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Review Article

Management of respiratory viral infections in hematopoietic cell transplant recipients

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Abstract: Advances in stem cell transplantation procedures and the overall improvement in the clinical management of hematopoietic cell transplant (HCT) recipients over the past 2 decades have led to an increase in survival duration, in part owing to better strategies for prevention and treatment of post-transplant complications, including opportunistic infections. However, post-HCT infections remain a concern for HCT recipients, particularly infections caused by community respiratory viruses (CRVs), which can lead to significant morbidity and mortality. These viruses can potentially cause lower respiratory tract illness, which is associated with a higher mortality rate among HCT recipients. Clinical management of CRV infections in HCT recipients includes supportive care and antiviral therapy, especially in high-risk individuals, when available. Directed antiviral therapy is only available for influenza infections, where successful use of neuraminidase inhibitors (oseltamivir or zanamivir) and/or M2 inhibitors (amantadine or rimantadine) has been reported. Data on the successful use of ribavirin, with or without immunomodulators, for respiratory syncytial virus infections in HCT recipients has emerged over the past 2 decades but is still controversial at best because of a lack of randomized controlled trials. Because of the lack of directed antiviral therapy for most of these viruses, prevention should be emphasized for healthcare workers, patients, family, and friends and should include the promotion of the licensed inactivated influenza vaccine for HCT recipients, when indicated. In this review, we discuss the clinical management of respiratory viruses in this special patient population, focusing on commercially available antivirals, adjuvant therapy, and novel drugs under investigation, as well as on available means for prevention.

Keywords: RSV, influenza, parainfluenza, adenovirus, rhinovirus, metapneumovirus, HCT, transplant, cancer, immunocompromised host, antiviral therapy, infection prevention

Over the past 2 decades, advances in stem cell transplantation procedures and improvements in the clinical management of hematopoietic cell transplant (HCT) recipients, including better strategies for the prevention and treatment of post-transplant complications such as opportunistic infections, have led to an increase in survival duration [1]. HCT recipients are, however, still particularly susceptible to community respiratory viruses (CRVs) owing to a decreased host immune response, mainly because of a shortage of T cell lymphocytes [2]. CRVs, including respiratory syncytial virus (RSV), influenza virus, parainfluenza virus (PIV), human adenovirus (HAdV), human metapneumovirus (HMPV), human rhinovirus (HRhV), and human coronavirus (HCoV), have been reported to cause infections in this population at incidences between 1% and 30%, as shown in **Figure 1** [3-7]. Other newly discovered viruses such as human bocavirus (HBoV) are emerging as potential causes of respiratory infections, but data on their impact in this population are lacking. All of these CRVs can potentially cause lower respiratory tract illnesses (LRTI) (rates of LRTI range from 5% to 50%), which could be associated with high mortality rates (10% to 50%) in HCT recipients [3-8]. As demonstrated in **Figure 1**, HAdV, HRhV, and HCoV have equally higher incidences in HCT recipients, whereas LRTI rates are higher for RSV, influenza, PIV, HAdV, and HMPV. Other late complications, such as bronchiolitis obliterans and organizing pneumonia, have been associated with some of these viral

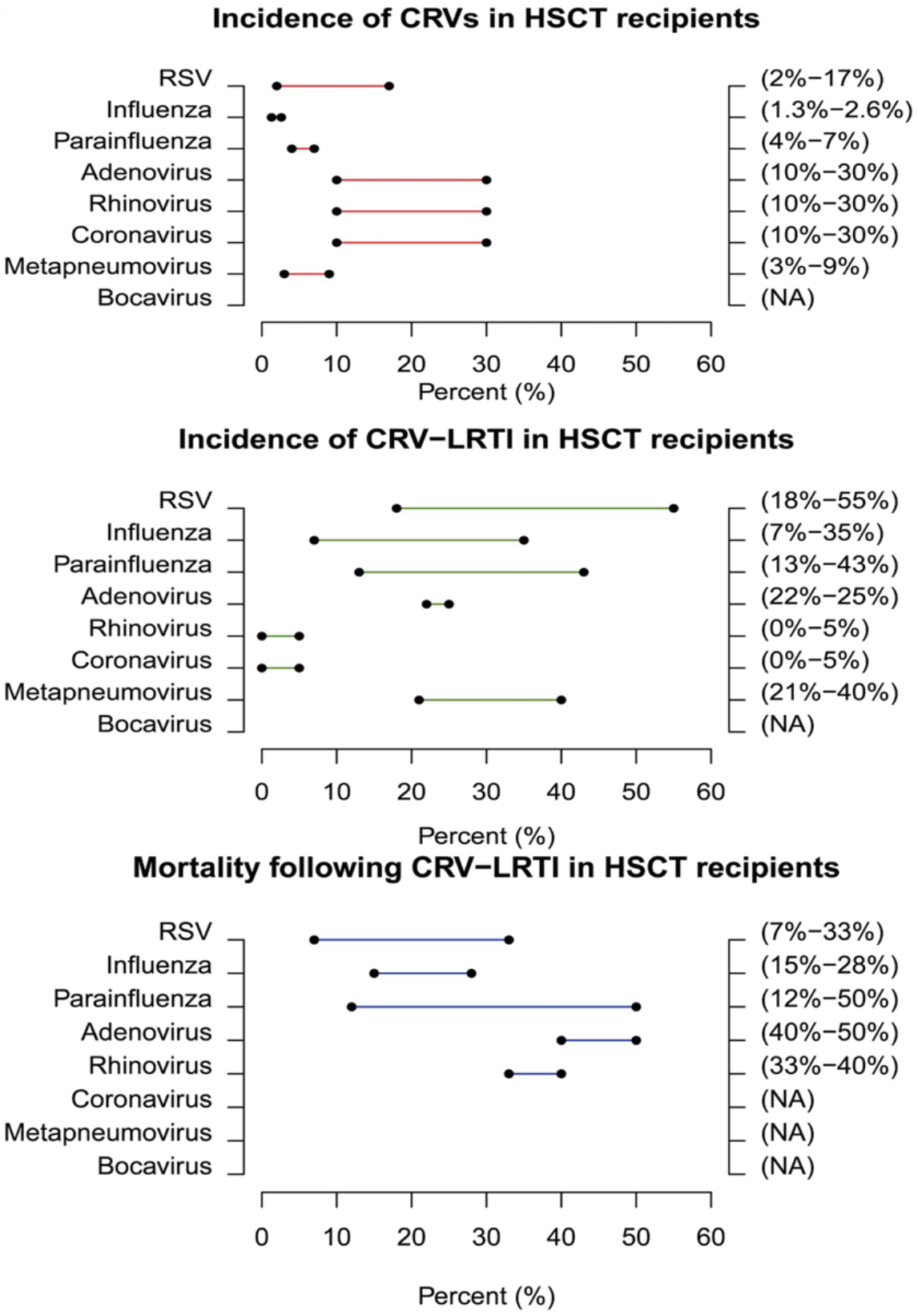

Figure 1. Incidence of respiratory viral infections and associated LRTI and mortality in HSCT recipients. Data obtained from [3, 5, 6, 21]. *CRV indicates common respiratory viral infections; HSCT, hematopoietic stem cell transplant; LRTI, lower respiratory tract infection; and NA, data not available.

infections (i.e., RSV, PIV, and HMPV) [8, 9], but the direct relationship needs to be better elucidated.

HCT recipients with CRV infections may present with various combinations of upper respiratory tract infection (URTI) symptoms such as rhinorrhea, nasal or sinus congestion, cough, low-grade fever, headache, otitis media, wheezing, and sore throat. Some patients may present with LRTI, with symptoms including dyspnea and hypoxemia and radiologic findings that include new or changing bilateral interstitial infiltrates. These signs and symptoms are suggestive of viral etiology, but laboratory confirmation is needed for a definitive diagnosis. Viral culture is the gold standard for diagnosing CRVs, but the time required for a culture to become positive is a limiting factor, especially in immunocompromised patients, where prompt institution of treatment is of utmost importance [10, 11]. Direct immunofluorescence antigen testing is a rapid and inexpensive alternative, but it has low sensitivity (50% to 93%) [12-17]. More sensitive and specific modalities include molecular assays (e.g., multiplex polymerase chain reaction [PCR]) that test for multiple different viruses [18-20], and real-time PCR is becoming the most preferred method for diagnosing viral infections.

The management of CRV infections in HCT recipients includes supportive care and, when available, antiviral therapy, especially in individuals at high risk of developing LRTI. Some evidence of successful antiviral therapy has been reported with ribavirin for RSV, oseltamivir, zanamivir, and/or M2 inhibitors for influenza, and cidofovir for HAdV. There are also some anecdotal reports of PIV and HMPV infections being successfully treated with a combination of ribavirin and intravenous immunoglobulins (IVIGs). However, none of these regimens have been tested in randomized controlled trials to determine their efficacy in HCT recipients and, therefore, are not licensed by the US Food and Drug Administration (FDA) for virus-specific therapy in these patients.

With the high morbidity and mortality rates associated with CRV infections and the lack of directed antiviral therapy for most of these infections, prevention remains the mainstay for reducing their incidence and controlling transmission in HCT recipients. A licensed vaccine is only available for the influenza virus, and its use should be encouraged in all HCT recipients, when indicated, as well as in healthcare workers and family members. Infection control measures should be emphasized for healthcare workers and patients alike and should focus on basic precautions such as frequent hand washing and the use of protective equipment such as face masks, gowns, and gloves.

In this review, we discuss the available data behind the use of antiviral therapy, adjuvant therapy, and novel investigational drugs, as well as available means for prevention, in each respiratory virus with a significant incidence in HCT recipients.

Respiratory syncytial virus

This paramyxovirus (RNA virus) affects 2-17% of HCT recipients on a seasonal basis, with the highest incidence between the fall and spring [16, 21-25]. Factors reported to be associated with the acquisition of RSV infection include male sex, allogeneic transplantation, cytomegalovirus seropositivity, and pre-engraftment status [25-27]. URTI is the most common presentation and may progress to LRTI in 17% to 84% of patients [5, 21, 22, 27-32]. Risk factors associated with progression to LRTI include older age, myeloablative regimen, lymphopenia, mismatched or unrelated donor transplant, graft-versus-host disease (GVHD), and pre-engraftment status or early post-transplantation period [5, 21, 22, 24-26, 29, 33]. RSV-LRTI in HCT recipients increases the likelihood of a fatal outcome; therefore, prompt diagnosis and early intervention at URTI stage may be indicated in patients at risk of LRTI [21].

Treatment

Aerosolized ribavirin is the only drug that has been approved by the FDA for the treatment of high-risk infants and young children hospitalized with RSV-LRTI [34]. In our recent systematic review on this subject, we reported that ribavirin-based therapy had variable success rates for preventing RSV-associated morbidity or mortality in high-risk HCT recipients [21]. In that review, we examined published studies to determine the efficacy of various routes of ribavirin administration (oral, intravenous, and

aerosol), with or without immunomodulators (palivizumab and IVIGs), as therapy for RSV infections in adult HCT recipients. Based mostly on retrospective data, we found that patients treated with ribavirin with or without an immunomodulator had better outcomes than those not treated (16% vs. 45% rate of progression to LRTI and 35% vs. 70% mortality rate) [21]. In a recently published randomized clinical trial in HSCT recipients with RSV-URTI comparing two dose schedules of aerosolized ribavirin (continuous vs. intermittent), both of them were identified to be effective in preventing RSV-LRTI [35]. Time of administration may play an important role in the success of ribavirin-based therapy, with those treated at URTI stage having more favorable outcomes than those treated at LRTI stage, irrespective of the regimen [21].

An investigational monoclonal antibody, motavizumab, was compared with palivizumab for RSV prophylaxis in *in vitro* experiments, in a cotton rat model, and in phase III trials in preterm infants which showed comparative efficacy for these two drugs [36-38]. However, the FDA did not approve motavizumab in a recent filing, in part because the drug caused some non-fatal hypersensitivity adverse events, which may have been more severe in the sick child population where it is indicated than in healthy children [39]. ALN-RSV01 (Alnylam Pharmaceuticals, Cambridge, MA) interferes with viral replication and has shown some promising results in two randomized clinical trials. When used for prophylaxis, it reduced the occurrence of RSV infection by 44% in healthy individuals [40]. In lung transplant recipients, ALN-RSV01 decreased the incidence or the progression of bronchiolitis obliterans when used as therapy for RSV infection (6.3% vs. 50% in treated vs. non-treated groups, respectively) [41]. Whether this drug will be tested in phase III trials, and specifically in HCT recipients, is not known.

Prevention

No vaccine is yet available for RSV. Passive immunoprophylaxis for high-risk HCT recipients with RSV-IVIG was tested in a small study, which failed to determine its efficacy [42]. On the other hand, the use of palivizumab for prophylaxis in young children undergoing HCT was suggested by the 2009 international HCT guidelines [43]. It was also successful in controlling an outbreak of nosocomial transmission of RSV in a HCT unit and is well tolerated in this patient population [44, 45]. However, the high cost of these drugs combined with a lack of clear evidence of efficacy in this patient population precludes their wide-scale acceptance. Infection control measures to prevent new infections and subsequent transmission remain the best approach for decreasing the burden of RSV in HCT recipients. Overall awareness among healthcare personnel and caregivers about the possible deleterious outcomes of RSV infections in HCT recipients and the importance of their early detection may have a major impact on the incidence of RSV infections and subsequent complications. More specifically, adherence to contact and respiratory droplet isolation, along with hand hygiene, will help reduce RSV infections in HCT recipients.

Influenza virus

This orthomyxovirus causes seasonal outbreaks in HCT recipients, especially during the winter months. It has 2 types of glycoproteins (hemagglutinins [H1, H2, and H3] and neuraminidases [N1 and N2]), which undergo antigenic drifts and shifts that cause epidemics and pandemics, respectively. Patients may develop various combinations of constitutional symptoms (e.g., fatigue, malaise, myalgia) and URTI symptoms (e.g., rhinorrhea, cough, sore throat), thus presenting with the typical 'flu-like' illness, or may present with minimal respiratory symptoms and/or fever. The incidence rate of influenza infection in HCT recipients ranges from 1.3% to 2.6% [3, 6]; however, this rate can vary depending on the dominant strain of influenza virus during a particular season. Progression to LRTI is particularly common in immunocompromised hosts such as HCT recipients [46, 47]. The incidence rates of LRTI can range from 7% to 35%, and the associated risk factors for this outcome include lymphocytopenia and recent transplant [3, 6]. Mortality rates following LRTI can range from 15% to 28% [6]. Influenza infection is suspected in patients with "flu-like" symptoms during community outbreaks; however, prompt confirmation by immunofluorescence assays, enzyme immunoassays, cultures, or PCR-based assays is needed, especially in immunocompromised patients, as early initiation of antiviral therapy may positively affect outcome [10, 11].

Table 1. Antiviral susceptibility patterns for various strains of human influenza virus[a,b,c]

	Oseltamivir	Zanamivir	M2 Inhibitors[d]
Pandemic 2009/H1N1	Susceptible	Susceptible	Resistant
Seasonal H1N1	Mostly resistant	Susceptible	Mostly susceptible
Seasonal H3N2	Susceptible	Susceptible	Susceptible
Influenza B	Susceptible	Susceptible	Resistant
Avian H5N1	Susceptible	Susceptible	Variable

[a]Table obtained from [3], [b]Centers for Disease Control and Prevention, http://www.cdc.gov/h1n1flu/recommendations.htm, [c]WHO Guidelines for the Pharmacologic Management of Pandemic (H1N1) 2009 influenza and other influenza viruses http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html, [d]amantadine and rimantadine.

Treatment

The two main classes of anti-influenza drugs are neuraminidase inhibitors (e.g., oseltamivir and zanamivir) and M2 inhibitors (e.g., amantadine and rimantadine). Prompt initiation of therapy, preferably within 24-48 hours of onset of symptoms, is essential to prevent complications in patients with cancer, including HCT recipients [10, 11]. Nausea and vomiting are the most common side effects of oseltamivir, whereas central nervous system toxicities have been reported more frequently with amantadine [3].

Recommendations for the treatment of influenza infections have changed over the past few years to address the changes in the susceptibility patterns of different strains of influenza virus each season (**Table 1**). While its resistance to oseltamivir has increased, seasonal H1N1 has remained susceptible to zanamivir and M2 inhibitors [48-50] (http://www.cdc.gov./h1n1flu/immunosuppression/index.htm; http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html.), whereas the rece-nt pandemic 2009/H1N1 strain was only susceptible to oseltamivir and zanamivir. In a retrospective study comparing seasonal influenza with pandemic 2009/H1N1 in children with cancer, early initiation of antiviral therapy was critical in preventing LRTI and death from both strain [11].

Intravenous formulations of neuraminidase inhibitors such as peramivir and zanamivir are still being evaluated in phase III clinical trials [51-54]. This intravenous route may be advantageous for patients with graft versus host disease (GVHD) of the gastrointestinal tract, because of possible decreased absorption and less bioavailability of oral drugs, or for those with LRTI or lung injury, where the inhalation route of the drugs may not be appropriate. DAS181 is a new investigational antiviral drug that acts by removing from the respiratory epithelial cell surface the sialic acid residues that are essential for viral entry and infection [55, 56]. This drug is undergoing phase II trials after promising results were seen against oseltamivir- and zanamivir-resistant strains *in vitro* and in mouse models [57-60]. Favipravir (T-705), another drug under investigation that inhibits viral replication by targeting viral-specific RNA-dependent RNA polymerase, is currently undergoing phase II trials [61-64]. Finally, the long-acting neuraminidase inhibitor laninamivir had efficacy comparable to that of oseltamivir for the treatment of influenza infection in a large double-blind, randomized, non-inferiority clinical trial [65]. It may also be effective against oseltamivir-resistant influenza strains and is currently available in Japan [66, 67]. Adjunctive therapy for influenza infections has yielded conflicting results. For example, corticosteroid therapy, possibly owing to its anti-inflammatory properties, has been shown to decrease the rates of LRTI; however, it has also been observed to prolong viral shedding [10, 47, 68].

Prevention

Intramuscular inactivated influenza virus vaccine is recommended annually for immunocompromised patients such as HCT recipients who are able to mount an immunologic response to the vaccine and for healthcare personnel, close family members, and friends [69]. HCT recipients may not, however, have the desired immune response to the influenza vaccine; which can be up to 50% lower than that observed in the general population [70-72]. Therefore, the Advisory Committee on Immunization Practices recommended daily chemoprophylaxis with an effective antiviral

drug for immunocompromised individuals during community outbreaks [69]. Furthermore, the updated guidelines of the American Society of Bone Marrow Transplantation recommended annual inactivated influenza vaccination before the beginning of the influenza season and before transplantation or 4 to 6 months following transplantation [43]. The vaccine should be administered prior to the onset of the influenza season to avoid new infections and related complications. The main two contraindications for influenza vaccine are febrile illness and severe allergy to eggs [73]. Additionally, in cases of community or nosocomial outbreaks, prophylaxis and preemptive treatment with a strain-specific antiviral agent should be administered to all HCT recipients within 24 months of transplantation and to those who have GVHD and/or are taking immunosuppressive therapy [43]. The efficacy of oseltamivir prophylaxis (75 mg/day) in reducing the incidence of influenza infections during the peak of the season was reported by a randomized, double-blind, placebo-controlled trial in immunocompromised patients [74]. On the other hand, some studies have shown that oseltamivir prophylaxis may occasionally lead to the selection of resistant influenza strains, as during the 2009/H1N1 pandemic [75-77]. Last, but not the least, infection control practices should be strictly observed to prevent new infections and reduce transmission during community and nosocomial outbreaks.

Parainfluenza virus

PIV is an enveloped, single-stranded, RNA paramyxovirus comprising four antigens sharing serotypes. PIV infects 2.5% to 7.1% of HCT recipients, with the highest incidence observed during the summer season [4, 26, 78-80]. PIV type 3 is responsible for up to 90% of these infections, with URTI being the most common presentation following an incubation period of 1 to 4 days. The main risk factors reported in the literature for acquiring PIV in HCT recipients are a transplant from an unrelated donor [26] and CD4 lymphopenia in T-cell-depleted patients [81]. PIV is clinically indistinguishable from other CRVs encountered in immunocompromised patients; therefore, laboratory confirmation is important. Modalities used to diagnose PIV include rapid antigen testing, enzyme immunoassays, real-time PCR, and viral cultures [14, 82-84]. One of the most common complications following PIV-URTI is progression to LRTI, which occurs at a rate of 20% to 39% in HCT recipients, with an associated mortality rate of up to 30% [4, 80]. The associated risk factors for progression to LRTI include neutropenia, lymphopenia, systemic corticosteroid use, high APACHE II score at presentation, and pulmonary co-infections [79, 81]. Furthermore, subsequent late airflow obstruction may be associated with PIV-URTI as well as PIV-LRTI [9].

Treatment

Ribavirin use for the treatment of PIV infections has shown promising results in animal models and children with severe combined immunodeficiency [85, 86]. However, ribavirin therapy, with or without IVIG, has had conflicting results in PIV-infected HCT recipients in the absence of randomized clinical trials [4, 8, 79, 80, 87]. Mainly in large case series, ribavirin had no effect on viral shedding, duration of symptoms, length of hospital stay, progression to PIV-LRTI, or mortality associated with these infections in HCT recipients [4, 79, 80]. Many novel drugs, such as DAS-181 (a recombinant sialidase protein) and BCX2798 (a hemagglutinin-neuraminidase inhibitor), are being evaluated for the treatment of PIV infections [88-90]. However, no PIV-specific antiviral therapy is commercially available, and clinical management of HCT recipients relies on supportive care. The impact of IVIG on overall outcome still needs to be determined.

Prevention

In the absence of an effective therapy or vaccine, infection control measures are the mainstay for preventing the spread of PIV in HCT recipients. Contact isolation, hand hygiene, and wearing masks and gloves, along with universal precautions, should be emphasized for healthcare personnel, family members, and visitors, as 17% to 22% of these infections may be acquired in the healthcare setting [4, 79].

Human adenovirus

Occurring throughout the year, HAdV belongs to the Adenoviridae family of DNA viruses with 6 subgroups and 51 known serotypes. It may infect up to 3% of HCT recipients overall, but has a higher incidence in allogeneic (6%) and

pediatric (24-32%) HCT recipients [6, 16, 91-94]. Since T lymphocytes are crucial for building an immune response against HAdV infections, HCT recipients are most susceptible to these infections during post-transplant T cell suppression [95]. Consequently, risk factors unique to HCT recipients that may lead to acquiring adenoviral infections are GVHD, transplant from an unrelated donor, total body irradiation, presence and severity of T-cell depletion, recent transplantation, and T cell suppression following transplantation [95-99]. The clinical presentation may be similar to other respiratory viruses; however, any organ system can be affected and disseminated disease can occur without involvement of the respiratory system. The mortality rate in HCT recipients can be high (15-28%), especially in those with disseminated disease following DNAemia or LRTI [94, 95, 100, 101].

Many diagnostic tests are available for HAdV detection, including enzyme immunoassays, immunofluorescence assays, PCR assays, and viral cultures [12, 13]. Additionally, quantitative viral loads were shown to predict clinical response and prognosis, with high titers (more than 1 x 10^6 DNA copies/mL) correlating with increased risk of death [102, 103].

Treatment

A lack of randomized controlled trials makes it difficult to ascertain the efficacy of available antiviral drugs for the treatment of HAdV infections, especially in HCT recipients. Cidofovir, a monophosphate nucleoside analogue of cytosine, appears to be the most effective agent *in vitro* against HAdV [104-106], and no HAdV strains have been shown to be clinically resistant to this drug [107]. In a recent review of the management of HAdV in HCT recipients, Lindemans *et al* recommended that vigilant monitoring using PCR assays in combination with preemptive cidofovir therapy may be the best strategy currently available to "bridge the severely immunocompromised period" following HCT [106]. Preemptive treatment with cidofovir, before dissemination of HAdV or end-organ disease, may be of prime importance, given the high mortality rates associated with these conditions [108]. However, the main limiting factor in cidofovir use is its associated side effects, mainly the high incidence of nephrotoxicity, including increased serum creatinine levels (up to 25% of cases), proteinuria following renal proximal tubule dysfunction (50% of cases), and, rarely, Fanconi syndrome (1% of cases) [105, 109, 110].

CMX001, a lipid conjugate of cidofovir, is an oral investigational drug with activity against HAdV in animal models [111] and in humans [112] and without untoward nephrotoxic effects. A few immunocompromised patients with adenoviral infections have been successfully treated with CMX001, without any serious adverse events reported [113, 114]. Currently, oral CMX001is undergoing study in a phase II trial for the treatment of HAdV infections in HCT recipients.

Other drugs used for the treatment of HAdV diseases include ribavirin (oral or aerosolized) and ganciclovir; however, the data derived are mostly from uncontrolled studies, and the results are conflicting. Therefore, these drugs are not routinely recommended for the treatment of adenoviral diseases [97, 115-118]. Immunotherapy with specific and non-specific T cells given exogenously has also been tried in several small studies with favorable outcomes [119-122].

Prevention

After production of adenovirus vaccine was stopped in 1996 because of a lack of funding, a new live oral vaccine against adenovirus types 4 and 7 was approved by the FDA in March 2011 for new military recruits entering basic training or military personnel who may be at higher risk for infection (http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-adenovirus.pdf). For haploidentical stem cell transplant or cord blood transplant recipients, weekly PCR surveillance and pre-emptive therapy with cidofovir may be used to decrease the risk of disseminated disease [95, 104]. As mentioned above, maintaining T cell function by using a reduced-intensity conditioning regimen and exogenous immunotherapy may be a good strategy to prevent reactivation of latent adenoviral infection and disseminated disease in HCT recipients [120-124]. Overall, general safety precautions, along with infection control measures, are recommended to decrease its horizontal transmission.

Table 2. Infection control guidelines at various levels of intervention

Level of intervention	Strategies for prevention
Patient level (HCT recipients)	HCT recipients should be educated about risks associated with respiratory viral illnesses and encouraged to seek medical attention early on.
	Patients seen in outpatient clinics with URTI symptoms should be immediately placed in private rooms. Masks and alcohol-based gel should be provided to avoid transmission during outpatient visits.
	Isolation and cohorting (in case of a nosocomial outbreak) of immunocompromised patients with CRV infections should be practiced.
	All admitted HCT recipients with CRV infections should occupy private rooms.
	Patients scheduled to undergo intensive induction chemotherapy should postpone their treatment regimens before conditioning therapy begins if they have evidence of URTI
	Diagnosing and treating pulmonary coinfections with appropriate therapy can reduce mortality in these patients.
	Influenza vaccine administration prior to influenza season, if appropriate, and chemoprophylaxis with a specific antiviral agent (oseltamivir or zanamivir, based on outbreak virus strain) are recommended, when vaccine is not appropriate.
Healthcare personnel level	Symptomatic healthcare workers should be restricted from direct patient contact.
	Adherence to contact and droplet precautions and the use of gowns, masks, and gloves for contact isolation during any patient contact is critical.
	The necessity of hand washing between patient visits must be stressed to all staff.
	Influenza vaccine should be given prior to influenza season.
	Unvaccinated staff should undergo chemoprophylaxis or have their access to HCT recipients restricted unless they wear masks.
Institutional level	Information regarding CRV infections should be offered to patients, their families, and staff members before the beginning of each winter season.
	Screening and restricting visitors with respiratory symptoms, especially during the respiratory illness seasons, should be practiced, and masks should be provided to those who screen positive.
	Vaccination of all caregivers and family members in close contact with immunocompromised patients is essential.
	Active surveillance and sanitization of environmental surfaces contaminated with PIV is recommended [27].
Community level	Awareness of the impact and transmission of these CRV infections in HCT recipients should be increased.
	Support of research for developing novel antiviral drugs and potent vaccines is important.
	Efforts should be made to increase awareness of the importance of influenza (or other available) vaccinations.
	Public health education about hand washing and personal hygiene to prevent transmission of these viruses and control an outbreak/pandemic is essential.

Human rhinovirus

Commonly known to cause "the common cold" in the general population, these non-enveloped RNA picornaviruses may cause severe infections in immunocompromised hosts such as HCT recipients [125-127]. Although they occur throughout the year, fall and spring are the peak seasons for these infections, with the highest incidence in children, who also act as reservoirs for this virus. Self-inoculation and respiratory droplets are the common modes of transmission [128]. An incidence rate of 32% was reported in HCT recipients [125], and rates of progression to LRTI and mortality could be as high as 55% and 33%, respectively [6, 125, 126]. The prognosis largely depends upon the severity of immunosuppression.

Treatment

Currently, no specific antiviral therapy is available, and treatment is mainly supportive with antihistamines, decongestants, and non-steroidal anti-inflammatory drugs [3]. Many novel drugs, such as pleconaril, BTA-798, and inhaled interferon-β 1a (SNG001), are being tested in the general patient population with rhinovirus infections; however, their role in HCT recipients is uncertain [129, 130].

Prevention

A vaccine for human rhinovirus seems implausible at the moment because of the sheer number of strains causing infections [128, 131], and general infection control practices are recommended for controlling its horizontal transmission.

Other viruses

Human coronavirus (NL63 and HK)

HCoV is commonly encountered in the fall and spring seasons and may cause respiratory illnesses every 2-4 years. The clinical presentation is very similar to rhinovirus infections, and a definitive diagnosis can be made using PCR-based methods. Generally a self-limiting disease, this infection can progress to LRTI in HCT recipients [132]. Data are limited on the mor-

bidity and mortality of these infections in immunocompromised hosts; however, a higher incidence rate was reported when compared to immunocompetent hosts (8.8% vs. 4-5%, respectively) [8]. Neither specific antiviral therapy nor a vaccine is available for HCoV, and supportive care with general infection control practices is recommended.

Human metapneumovirus

This newly discovered negative sense RNA paramyxovirus [133], which is genetically very similar to RSV, is reported to infect about 5-9% of HCT recipients [27, 134]. The rate of progression to LRTI can range from 21% to 40%, and the mortality rate increases with the onset of LRTI (33-40%) [6] . High fatality rates (80%) in HCT recipients with positive bronchoalveolar lavages for HMPV and the potential for the virus to cause bronchiolitis obliterans, based on histological assessment, have been reported [135]. With clinically indistinguishable presentation compared to other respiratory viruses and unreliable growth of diagnostic cultures, this infection is best diagnosed using PCR-based assays or direct antigen detection. No drugs are currently licensed to treat HMPV infection, and the only drug shown to be active against this virus is ribavirin; however, there is a dearth of knowledge about this virus and its treatment [136, 137]. A recent retrospective study examined the efficacy of ribavirin combined with IVIG in HCT recipients with HMPV-LRTI. No difference in mortality rates was observed between treated (n = 13) and untreated (n = 10) patients [138]. There is no vaccine available for HMPV, and general infection control practices are recommended for controlling its transmission.

Human bocavirus

A seemingly common virus affecting children worldwide, the impact of HBoV in HCT recipients is unclear [139]. A recent survey of 51 children with acute lymphoblastic leukemia identified HBoV in 5.6% of nasal swabs [140]. No drugs or vaccine is currently available for HBoV.

Conclusions

Despite overall advances in clinical management, respiratory viruses still remain a source of concern for HCT recipients because of the significant morbidity and mortality associated with these infections and the lack of directed antiviral therapy for most of these viruses. Randomized clinical trials are needed to determine the efficacy of novel antiviral agents, and future research should focus on developing potent vaccines to prevent outbreaks and epidemics in the community. Prevention of CRVs should be emphasized for healthcare workers and patients alike, with a focus on general safety precautions (**Table 2**).

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Conflict of interest statement

Authors have no conflicts of interest to declare.

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