicity must be postulated upon repeat administration, but there is currently little evidence of this in immunocompromised patients. In a number of case series, DAS181 inhalation was followed by improved pulmonary function and reduced viral loads in immunosuppressed patients (165, 166). In those that failed to

| Series       | Age (yr) | Serotype | Posttreatment viral load | Pulmonary function | Posttreatment | Mortality |
|--------------|----------|----------|--------------------------|--------------------|---------------|-----------|
| Chalkias et al. (221) | 64       | HPIV-1   | 1.91-log decrease        | Intubated          | Extubated     | N         |
|              | 69       | HPIV-3   | 1.81-log decrease        | Intubated          | Extubated     | N         |
| Waghmare et al. (165) | 12       | HPIV-3   | Negative (D+48)          | N                  |               |           |
|              | 7 mo     | HPIV-2   | Negative (D+69)          | N                  |               |           |
|              | 4        | HPIV-3   | Negative (D+4)           | N                  |               |           |
|              | 3        | HPIV-3   | Negative (D+45)          | N                  |               |           |
| Chen et al. (166) | 63       | HPIV-3   | Negative (D+8)           | FEV₁ = 0.76 liters,  |                | Y (D+14) |
|              |          |          |                          | DLCO = 36%         |               |           |
| Guzman-Suarez et al. (222) | 55       | HPIV-3   | 1-log decrease (D+2)    | FEV₁ = 0.93 liters, |                | N         |
|              |          |          |                          | FVC = 1.12 liters  |               |           |
|              | 59       | HPIV-3   | Unchanged (D+2)          | FEV₁ = 1.52 liters, |                | N         |
|              |          |          |                          | FVC = 1.74 liters  |               |           |
| Dhakal et al. (223) | 74       | HPIV-3   |                          | Intubated          | Intubated w/ improved | Y         |
|              | 35       | HPIV-3   |                          | Intubated          | Intubated w/ improved oxygen requirements | N         |
| Drozd et al. (224) | 64       | HPIV-3   | Negative (D+6)           | High flow mask     | Nasal cannula | N         |
| Salvatore et al. (225) | 53       | HPIV-1   | 3.94-log₁₀ decrease (D+10) | 90% on 90% FIO₂ (vent) | 100% on 55% FIO₂ (vent) | Y (D+21) |
|              | 69       | HPIV-3   | 96% on 50% FIO₂ (facemask) | 95% on 4-liter NC | N             |           |
|              | 64       | HPIV-3   | 1.14-log₁₀ decrease (D+5) | 96% on 35% FIO₂ (vent) | 97% on 50% FIO₂ (vent) | N         |
|              | 66       | HPIV-4   | 96% on 31 NC             | 96% on 2-liter NC | N             |           |
|              | 67       | HPIV-3   | 97% on 50% FIO₂ (facemask) | 98% on 50% FIO₂ (vent) | Y (D+10) | N         |
|              | 58       | HPIV-4   | 94% on 3-liter (NC)      | 99% on 50% FIO₂ (vent) | N         |           |
|              | 65       | HPIV-3/4 | 95% on RA                | 99% on RA         | N             |           |
|              | 29       | HPIV-1   | 98% on 3-liter NC        | 99% on 3-liter NC | N             |           |
|              |          |          |                          | (off oxygen D+10) |               |           |
|              | 50       | HPIV-1   | 0.19-log₁₀ increase (D+7) | 96% on 3-liter NC | 95% on 3-liter NC | N         |
|              | 65       | HPIV-3   | 94% on 5-liter NC        | 95% on 2-liter NC | N             |           |
|              | 72       | HPIV-3   | 90% on RA                | 94% on RA         | N             |           |
|              | 65       | HPIV-3   | 97% on RA                | 97% on RA         | N             |           |
|              | 60       | HPIV-3   | 1.60-log₁₀ increase (D+5) | 96% on 6-liter NC | 97% on 4-liter NC | Y (D+21) |
|              |          |          |                          | (off oxygen D+6) |               |           |
|              | 66       | HPIV-4   | 98% on RA                | 99% on RA         | N             |           |
|              | 59       | HPIV-4   | 100% on RA               | 100% on RA        | N             |           |
|              | 71       | HPIV-4   | 94% on RA                | 95% on RA         | N             |           |

aLiterature search was conducted using PubMed. Studies were included if DAS181 was used therapeutically to treat HPIV in immunocompromised patients. Viral load, pulmonary function, and mortality were assessed from data available in the study text. No studies were excluded. D + #, days after end of treatment; NC, nasal cannula; RA, room air; HPIV, human parainfluenzavirus; DLCO, diffusion capacity of lung for carbon monoxide.
respond, most had clinically significant coinfections. A randomized, placebo-controlled study of DAS181 in immunocompromised patients with HPIV has been completed (ClinicalTrials registration number NCT01644877), and preliminary results were presented at a recent meeting (tct.confex.com/tct/2019/meetingapp.cgi/Paper/13497).

Other CARVs in SOT and Allogeneic HCT

Numerous other viruses have been detected in respiratory samples, including annello-, polyoma-, and picornavirus genera, such as parechovirus, Aichi virus, and Saffold virus. Some of these agents have been shown to change in abundance according to time and immunosuppression posttransplant (38, 167–171) but will not be reviewed here. Other regularly detected CARVs in SOT and HCT include HRV, HCoV, HAdV, and HBoV, yet information on clinical presentation and impact is limited to selective case series in SOT and retrospective studies in allogeneic HCT recipients. A significant component of the uncertainty regarding these agents derives from the fact that (i) prolonged asymptomatic shedding has been observed (172); (ii) there are numerous serotypes/genotypes of HRVs and other enteroviruses, HCoVs, and HAdVs that are not readily differentiated or quantified by multiplex NAT diagnostics; (iii) the serotype/genotype may confer only limited cross-immunity; and (iv) the respective immune status with respect to antibody titers or cellular immunity has not been consistently assessed (173–177). Thus, persistent and prolonged shedding versus re-/superinfection with another subtype is not readily identified. Clearly, dedicated comprehensive clinical and diagnostic studies are needed to shed more light on the role of these CARVs in RTID and the associated risk factors.

Human rhinoviruses. HRVs belong to the Picornaviridae and have been merged into the genus Enterovirus, which share nonenveloped icosahedral virions of 30-nm diameter surrounding a single-stranded 8-kb-long RNA of positive polarity (https://viralzone.expasy.org/). HRVs have been little investigated in SOT, but a retrospective study on 116 lung transplant recipients identified HRV in 11% of patients, whereby higher HRV loads correlated with the presence of RTID (174). Recent prospective data in 98 lung transplant recipients from Spain identified HRV in approximately half of the upper RTID episodes (47 of 97, or 48.5%) and a third of lower RTIDs (23 of 65, or 35.3%), including in 2 fatal cases (55). Similarly, HRVs were retrospectively identified in 33.9% of 116 mostly lower RTID episodes among 250 lung transplant patients. In both studies, lower RTID was independently associated with acute rejection and CLAD, but even though HRV represented the largest CARV genus, a specific attribution was not possible.

In allogeneic HCT, HRVs are the most frequently diagnosed entities among children according to a large retrospective multicenter study, contributing 162 (62%) of 259 CARV events in the first year posttransplant (74). A quarter of these children had a diagnosis of lower RTID at onset and approximately one-half required some form of respiratory support, but ICU admission remained rare, 6 of 162 (4%). A diagnostic surveillance study reported a cumulative HRV incidence until day +100 of 22.3% (45 of 215) adult HCT recipients. The median duration of HRV shedding was for 3 weeks but lasted more than 3 months in 6 patients, and lower RTID was seen in 2 patients (178). In a study of 195 adult patients from Hong Kong from December 2010 to March 2015, HRVs were detected in 38 episodes (19.9%) as the sole CARV, of which 9 (23.7%) presented with lower RTID, 4 (10.4%) required ventilatory support, and 2 (5.3%) died (111). The immunodeficiency score was not predictive of lower RTID or death, but the numbers were small (111). A recent retrospective study of 382 allogeneic HCT patients from Australia identified 65 episodes in 56 (14.7%) patients with CARV-RTID until day +100, which involved HRV in 69.2%. Lower RTID occurred in 18 cases (40%), requiring ICU transfer and mechanical ventilation in 7 (15.6%) (179). Similarly, HRV was detected in 8% of 77 bronchoalveolar lavage samples obtained from HCT patients with new-onset lower RTID and possibly contributed, together with other coinfections, to a high fatality rate of 83% (3). A large retrospective study from the United States identified 697 HRV-positive HCT patients transplanted between 1993 and 2015 (180). Patients with HRV upper RTID had a 90-day mortality of 6%, whereas the mortality rate...
was 41% for those with lower RTID. The survival rate was not significantly affected by copathogen detection, but in multivariate analysis, the overall mortality was associated with a degree of respiratory failure, captured as oxygen use ($P = 0.015$); immunodeficiency, captured as a low monocyte count of $<300/\mu l$ ($P = 0.027$); or steroid dose greater than $1 \text{mg/kg/day}$ ($P = 0.003$) before diagnosis. In univariate analysis, a low lymphocyte, but not monocyte, count of $<300/\mu l$ was significantly associated with respiratory failure. This raises questions about the different functional effector or surrogate roles of lymphocytes versus monocytes, as well as the significance versus severity of lower respiratory tract, with its colder body temperature, have a clinical impact similar to that of HRSV, HPIV, or IV-A/B once established as lower RTID (180). Indeed, a comparative study of 47 HRV cases versus controls matched for time of transplant, stem cell source, and malignancy identified a 2-fold increased rate of hospital readmissions ($P < 0.007$) (181). HRV infection pretransplant was noted in 13 patients, but the authors could not identify an increase in poor outcome (181). In view of the prolonged shedding, defining predictors of HRV lower RTID and mortality, such as grading SID or ISI, are warranted to guide decisions regarding transplant deferral and/or selective treatment of allogeneic HCT patients at highest risk (5). In a recent retrospective single-center study of 588 HRV upper RTID events in 150 autologous and 438 allogeneic HCT recipients, 16 and 84 were found to progress to lower RTID, respectively (182). Following multivariate analysis, a novel weighted risk score was derived consisting of a total of 99 points, which were given at upper RTID diagnosis, including for steroid use (20 for $\geq 2 \text{mg/kg bodyweight}$; 12 for $\geq 1$ to $<2 \text{mg/kg}$), 16 for lymphocyte counts of $<100/\mu l$, 14 for allogeneic/unrelated donor, and 12 for a positive CMV recipient status. Other less obvious scoring factors were 11 for low serum albumin of $<30 \text{mg/liter}$, 14 for recipient statin use, and 12 for previous HRV events. In the total population, four risk strata of scores of $<16$, 16 to $<27$, 27 to $<46$, and $\geq 46$ were associated with progression to lower HRV RTID within 90 days of 9%, 12%, 22%, and 42%, respectively. Using a binary model for HRV events in allogeneic HCT patients only, a score of $\geq 27$ was associated with a cumulative incidence of 28% versus 11%. Further studies will be needed to evaluate the clinical utility of this HRV progression score as well as the comparison with other risk scores. In addition, more data on the role of HRV types, viral loads in respiratory fluids and in blood, and possibly variants detected by next-generation sequencing are needed (173, 174).

**Human coronaviruses.** HCoVs belong to the *Coronaviridae* family, and the species circulating in humans, HCoV-229E, -NL63, -OC43, and -HKU1, belong to the *Alphacoronavirus* (HCoV-229E and -NL63) and *Betacoronavirus* (HCoV-OC43 and –HKU1) genera, respectively. Animal CoVs are known for respiratory zoonosis, such as the past severe acute respiratory syndrome (SARS) outbreak and the ongoing Middle East respiratory syndrome (MERS)-CoV transmissions, with severe RTIDs justifying the name (183). The virions are enveloped particles of 120 nm surrounding a helical capsid and a very large single-stranded RNA genome of approximately 30 kb (https://viralzone.expasy.org/). HCoVs have been linked to severe pneumonia in case studies in HCT and lung transplant programs (184), but only recently, more comprehensive data have become available due to NAT-based diagnostics specifically detecting HCoV-229E, -NL63, -OC43, and -HKU1 (185). A prospective study of 279, mostly adult, transplant patients from Switzerland identified all 4 HCoVs in 29 (5.4%) of 540 BAL fluid samples. Of these, 18 (62%) had a new infiltrate on chest X-rays, and 9 (31%) were admitted to ICU (185). A large retrospective U.S. study compared HCoV detection in 85 immunocompromised and 1,152 nonimmunocompromised children with median ages of 6.3 and 1.6 years, respectively (186). The overall rates of HCoV lower RTID were not different between the groups, but severe lower RTID defined clinically by oxygen requirement was more frequently seen in immunocompromised children (adjusted OR, 2.5; 95% CI, 1.2 to 4.9; $P = 0.01$) and was not attributable to one or another HCoV species. Underlying respi-
ratory disorders, HRSV infection, other copathogens, and younger age were significant in the univariate analysis.

In adult allogeneic HCT recipients, HCoVs were the second most frequently detected CARVs after HRV and were followed by IV-A/B (178, 187). Prolonged shedding of more than 21 days was common and not different between the types but rather reflected the immunodeficiency of the host- and treatment-related factors (178, 188) associated with high HCoV loads, steroid dosing of >1 mg/kg, and myeloablative conditioning (188). No association between lymphocyte or monocyte count and the rate of progression was observed. HCoV lower RTID ranged from 0% to 10% of allogeneic HCT patients. Focusing on 35 patients (allogeneic HCT, N = 28; hematologic malignancy, N = 7) having 37 episodes with HCoV lower RTID, 21 (60%) required oxygen therapy at diagnosis, and the overall mortality was 54% (n = 19) (189). Other pathogens were detected in 21 (57%) episodes, including viruses in 12, fungi in 10, and bacteria in 8, but were not significantly associated with mortality. In fact, the 90-day mortality rate of HCoV lower RTID was not statistically different from those observed in patients with IV-A/B (n = 36), HRSV (n = 113), or HPIV (n = 119) in the same center (189). The key factors in multivariate models were bone marrow as stem cell source (adjusted HR, 1.64; 95% CI, 1.13 to 2.40), oxygen use at diagnosis (adjusted HR, 3.00; 95% CI, 1.98 to 4.53), monocyte counts of <300/μl (adjusted HR, 1.87; 95% CI, 1.12 to 3.13), and neutrophil count of <500/μl (adjusted HR, 1.61; 95% CI, 1.00 to 2.58) (189).

**Human adenoviruses.** HAdVs belong to the *Adenoviridae* family, characterized by nonenveloped virions of 60- to 90-nm diameter containing a linear double-stranded DNA of approximately 37 kb. HAdVs are known to persist for prolonged times, typically in lymphoid-rich tissues, and shedding into mucosal sites has been reported. HAdVs include more than 80 different types, which are grouped into 7 species (A to G), some having a higher propensity to cause RTID, such as HAdV-1, -3, -7, -16, -21, and -50 (subtype B1); HAdV-11, -14, -34, and -35 (subtype B2); HAdV-1, -2, -5, and -6 (subtype C); and HAdV-4 (subtype E) (190). These HAdVs cause approximately 1% to 10% of febrile RTIDs in adults and children. Immunocompromised young children with no or limited preexisting HAdV-specific immunity are at the highest risk for organ-invasive disease, particularly those after allogeneic HCT and SOT (191). HAdVs can disseminate to other organs with corresponding local disease manifestations, including parapneumonic effusion, hepatitis, gastrointestinal disease, and, more rarely, central nervous system disease. Although respiratory HAdVs are detectable year round (Fig. 1), the impressive HAdV disease potential is demonstrated in regional and institutional outbreaks of certain subtypes (192–197).

In SOT, comprehensive data on HAdV RTID are mostly available from lung transplantation, indicating rates of 1% to 10% among adult and pediatric patients (198–200). In a small prospective study of 16 mostly pediatric lung transplant patients, HAdV RTID was identified in 8 patients and was significantly associated with BOS. However, HAdV RTID was rare in a recent prospective study of adult lung transplant recipients and not associated with CLAD (55). Although there may be a predilection for HAdV involvement of the respective allograft, such as lung, heart, liver, and kidney, the manifestations in non-lung allografts may result from secondary spread from a mucosal entry site to these internal organs, with the possible exception of intestinal transplant recipients. In a kidney transplant recipient, HAdV multiorgan involvement was described as presenting as a febrile illness with sinusitis and conjunctivitis, and the patient was eventually diagnosed with renal allograft nephritis (201). In two other cases, pulmonary infiltrates and hepatitis occurred (202). This emphasizes the role of systemic humoral and cellular immunity and may explain the susceptibility of the pediatric population. However, in a small prospective study of 75 pediatric kidney transplant recipients, HAdV DNAemia was detected in 11 (14.7%) patients at a median of 173 days (interquartile range, 109 to 310 days) posttransplant, of whom 5 (6.7%) were symptomatic, including showing hematuria in 2 cases and acute febrile RTID in 3 cases (198).

In allogeneic HCT, HAdV replication is more frequently detected, which is, however, mostly due to the widespread screening of blood and gastrointestinal specimens from...
a- or presymptomatic patients considered to be at highest risk, such as children and those receiving alemtuzumab therapies (203). Conversely, HAdV is less frequently reported in respiratory specimens from allogeneic HCT patients with RTID (204, 205). Accordingly, the levels and dynamics of HAdV in different anatomic sites is not well understood, with the exception of blood and stool samples, and no generalized thresholds using international calibrators have been established (203, 206, 207). A large retrospective study of 687 allogeneic HCT patients identified HAdV in 64 (9.3%) cases presenting mostly as gastrointestinal disease or hemorrhagic cystitis but in 3 (0.5%) cases as HAdV pneumonitis, which eventually had a lethal outcome (204). A retrospective study of 572 pediatric HCT patients of a median age of 6.2 years identified HAdV by NAT in 76 (13.3%) patients, consisting of 8 (11%) autologous and 68 (89%) allogeneic HCT patients. In only a quarter of the latter, RTID attributable to HAdV was diagnosed using nasopharyngeal and bronchoalveolar lavage fluids (205). Thus, HAdV contributes to significant posttransplant RTID complications in less than 10% of allogeneic, preferentially pediatric HCT recipients.

Treatment of HAdV-RTID is limited to reducing immunosuppressive treatment and the off-label administration of intravenous cidofovir (199, 204, 208), systemic ribavirin, ganciclovir, and acyclovir (209, 210). Frequently, these antiviral agents have been combined with IVIG, but the overall response was either disappointing, moderate, or confounded by immune recovery of overall lymphocyte counts, including HAdV-specific T cells, best demonstrated in allogeneic HCT recipients (211). Thus, newer agents with more potent antiviral activity, such as oral or intravenous brincidofovir (formerly called CMX001) and adoptive T-cell transfer from an HCT donor or third party are currently being investigated as potentially more effective therapies (210, 212–214).

Human bocaviruses. HBoVs belong to the Parvoviridae family, characterized by small nonenveloped virions of 25-nm diameter containing a 5-kbp single-stranded DNA carrying at either end telomeric hairpin loops of approximately 150 bp to facilitate genome replication (https://viralzone.expasy.org/). HBoV1 was first detected in respiratory secretions of children with lower RTIDs involving none of the hitherto known respiratory agents, but at least three additional types have been described, of which HBoV2 has been associated with gastroenteritis in infants (167). Similar to human parvovirus B19, detection of HBoV genomes may persist for prolonged periods, which, together with the frequent codetection with other CARVs, has complicated the attribution to disease and to RTID in particular as persistence, reactivation, or super-/reinfection (215, 216). This problem has been partly addressed by quantitative NAT in a large retrospective cohort of 426 patients contributing 685 respiratory specimens (217). The HBoV detection rate was 14.1% in 283 children and 1.4% in 143 adults, peaking in winter-early spring and in infants less than 1 year old. However, two-thirds represented coinfections. The single HBoV infections almost exclusively occurred in children less than 1 year old, having HBoV DNA loads above 5 log_{10} c/ml, but was found in none of the adults. Although these data suggest a cutoff, confirmatory studies of bystander versus copathogen have not been rigorously conducted, and most reports on HBoV detection in transplant recipients by multiplex NAT are only qualitative. Another approach to identify significant HBoV exposure has been taken by examining the HBoV1 IgG and IgM seroresponse. Recent data were gathered from 759 otherwise healthy children from Brazil (mean age, 2.2 years; range, 1.2 to 3.4 years) presenting with community-acquired lower RTID (218). Acute or recent HBoV1 exposure was serologically identified in 38 (5%) children, including 4 of 8 cases in which HBoV1 was the only viral pathogen detected (218). Although serological responses may not be reliable in immunosuppressed transplant patients, this topic has not been well studied in SOT or allogeneic HCT.

Since immunocompromised and transplant patients are more likely to have coinfections, the role of HBoV1 (co)detection in RTID has been difficult to understand. A prospective study focusing on 522 bronchoalveolar lavage specimens from 299 adults, including HCT and lung transplant recipients, identified HBoV in 3 (1%) cases (32). A recent study from Brazil detected HBoV in 6 (3%) of 192 viral RTID episodes after
allogeneic HCT, five of which occurred as coinfection and only one in a case of lower RTID (218). Unlike the well-known parvovirus B19, HBoV1-DNAemia was not detectable in a study of 53 children from Finland after allogeneic HCT (219). Thus, low rates (220), especially in adults, frequent coinfections, together with extended low-level persistence (215) more commonly seen for Paroviridae render a simple attribution of HBoV1 to disease and necessity of treatment by, e.g., IVIG questionable.

CLOSING REMARKS AND OUTLOOK

CARVs are a common cause of morbidity and mortality among transplant patients and reflect the local activity in the community. Increasing use of modern molecular diagnostics in real time has expanded our understanding of the epidemiology of these viruses. Importantly, viruses once thought to be rare and clinically unimportant, notably rhinovirus and coronaviruses, are now being recognized as significant and common. Prediction of clinical impact remains important in order to optimize vaccine/prophylaxis strategies and to target antiviral interventions. The vulnerability of the patient and the pathogenicity of the respective CARVs, as well as the dynamics of progression to lower RTID, need to be considered. Clinical and laboratory scores, such as the ISI or SID grading, may help to guide early and extended antiviral (combination) treatment if further developed and validated. Currently approved therapies are only available for influenza and HRSV. Notably, newer classes of antivirals and antibodies are undergoing advanced development for the treatment of influenza, HRSV, HPIV, and adenovirus. Massive parallel sequencing techniques providing comprehensive and (semi)quantitative information on the respiratory virome as part of the microbiome and the respective host transcriptome response will generate new insights into pathogenesis of CARVs in transplant patients. Integrating this information into the real-time risk assessment and corresponding treatment approaches is likely to permit reducing the impact of respiratory viruses in the transplant population.

ACKNOWLEDGMENTS

We are very thankful to Patrick Lane of ScEYEnce Studios for working with us to prepare the graphically enhanced figures. We also thank Erika Hofmann, Basel, for excellent assistance with the references and the bibliography.

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