

REVIEW

Antiviral therapy for respiratory viral infections in immunocompromised patients

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ABSTRACT

Introduction: Respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, coronavirus, human metapneumovirus, and rhinovirus) represent the most common causes of respiratory viral infections in immunocompromised patients. Also, these infections may be more severe in immunocompromised patients than in the general population. Early diagnosis and treatment of viral infections continue to be of paramount importance in immunocompromised patients; because once viral replication and invasive infections are evident, prognosis can be grave.

Areas covered: The purpose of this review is to provide an overview of the main antiviral agents used for the treatment of respiratory viral infections in immunocompromised patients and review of the new agents in the pipeline.

Expert commentary: Over the past decade, important diagnostic advances, specifically, the use of rapid molecular testing has helped close the gap between clinical scenarios and pathogen identification and enhanced early diagnosis of viral infections and understanding of the role of prolonged shedding and viral loads. Advancements in novel antiviral therapeutics with high resistance thresholds and effective immunization for preventable infections in immunocompromised patients are needed.

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1. Introduction

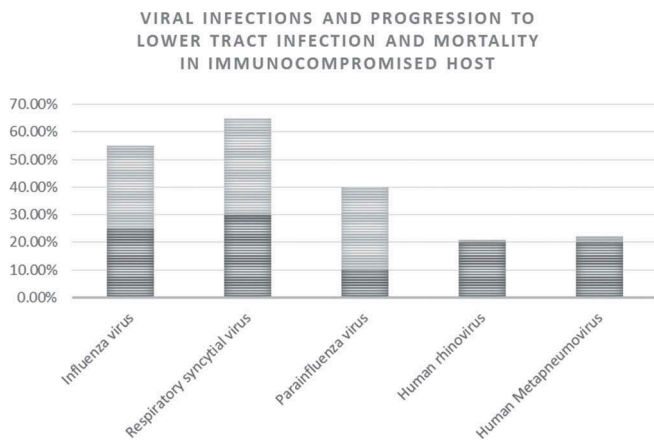
The spectrum of immunocompromised hosts has expanded over the past decade owing to prolonged survival of patients with various malignancies and advances in both solid-organ and hematopoietic stem cell transplantation. Novel immunosuppressive therapies create diverse immune deficits that generate a substrate for opportunistic infections [1]. These patients are defined by higher susceptibility to infections by organisms with lower native virulence than in immunologically normal hosts.

Influenza, parainfluenza, respiratory syncytial virus, coronavirus, human metapneumovirus, and rhinovirus represent the most common cause of respiratory viral infections in immunocompromised patients [1]. Most of these infections are seasonal, and the viruses cause a wide range of upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs). However, adverse outcomes are far more likely in immunocompromised patients than in nonimmunocompromised individuals and include progression to pneumonia, respiratory failure, and increased mortality rates (1–4). In fact, the LRTI rates and mortality rates for hematopoietic stem cell transplant (HSCT) recipients and patients with hematological malignancies reportedly range from 10% to 50% [2–5]. Long-term complications associated with respiratory viral infections, such as airflow obstruction and bronchiolitis obliterans, have developed in HSCT and lung transplant recipients [6,7]. Figure 1 highlights the high rates of progression to LRTI and death among immunocompromised patients with common respiratory viral infections.

The management of viral infections is challenging because viruses are intracellular parasites that use many of the host's own pathways to replicate and propagate. Therefore, antiviral agents need to target specific viral components to avoid potential damage to host cells. Figure 2 highlights the life cycle of viral replication and site of action of various antiviral agents. Advances in the treatment of respiratory infections have been made over the past decades. Table 1 highlights the current available agents for treatment of respiratory viral infections and Table 2 lists the agents currently in the pipeline for these different viruses. The purpose of this review is to provide an overview of the main antiviral agents that are used in the management of respiratory infections in immunocompromised patients focusing on its clinical relevance and our experience, as well as to provide an update on the current investigational agents in the pipeline.

2. Influenza virus

The influenza virus is among the most common human respiratory viruses and belongs to the Orthomyxoviridae family. Four types of influenza viruses are A, B, C, and D. Human influenza A and B viruses cause seasonal epidemics of disease almost every winter in the United States. Influenza type C infections cause a mild respiratory illness and are not thought to cause epidemics. Influenza D viruses primarily affect cattle and are not known to infect humans [17].



Black-Ranges on lower tract respiratory infection.
 Gray-Ranges on Mortality.

Figure 1. Rates of progression to lower respiratory tract infection and death among immunocompromised patient.

Influenza A viruses are grouped into subtypes based on antigenic characteristics of 2 proteins on their surfaces, hemagglutinin (HA) and neuraminidase (NA) with 18 different HA subtypes and 11 NA subtypes. Influenza A viruses can be further broken down into different subtypes. The most

common subtypes of influenza A virus affecting humans are H1N1 and H3N2. Influenza B viruses are not grouped into subtypes but can be further broken down into lineages. Currently, circulating influenza B viruses belong to 1 of 2 lineages: B/Yamagata and B/Victoria [18].

The seasonal prevalence of influenza infections in immunocompromised patients, including solid-organ transplant and HSCT recipients, closely parallels the community-wide prevalence, with peaks from December to February, with Influenza B activity sometimes seen in April and May [19]. However, the illness has the potential to be more severe in this population than in healthy host [20]. Without treatment reported, mortality rate range from 25% to 40% in immunocompromised patients, and is related to complications including pneumonia, and bacterial and fungal superinfections [21]. In a retrospective study, we identified profound lymphocytopenia (absolute lymphocyte count <200 cells/mL), age greater than 65 years, and neutropenia (absolute neutrophil count <500 cells/mL) as potential risk factors associated with progression from URTI to LRTI [22]. Early antiviral therapy within the first 48 h after presentation has been associated with improved prognosis in several studies [23–25].

The two main groups of antivirals used to treat influenza are M2 inhibitors (amantadine and rimantadine), which only

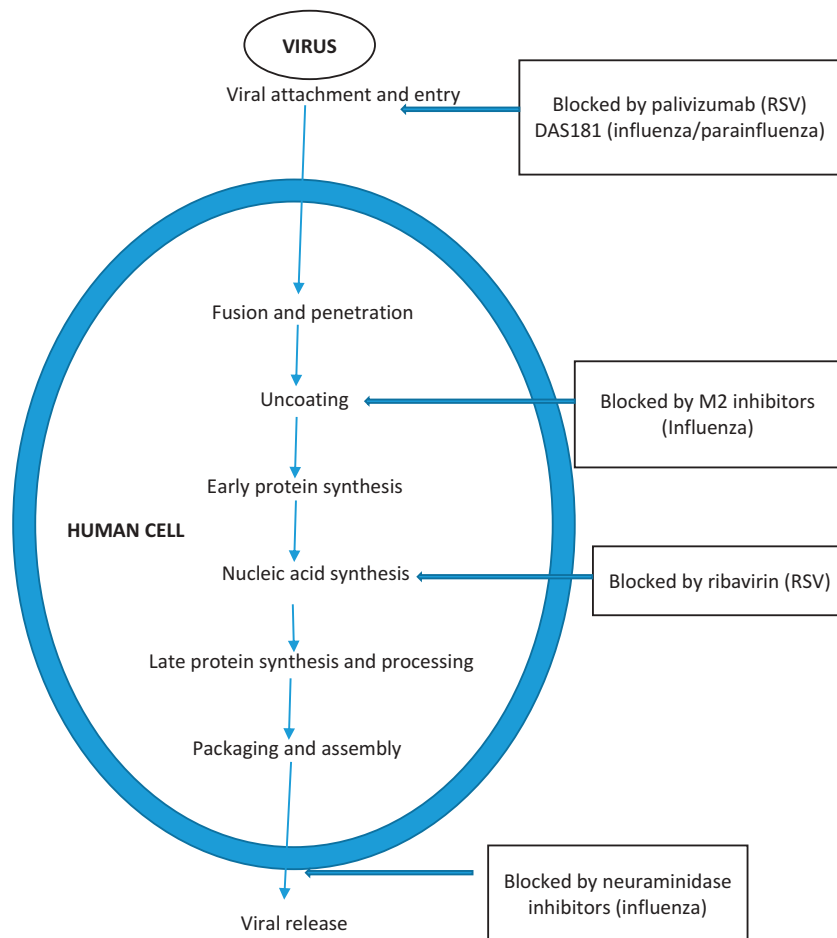


Figure 2. Viral replication and site of action of anti-viral agents. (Reproduced, with permission, from Katzung BG, editor: Pharmacology: Examination & Board Review, 11th Ed. McGraw Hill, 2015.) RSV: Respiratory syncytial virus.

Table 1. Antiviral therapy approved for treatment and prophylaxis of common respiratory viral infections.

Viral infection	Antiviral agents	Drug class/Mechanism of action	Dosage and duration of treatment regimen	Concerns for drug resistance
Influenza virus	Oseltamivir	NAI	75 mg orally twice daily Recommended duration is 5 days Longer duration (10 days) for immunocompromised individuals [8] Two inhalations (10 mg) twice daily for 5 days [8]	Influenza A(H1N1) virus strains H275Y substitution leads to resistance [10,11]
	Zanamavir	NAI	Intravenous zanamivir available through compassionate use program Single dose of 600 mg administered intravenously [8]	Influenza A (H1N1) with both an H275Y and an E119D or E119G NA substitution lead to resistance to zanamivir [12,13].
	Peramivir	NAI	Longer duration of 5 days in high-risk patients [9].	Influenza A(H1N1) virus with H275Y substitution leads to resistance to peramivir [14]
	Amantadine	M2 inhibitor	200 mg given once daily or 100 mg given twice daily over 24–48 h after symptoms resolve (duration of therapy is generally 5 days) [8]	Mutations of the pore-lining residues in the ion channel prevents adamantane and rimantadine from entering the channel
Respiratory syncytial virus	Rimantadine	M2 inhibitor	100 mg twice daily for 5–7 days [8]	None reported
	Ribavirin	Inhibits enzyme dehydrogenase and reduces the cellular deposits of guanidine necessary for viral growth [15]	Aerosolized ribavirin can be administered as 2 g for 2 h every 8 h or as 6 g over 18 h every day for 7–10 d [16] Oral ribavirin – loading dose of 600 mg followed by 200 mg every 8 h on the first day, 400 mg every 8 h the second day, and then escalation to a maximum of 30 mg/kg/day [16]	
Parainfluenza virus	None licensed			
Human rhinovirus	None licensed			
Human Metapneumovirus	None licensed			

NAI: neuraminidase inhibitors

act against influenza A, and NA inhibitors active against influenza A and B: oseltamivir, zanamivir, and peramivir.

2.1. M2 inhibitors

M2 inhibitors inhibit the ion channel of the M2 protein in the influenza A virus, leading to defects in uncoating and assembly of the virus (Figure 2). The influenza virus enters its host cell via receptor-mediated endocytosis; thereafter, it is localized on endocytotic vacuoles. The M2 proton channel transports the ions needed for acidification of the influenza virus inside the vacuoles. This acidification is required for dissociation of the M1 protein from the ribonucleoprotein complexes and the onset of viral replication [26,27].

The recommended dose of amantadine is 200 mg given once daily or 100 mg given twice daily (duration of therapy is generally 5 days) [8]. The most common side effects of these agents are gastrointestinal (nausea and vomiting) and effects on the central nervous system, including anxiety, insomnia, impaired thinking, confusion, lightheadedness, and hallucinations [8].

Resistance of influenza A infection to M2 inhibitors results from mutations of the pore-lining residues in the ion channel, keeping adamantane and rimantadine from entering the channel [28]. According to data from the World Health Organization Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at the US Center for Disease Control and Prevention (CDC), the rates of M2 inhibitors resistance have increased from 0.4% in 1994–1995 season to 12.3% in 2003–2004 [29]. However, during the 2005–2006 season, rates as high as 92% were reported for the influenza A

(H3N2) virus [30]. Recent CDC data demonstrate high prevalence of M2 inhibitors resistance in all influenza A (H3N2) and influenza A (H1N1) pdm09 virus isolates tested [31]. Currently, the current Advisory Committee on Immunization Practices (ACIP) guidelines for treatment of influenza infections, **do not** recommend the routine use of amantadine and rimantadine in the USA for therapy or chemoprophylaxis for currently circulating influenza A virus strains [8].

2.2. Neuraminidase inhibitors (NAIs)

NAIs block the active site of neuraminidase, resulting in uncleaved sialic acid residues on the host cell surface and viral envelopes (Figure 2). Uncleaved sialic acid bound to viral HA causes viral aggregation on the host cell surface, which reduces the amount of virus released [8]. NAIs are virustatic, not virucidal, and early administration of them is a key factor in the development of resistance to the virus and their effectiveness. Treatment with these inhibitors should neither be delayed while awaiting the results of diagnostic testing nor withheld from infected patients with indications for therapy who present more than 48 h after the onset of symptoms, particularly patients needing hospitalization [8]. In particular, the NAIs zanamivir and oseltamivir are first-line agents for treatment of and prophylaxis for influenza.

Oseltamivir is an oral NAI usually prescribed as 75 mg orally twice daily (renally adjusted). The recommended duration of antiviral therapy is 5 days [8]. However, a longer duration (10 days) may be considered for severely ill patients or

Table 2. Antiviral therapy in the pipeline for treatment and prophylaxis of common respiratory viral infections.

Viral infection	Antiviral agent	Mechanism of action	Phase of development, p population
Influenza virus	DAS181 (Ansun BioPharma, San Diego, CA, USA)	Recombinant fusion protein that binds to cells and efficiently removes cell-surface sialic acid residues from respiratory epithelium, inhibiting viral infection	Phase II clinical trials in immunocompromised subjects
	Favipiravir (T705; Toyama Chemical, Tokyo, Japan)	Nucleotide analog and inhibitor of the viral RNA polymerase of influenza	Phase III clinical trials. Uncomplicated influenza in adults
	Laninamivir (CS-8958; Biota)	Long-acting NAI	Phase III clinical trials in children and adults
	JNJ-63623872 (VX-787; Janssen Pharma, Titusville, USA)	Nonnucleoside inhibitor targeting PB2, an influenza RNA polymerase protein	Phase I clinical trials, and a Phase II trial in combination with oseltamivir in adults and elderly hospitalized patients
	Nitazoxanide (NT-300; Romark Laboratories, Florida, USA)	Inhibits the maturation of influenza virus HA	Phase III clinical trial
	MEDI8852 (AstraZeneca, Gaithersburg, Maryland, USA)	Monoclonal antibody targeting the highly conserved epitope in the HA stalk of influenza A virus	Phase IIa in adults with uncomplicated influenza, and phase IIb in adults hospitalized with influenza A
Respiratory syncytial virus	VIS410 (Visterra, Inc., Cambridge, MA, USA)	Anti-HA antibody, which bind to a conserved region of the HA stalk of the influenza virus	Phase IIa clinical trial in healthy subjects
	ALN-RSV01 (Alnylam Pharmaceuticals, Cambridge, MA, USA)	Small-interfering RNA (siRNA) that inhibits RSV replication by interrupting synthesis of the viral nucleocapsid protein	Phase II clinical trial in Lung transplant
	RI-001 (ADMA Biologics, Inc., Hackensack, NJ, USA)	Polyclonal high-titers RSV immunoglobulin	Phase II in immunocompromised patients
	MDT-637 (MicroDose Therapeutx, Monmouth Junction, NJ, USA; Gilead Sciences, Foster City, CA, USA)	Antiviral fusion inhibitors	Phase I clinical trial in healthy adults
	GS-5806 (Gilead Sciences, Foster City, CA, USA)	Antiviral fusion inhibitors	Phase IIb in hematopoietic stem cell transplant
	AL-8176 (Alios, South San Francisco, CA, USA)	Nucleoside inhibitor of the L-protein	Phase II in adults 60 years old and older
Parainfluenza virus	DAS181 (Ansun BioPharma, San Diego, CA, USA)	Sialidase fusion protein effectively cleaves sialic acid from respiratory epithelial cells, preventing viral entry into the cells	Phase II in immunocompromised subjects with lower tract respiratory infection
	BCX2798 and BCX2855 (BioCryst Pharmaceuticals, Inc., Birmingham, AL, USA)	Combined hemagglutinin neuraminidase inhibitor	<i>In vitro</i> and mice studies
Human rhinovirus	Vapendavir (Aviragen Therapeutics, Alpharetta, GA, USA)	Binds to the HRV VP1 capsid protein and prevents the release of viral RNA into the target cells	Phase II in asthmatic adults
Human Metapneumovirus	MAB 338 (Medimmune, Gaithersburg, MD, USA)	Target HMPV fusion proteins	<i>In vitro</i> . No clinical trials
	Human Fab D57	Human monoclonal antibody fragment with biological activity against the fusion protein	<i>In vitro</i> . No clinical trials

NAI: neuraminidase inhibitors

HA: hemagglutinin

immunocompromised individuals [8]. This antiviral therapy is most likely to provide the most benefits when initiated within the first 48 h after an infection occurs, so treatment should be initiated as soon as possible [8,32].

Some experts recommend higher dose of orally administered oseltamivir (e.g. 150 mg twice daily in adults with normal renal function) for the treatment of influenza infection in immunocompromised patients and those who are hospitalized and severely ill [8]. However, no clear evidence indicates that doubling the dose of oseltamivir is a more effective treatment than administering the normally prescribed dose in hospitalized patient, with or without severe illness [33,34]. In a randomized trial of hospitalized patients with severe influenza, mortality rates were similar for patients who received oseltamivir at the double and standard doses [33]. However, 4 patients on the standard dose arm who were infected with influenza A (H1N1) virus without the H275Y substitution at baseline acquired this substitution while on treatment. Although no inferences can be made so far due to the small number of patients, using higher dose to prevent resistance and clinical failure in severely ill

patients or immunocompromised patients still need to be determined in future studies [33]. In addition, a prospective study of adults hospitalized with influenza A and B infections treated with a single or double dose of oseltamivir twice daily demonstrated no differences between the groups in viral clearance, fever duration, oxygen supplementation, or hospitalization length [34].

Patients receiving antiviral medications whose infections do not respond to treatment may have infections with antiviral-resistant influenza viruses. Authors reported oseltamivir resistance, sometimes occurring within 1 week after treatment initiation, in immunocompromised patients with influenza A (H1N1) viral infections in the 2009 pandemic (pdm09) [35]. Genotypic and phenotypic antiviral susceptibility testing are currently available to check the presence of mutations conferring resistance [36]. The more common emergence of resistance to oseltamivir in immunocompromised patients probably partly owes to prolonged viral shedding despite the use of antiviral therapy [37]. Use of infection control measures is vital to reduce the risk of oseltamivir-resistant virus transmission in immunocompromised patients [32].

The pooled incidence rate of Oseltamivir resistance for seasonal influenza A(H1N1) infections was estimated to be about 2.6% by a systematic review in 2009 [38]. However, in Europe during the 2007–2008-winter season, rates of influenza A(H1N1) resistance were higher (up to 68%) [39]. Authors reported that a specific substitution of the seasonal influenza A (H1N1) virus strains H275Y (histidine-to-tyrosine substitution in neuraminidase), caused resistance in most of these cases [10,11]. Most circulating influenza A (H3N2) and influenza A (H1N1) pdm09 are still susceptible to oseltamivir and zanamivir. Of the influenza A (H1N1) pdm09 infections tested during the 2013–2014 influenza season, 98.2% were susceptible to oseltamivir, and 100% were susceptible to zanamivir [40].

Usually mild and limited to the first 2 days of treatment, nausea and vomiting are the most common reported toxic effects of oseltamivir, occurring in about 15% of recipients [41,42].

Zanamivir is administered via an inhaler in a dose of 2 inhalations (each inhalation of 5-mg) twice a day [27]. The chemoprophylaxis dosage of zanamivir is 10 mg (2 inhalations) administered once a day [8]. In randomized trials, this treatment shortened the duration of influenza symptoms by 1–3 days [43–46].

Use of intravenous (IV) zanamivir was evaluated in a recent phase III clinical trial where the efficacy and safety of 300 mg or 600 mg of intravenous zanamivir twice daily were compared to 75 mg of oral oseltamivir twice daily for the treatment of hospitalized patients with influenza infections. The preliminary analysis showed no statistical difference in the time to clinical response (primary outcome variable) between IV zanamivir at 600 mg and oseltamivir, or between IV zanamivir at 600 mg or 300 mg [47]. It is currently available for compassionate use from its manufacturer via a US FDA Emergent Investigational New Drug application, and in a compassionate-use program in Europe [48,49]. Zanamivir is currently the therapy of choice for oseltamivir-resistant influenza infections. However, the literature contains few cases of influenza virus with zanamivir resistance. Infections with the H1N1 influenza strain possessing both an H275Y NA substitution (oseltamivir resistance) and an E119D (with aspartic acid replacing glutamic acid at position 119) or E119G (with glycine replacing glutamic acid at position 119) NA substitution are resistant to zanamivir [12,13].

The main adverse reactions to zanamivir are related to bronchospasm. Use of inhalation powder to treat influenza infection is not recommended for patients with underlying airway issues (i.e. chronic obstructive pulmonary disease, asthma [8]. Also, as it contains a lactose carrier, it can clog ventilator tubing nebulizers and mechanical ventilators [50].

Peramivir is active against influenza A and B and was approved by the FDA in 2014 for treating uncomplicated influenza infections in adults [51]. It is the first NAI approved for IV use and is administered as a single IV dose of 600 mg because of its strong and prolonged affinity for the NA in influenza virus. Peramivir use should be considered for patients who are unable to tolerate oral or enteric drugs [51,52]. Use of a single dose of 600 mg of peramivir administered intravenously, alleviated influenza symptoms an average of 21 h sooner and fever approximately 12 h sooner than in patients given a placebo in a published report [52].

A study of patients at high risk for complications (including patients with diabetes, with chronic respiratory disease, or receiving immunosuppressive therapy), given peramivir for up to 5 days demonstrated shorter durations of illness than in patients given a single dose, and hence a longer duration of treatment for immunocompromised patients is suggested [9]. Also, an open-label, randomized study of high-risk patients during the 2009 influenza A (H1N1) pdm09 demonstrated that use of peramivir (300 mg twice daily or 600 mg once daily) for 5–10 days reduced viral shedding and produced clinical improvement [53].

Authors have reported cross-resistance of oseltamivir and peramivir in immunocompromised patients infected with influenza A (H1N1) virus containing the H275Y variant [54–56]. Therefore, patients infected with influenza A virus with a suspected or documented H275Y substitution should not receive peramivir [14].

Diarrhea is the most common reported adverse effect of peramivir [52]. More serious reactions associated with the central nervous system have included delirium and abnormal behavior leading to injury in patients with influenza who received oseltamivir or peramivir. Primarily reported among children, these neurological events often began abruptly and resolved rapidly [57,58]. The contribution of treatment with neuraminidase inhibitors to these events has yet to be established [59], as some of these adverse events may have been related to the influenza infection rather than its treatment. Authors have frequently reported neuropsychiatric symptoms in children with influenza infections; these symptoms were not always associated with the treatment with neuraminidase inhibitors [60–64].

2.3. Antivirals in the pipeline

DAS181 (Ansun BioPharma, San Diego, CA, USA) is a recombinant fusion protein with a sialidase derived from *Actinomyces viscosus* that cleaves sialic acid receptors in host cells (Figure 2) [65]. This protein binds to cells and efficiently removes cell-surface sialic acid residues from respiratory epithelium, inhibiting viral infection. Considering that DAS181 targets the host cells rather than the virus, it is less likely than virus-targeted drugs to induce treatment resistance. DAS 181 is administered via inhalation and has exhibited preclinical activity against numerous strains of influenza (A and B) and parainfluenza viruses (PIVs) [65,66]. In a phase II double-blind, placebo-controlled clinical trial assessing influenza viral load and patient safety in otherwise healthy influenza-infected participants, an inhaled DAS181 dosage of 20 mg per day reduced viral loads and viral shedding in the multiple-dose group more than in patients taking a placebo as measured using quantitative polymerase chain reaction ($P < 0.05$); however, there was no difference in alleviation of flu-like symptoms between the placebo and the treatment arms. Overall, DAS181 was well tolerated for up to 7 days when administered via daily inhalation for 5–7 days except for thrombocytopenia and liver test abnormalities in some instances.

Favipiravir (T705; Toyama Chemical, Tokyo, Japan) is an investigational antiviral drug that functions as a nucleotide analog and inhibitor of the viral RNA polymerase of influenza. Favipiravir is active against a broad range of influenza A, B, and C viruses, including highly pathogenic avian A (H5N1) and novel avian A (H7N9) viruses [67], as well as influenza viruses resistant to treatment with NAIs or M2 inhibitors [68]. Studies of preclinical cellular and mice models have demonstrated synergy of favipiravir with oseltamivir [69,70]. This drug is currently being tested in phase III clinical trials in the USA, Europe, and Latin America [69,70].

Laninamivir (CS-8958; Biota Pharmaceuticals, Alpharetta, GA, USA) is a long-acting NAI administered via a dry-powder inhaler. A phase III randomized controlled trial demonstrated the superiority of a single inhalation dose of laninamivir octanoate to a 5-day course of oral oseltamivir in adults with seasonal influenza [71]. The drug is potentially effective against oseltamivir-resistant viruses and is currently available in Japan. Laninamivir has been demonstrated to be effective in reducing transmission of influenza infection from patients to household contacts. In a randomized trial, household contact of patient with influenza infection were randomly assigned to receive a single dose of laninamivir, 2 doses of laninamivir given daily for 2 days, or a placebo. Family members in the laninamivir groups were less likely to develop clinical influenza as compared to the placebo group [72]. Daiichi Sankyo Company, Ltd. in Japan plans to study the drug for the prevention of influenza, in single inhalation dose, in both adult and children [73].

JNJ-63623872 (VX-787; Janssen Pharma, Titusville, USA) is a nonnucleoside inhibitor targeting PB2, an influenza RNA polymerase protein, inhibiting production of viral mRNA, and preventing cell death [74]. It demonstrated activity against all influenza A strains tested *in vitro*. Human studies have demonstrated significant decrease in virus shedding, when administered at a loading dose of 900 or 1200 mg on the first day followed by 600 mg once daily for 4 days [75]. A phase IIb trial evaluating the dosing and frequency of the drug in healthy patients with uncomplicated influenza infection is currently under way [76].

Nitazoxanide (NT-300; Romark Laboratories, Florida, USA), an antiparasitic agent, appears to inhibit the maturation of influenza virus HA [77]. In a phase IIb/III trial, the treatment with nitazoxanide 600 mg twice daily for 5 days was associated with reduction in symptoms duration and viral titers among patients with acute uncomplicated influenza infection [15]. Nitazoxanide has also shown synergistic effects *in vitro* with NAIs [78] and a current phase III trial to investigate the efficacy of this synergism has been completed and results are awaited [79].

MEDI8852 (AstraZeneca, Gaithersburg, Maryland, USA) is a monoclonal antibody targeting the highly conserved epitope in the HA stalk of influenza A virus [80]. It is currently being evaluated in a Phase Ib/IIa clinical trial for safety and efficacy of a single intravenous dose in combination with oseltamivir, and as a monotherapy in adult patients with confirmed acute, uncomplicated influenza A infections [81].

VIS410 (Visterra, Inc., Cambridge, MA, USA) is a neutralizing human IgG1 anti-HA antibody, which binds to a conserved

region of the HA stalk of the influenza virus [82]. In mice, it resulted in 100% protection from Influenza infection when administered prophylactically [83].

2.4. Bacterial coinfections

Coinfections with bacterial pathogens and influenza infection may lead to significant morbidity and mortality. Bacterial coinfection is associated with an increase in disease severity, hospital admission and even mortality, with *Streptococcus pneumoniae* and *Staphylococcus aureus* been the most common pathogens in such setting followed by, *Haemophilus influenzae*, and group A streptococci [84]. A recent meta-analysis by Klein et al. (2016) noted that older age, a higher APACHE II (Acute Physiology and Chronic Health Evaluation II) score, diabetes mellitus, and sepsis were risk factors predisposing to coinfections [84]. The American College on Immunization Practices (ACIP) recommends simultaneous antiviral and antibiotic treatment for severely ill patients with influenza infections [8]. Consistent with the ACIP guidelines, the Infectious Disease Society of America (IDSA) guidelines recommend appropriate use of diagnostic tests as guidance for targeted antibacterial therapy for hospitalized patients. Recommended antibacterial therapy includes cefotaxime, ceftriaxone, and respiratory fluoroquinolones. Treatment with vancomycin, linezolid, or other agents directed against methicillin-resistant *Staphylococcus aureus* (MRSA) is recommended for patients with confirmed or a compatible clinical presentation of MRSA infection (i.e. shock and necrotizing pneumonia) [85].

2.5. Respiratory syncytial virus

Respiratory syncytial virus (RSV), an enveloped, single-stranded RNA virus of the family Paramyxoviridae, frequently causes seasonal upper respiratory viral infections in infants and young children. Symptomatic RSV reinfections in immunocompetent adults often consist of URIs lasting 2–5 days. In immunocompromised patients such as HSCT and solid-organ transplant recipients, RSV infections may progress to severe and life-threatening LRTIs [86].

Investigators at the University Of Texas MD Anderson Cancer Center developed an immunodeficiency scoring index for RSV that accounts for major risk factors that identify HSCT recipients who are at high risk for progression of RSV infection to an LRTI and RSV-associated mortality [87]. Age, neutropenia, lymphocytopenia, graft-versus-host disease, use of myeloablative conditioning regimens, use of corticosteroids, a recent HSCT, and pre-engraftment are the main risk factors that are weighed in this index to categorize patients into prognostic risk groups [67]: low (0–2), moderate (3–6), and high (7–12) risk. The authors reported a statistically significant trend of higher incidence of LRTI- and RSV infection-associated mortality as the risk increased from low to moderate to high ($P < 0.001$). Patients in the high-risk group demonstrated greatest benefit of ribavirin-based therapy at the URTI stage and were at the highest risk for progression to LRTI and death in the absence of antiviral therapy. We suggest using the

immunodeficiency scoring index for RSV to identify high-risk patients who would benefit from treatment with aerosolized ribavirin.

As seen in HSCT recipients, researchers noted an association between a low lymphocyte count (mean, 580 cells/mm³) and RSV infection progression to an LRTI in solid-organ transplant recipients with lung transplant recipients having the highest risk of adverse outcomes [88]. Ribavirin is a nucleoside analog that resembles guanosine. As a monophosphate, ribavirin inhibits the dehydrogenase enzyme, which is essential for the synthesis of guanosine triphosphate, and reduces the cellular deposits of guanidine necessary for viral growth. It inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis (Figure 2) [89].

Aerosolized ribavirin is the only FDA-approved treatment of severe RSV-LRTIs in hospitalized infants and young children with underlying compromising conditions (prematurity, cardiopulmonary disease, or immunosuppression) [90]. RSV infections markedly increase morbidity and mortality rates in HSCT recipients. Ribavirin-based antiviral therapy is recommended by European guidelines for leukemia patients and HSCT recipients at high risk of complications [16,91]. In a systematic review of the literature by Shah et al. [92] and based mainly on retrospective studies, any form of ribavirin-based therapy (alone or in combination with immunomodulators) prevented URTIs from progressing to LRTIs (from 45% to 16%) and improved mortality rates (from 70% to 35%) when compared to no therapy in adult HSCT recipients [92]. Whether the benefits of aerosolized ribavirin versus the oral form justify its use in immunocompromised patients remain subject of controversy, especially given the recent drastic increase in the cost of the aerosolized form [93].

Researchers have systematically reviewed the use of oral ribavirin to treat various respiratory viral infections, including RSV infections [94]. The authors concluded that mortality rates were highly variable and often dependent on the underlying severity of illness rather than the effects of oral ribavirin; however, there were not randomized or control studies available for evaluation [94]. In 2004, Khanna et al. [95] reported that oral ribavirin had a good safety profile in 34 RSV-infected patients with upper or lower respiratory tract infection but could not draw a strong conclusion regarding its efficacy. The doses recommended in the European Conference on Infections in Leukaemia (ECIL-4) guidelines included a loading dose of 600 mg followed by 200 mg every 8 h the first day, 400 mg every 8 h the second day, and then escalation daily to a maximum of 30 mg/kg/day [16]. The IV formulation of ribavirin has been beneficial in some cases of RSV infection, but further trials are needed [96,97].

2.5.1. Immunomodulator-based therapy

Various other therapies such as, intravenous immunoglobulin (IVIG), RSV hyperimmunoglobulin, and palivizumab (a monoclonal RSV IgG), have been used for treatment and prevention of RSV infections in immunocompromised patients with mixed results. Early studies demonstrated that ribavirin in combination with RSV IVIG (RespiGam; MedImmune, Gaithersburg, MD, USA), an hyperimmune globulin preparation with high

concentrations of RSV-neutralizing antibodies, offered a mortality advantage over ribavirin alone in RSV-infected pediatric HSCT recipients with LRTIs [98]. However, production of RSV IVIG has since then been discontinued because of the introduction of alternatives such as palivizumab, an engineered anti-RSV monoclonal antibody.

Palivizumab is currently approved for prophylaxis for RSV infection in a select group of high-risk infants with bronchopulmonary dysplasia, infants with a history of premature birth (≤ 35 -week gestational age), and children younger than 24 months with hemodynamically significant congenital heart disease during the RSV infection season [99]. The American Academy of Pediatrics recommends a palivizumab dose of 15-mg/kg body weight administered monthly throughout the RSV infection season (first dose administered prior to commencement of the season and a maximum of 5 doses per season) [99].

Kassis et al. demonstrated the utility of palivizumab for prophylaxis in a HSCT unit following an RSV infection outbreak. Palivizumab was useful in preventing RSV infection in 16 RSV-negative patients considered to be at high risk for complications from RSV infection when combined with strict infection-control measures [100]. In contrast, palivizumab failed to demonstrate any impact on progression to LRTI or mortality in a case series of 40 allogeneic HSCT recipients infected with RSV [101]. Given the questionable efficacy and high cost of palivizumab, mainly for adult patients, routine use of it is not encouraged in the adult immunocompromised population [102].

In adult HSCT recipients with RSV pneumonia, uncontrolled studies suggested that use of combination therapy with ribavirin and IVIG improved survival [103,104]. Additional studies of RSV-infected lung transplant recipients demonstrated that combined treatment with ribavirin (nebulized or IV) with IVIG and/or corticosteroids reduced mortality rates, length of mechanical ventilation, and incidence of bronchiolitis obliterans [105]. Although combined use of ribavirin and IVIG has not been supported by a randomized trial, this expensive treatment is reserved for select patients with RSV-related LRTIs and severe immune deficiency [103,104].

2.5.2. Antivirals in the pipeline

ALN-RSV01 (Alnylam Pharmaceuticals, Cambridge, MA, USA) is small-interfering RNA (siRNA) that inhibits RSV replication by interrupting synthesis of the viral nucleocapsid protein, and treatment with this compound has demonstrated promising results in phase II clinical trials [106]. RNA interference is a natural process and siRNAs induce sequence-specific degradation of mRNA and thus reduce expression of the corresponding protein [106]. In a randomized, double-blind, placebo-controlled trial, researchers administered prophylactic ALN-RSV01 as a nasal spray before experimental inoculation in healthy adults wild-type for RSV and observed a 38% reduction in the number of infections [106]. In a phase IIa randomized, double-blind, placebo-controlled trial of adult lung transplant recipients with confirmed RSV URTIs, use of aerosolized ALN-RSV01 (0.6 mg/kg) daily for 3 days significantly reduced mean cumulative daily symptom scores ($P = 0.035$)

and the incidence of progressive bronchiolitis obliterans syndrome by day 90 more so than in patients given a placebo (6% vs. 50%; $P = 0.027$) [107]. Also, a recent phase IIb trial with lung transplant recipients demonstrated a trend of decreasing new or progressive bronchiolitis obliterans (BOS) incidence (14% vs. 30%; $P = 0.058$) at 180 days. The treatment effect was enhanced with initiation of ALN-RSV01 use fewer than 5 days after symptom onset [108]. Whether further development of this compound would be pursued remains unknown at the present time.

MDT-637 (MicroDose Therapeutx, Monmouth Junction, NJ, USA and Gilead Sciences, Foster City, CA, USA) and the GS-5806 (Gilead Sciences, Foster City, CA, USA) are both antiviral fusion inhibitors. Oral GS-5806 has shown safety and tolerability in healthy adults [109]. Currently, two phase IIb trials are underway to evaluate the antiviral effects, pharmacokinetics, safety, and tolerability of GS-5806 in HSCT recipients with either RSV URI or LRTI [110,111]. MDT-637 is delivered as a dry-inhalation powder and has been evaluated in a phase II trial to assess safety and tolerability in healthy adults [112].

AL-8176 (Alios, South San Francisco, CA, USA) is a nucleoside inhibitor of the L-protein [113] and has demonstrated efficacy in human challenge studies [114,115]. L-protein is an RNA-dependent RNA polymerase of RSV, and its inhibition impact future viral replication [113]. In a randomized, double-blind, placebo-controlled phase II challenge study conducted in healthy adult volunteers who were infected intranasally with RSV, AL-8176 was well tolerated and demonstrated significant reduction in RSV viral loads ($p < 0.0002$) and improvement in symptom scores ($p < 0.02$) when compared to placebo [114,115].

2.5.3. Monoclonal and polyclonal antibodies

Polyclonal high-titers RSV immunoglobulin (RI-001; ADMA Biologics, Inc., Hackensack, NJ, USA) is being tested in patients who are immunocompromised to prevent progression of URIs to LRTIs. Preliminary results are pending [116].

Motavizumab is a newly developed monoclonal antibody targeting a highly conserved antigenic site on the fusion glycoprotein of RSV. It had antiviral effects in hospitalized children but was not superior to palivizumab in seasonal RSV prophylaxis in preterm infants with chronic lung disease of prematurity at-risk for RSV related LRTI, hospitalization or death [117]. In 2010, FDA Antiviral Drugs Advisory Committee declined the request for licensure of motavizumab. The concerns raised included the lack of additional benefits of motavizumab over palivizumab and the additional risk of cutaneous hypersensitivity reactions [118].

2.6. Parainfluenza

Parainfluenza virus (PIV) is a single-stranded, enveloped RNA paramyxovirus comprising 4 antigens that share serotypes, although most clinical PIV infections are caused by types 1, 2, and 3. In the general population, most clinical PIV infections are caused by PIV-3 followed by PIV-1 and PIV-2 [119]. Although PIV infections often occur year round, peak seasonal activity reportedly occurs from late September to

December for PIV-1 and during the spring and summer months for PIV-3 [119].

PIV most commonly affects the upper respiratory tract after an incubation period of 1–4 days and is commonly associated with URIs in children. In immunocompromised patients, authors described progression to LRTI in about 37% of HSCT recipients and PIV-infected patients with hematological malignancies [120]. The risk factors for progression from PIV-URI to PIV-LRTI include lymphocytopenia, neutropenia at the onset of infection, use of corticosteroids during PIV-URI, and respiratory coinfections [120]. Risk factors for PIV-related mortality include lymphocytopenia, young age (<2 years), refractory or relapsed underlying hematological malignancies, an Acute Physiology and Chronic Health Evaluation II score greater than 15, respiratory coinfections, and steroid use at infection onset [120].

No antiviral agents are licensed to treat PIV, so its management is limited to supportive care. In some instances, physicians have used oral or aerosolized ribavirin with or without IVIGs for the treatment of PIV LRTI in immunocompromised patients with various outcomes [121]. New antiviral agents and vaccines in the pipeline may change the paradigm of PIV infection management, particularly in immunocompromised patients.

2.6.1. Ribavirin

Although, as described above, clinical providers have used oral and aerosolized ribavirin to treat PIV [122], the available data on their use for this infection remain controversial. Two recent systematic reviews on HSCT recipients and hematological malignancy patients demonstrated that ribavirin was not significantly more effective at preventing the progression of URI to LRTI or PIV-associated mortality than was supportive care alone [120,123]. Also, in lung transplant recipients with PIV infections, use of oral ribavirin for 14 days at 15–20 mg/kg/day in 2 divided doses (dose length) was associated with some benefits, including a lower rate of bronchiolitis obliterans syndrome within 6 months after development of the infection than that in a non-ribavirin group (5% vs. 24%; $P = 0.02$) [124]. Given, the lack of clear evidence of a positive outcome in PIV-infected patients as well as the absence of control studies, justified recommendation for the use of ribavirin for the treatment of PIV in immunocompromised patients cannot be made.

2.6.2. Antivirals in the pipeline

As described above, DAS181 is a novel sialidase fusion protein with activity against PIV *in vivo* and *in vitro* because it effectively cleaves sialic acid from respiratory epithelial cells, preventing PIV entry into the cells (Figure 2) [125]. DAS 181 have been administered on a compassionate-use basis for severe PIV infections in immunocompromised patients, with apparent clinical benefits and antiviral effects [126]. In a case series, 4 pediatric HSCT recipients with PIV detected in respiratory specimens (2 from the upper respiratory tract and 2 from the lower respiratory tract) received inhaled DAS181 for 5–10 days. Oxygen requirements and respiratory rates improved in all 4 patients, and their viral loads decreased within 1 week after therapy initiation [127]. In a similar case series, 16 HSCT

recipients received DAS181 daily to treat PIV infections (14 LRTIs and 2 URTIs). Of the 16 patient, 9 had complete clinical response, and 4 patients had a partial response to DAS181 therapy. Of 7 patients with virological and spirometric data, 5 had reduction in PIV viral load in nasopharyngeal secretions and 4 had improved forced expiratory volumes by the end of treatment [128]. In an ongoing phase II double-blind, placebo-controlled trial, investigators are examining the effects of DAS181 in immunocompromised patients with PIV-related pneumonia [129]. A recent report described the use of DAS181 in 13 HSCT recipients: 56% of them had responses to therapy, and 24% had partial responses. They also had greater than a 1-log reduction in PIV viral load [130].

BCX2798 and BCX2855 (BioCryst Pharmaceuticals, Inc., Birmingham, AL, USA) are new antiviral hemagglutinin neuraminidase inhibitors and have been evaluated in mouse models of infection with a virus similar to PIV, recombinant Sendai virus [131]. BCX2798 and BCX2855 have demonstrated antiviral activity against PIV-3 by markedly reducing pulmonary viral titers and mortality rates in rats when given intranasal within 24 h after development of infection [132]. Human studies of these two inhibitors have yet to be undertaken.

2.7. Human rhinovirus

Human rhinoviruses (HRVs) are positive-sense, single-stranded RNA viruses with icosahedral symmetry. They are characterized into three genetically distinct groups designated A, B, and C within the genus *Enterovirus* and family Picornaviridae. The viral capsid that encases the RNA genome is made up of four proteins: VP1, VP2, VP3, and VP4. The remaining nonstructural proteins are involved in viral genome replication and assembly [133]. HRV infections are responsible for more than one half of cold-like illnesses and cost billions of dollars annually in medical visits and missed days of work in the USA [134]. Peak incidence occurs in the early fall, with a smaller peak in the spring [135]. Both peak incidences are associated with URTI, otitis media, and sinusitis [133].

A recent study of patients going to the emergency room with influenza-like illnesses who also had hematological malignancies demonstrated that 40% of the patients (110/272) presented with HRV infections. Researchers found that the severity of HRV infection in these patients was similar to that of H1N1 influenza in the 2009 pandemic. Nearly 40% of patients with HRV-associated respiratory symptoms were admitted to the hospital, 29% had LRTIs, and 11% needed intensive care unit admission [136]. Other studies, including those with HSCT recipients, have replicated these results [137,138]. Markers for increased immunosuppression and illness severity in patients with HRV infections, including neutropenia (absolute neutrophil count ≤ 500 cells/ μ L), hypoalbuminemia (serum albumin level ≤ 3.2 mg/dL), and infections with a respiratory co-pathogen(s) were associated with progression to HRV-related pneumonia [138]. In contrast, Parody et al. [139] described a much lower rate of progression to LRTI (13%) in a similar patient population. Use of a different case definition for HRV infection may explain the disparity in the prevalence of LRTIs in these two reports.

Chronic HRV infection has occurred in lung transplant patients [140]. Furthermore, in a study of 36 adult lung transplant recipients, 13% of all bronchoalveolar fluid specimens obtained from 15 (42%) symptomatic patients over a 2-year period were positive for HRV [141].

Currently, treatment of HRV infection consists of supportive care. Antiviral medications for HRV are under investigation.

2.7.1. Antivirals in the pipeline

The viral capsid was the initial viral protein targeted in the development of drugs to inhibit viral replication. These drugs work by binding to the hydrophobic pocket of the viral capsid, resulting in a conformational change, increasing the stability of the virion and interfering with its ability to interact with the cellular receptor [142].

Vapendavir (Aviragen Therapeutics, Alpharetta, GA, USA) is an oral agent that binds to the HRV VP1 capsid protein and prevents the release of viral RNA into the target cells. Vapendavir exhibits antiviral activity against HRV-A and HRV-B serotypes; however, activity against HRV-C is not yet known. A phase II randomized, double-blind, placebo-controlled study of asthmatic adults with HRV URTIs showed lower severity scores for cold symptoms, greater mean reductions in asthma scores, and higher evening peak expiratory flow in those given vapendavir than placebo [143].

Pleconaril (Viropharma, Exton, PA, USA) was the first developed capsid-binding anti-HRV agent. Two phase III multicenter studies in the USA and Canada randomized 2,096 healthy subjects with self-diagnosed colds into groups receiving pleconaril at 400 mg orally twice daily or placebo for 5 days. In the primary-efficacy population, which consisted of 1,363 subjects with HRV RNA detected in nasal secretions, pleconaril-treated subjects experienced a 1-day reduction in the mean duration of illness compared to the placebo group (7.3 days versus 6.3 days; $P = 0.001$) [144]. In another study, researchers found an association between HRV susceptibility to pleconaril and clinical outcomes [145]. The FDA declined licensing of pleconaril owing to concerns of development of resistant virus strains. Additionally, interactions among cytochrome P-450 3A, hormonal contraception, and antiretroviral therapy for human immunodeficiency viral infection may reduce the effectiveness of pleconaril [146].

Rupintrivir (Agouron Pharmaceuticals, Inc., San Diego, CA, USA) is an *in vitro* 3C protease inhibitor that acts against many HRVs and Enteroviruses. Rupintrivir reduced viral loads and respiratory symptoms in healthy volunteers with experimentally induced rhinovirus colds and was well tolerated by the participants [147]. However, in trials of patients with natural infections, rupintrivir failed to reduce viral loads or symptom severity [148].

Inhaled interferon-beta (SNG001, Synairgen plc, Southampton, England) was tested in a phase II, placebo controlled randomized trial of adult asthmatics receiving inhaled corticosteroids and with a history of deterioration with colds, and was associated with significant improvement in asthma symptoms, 65% fewer moderate exacerbations,

improved morning peak expiratory flow rates, and reduced use of relief bronchodilators [149].

2.8. Human metapneumovirus

Human metapneumovirus (HMPV) is an enveloped, negative-sense, single-stranded RNA virus. It is the first human member of the *Metapneumovirus* genus in the Pneumovirinae subfamily within the Paramyxoviridae family. First identified in The Netherlands in 2001, serological studies of antibodies against HMPV indicated that the virus has circulated in humans for at least 50 years [150]. Phylogenetic analysis has identified two genotypes of HMPV: HMPV A and HMPV B [151]. HMPV uses a fusion mechanism to penetrate target cells. The fusion process consists of insertion of the hydrophobic fusion peptide into the target cell membrane and refolding of the F protein. This step requires the interaction of two specific domains: heptad repeats A and B [152]. Investigators have studied this process for development of it as a potential antiviral treatment.

HMPV causes respiratory infections and has a seasonal distribution comparable with those of influenza and RSV infections [153]. Although immunocompromised patients acquire HMPV infections at the same frequency as immunocompetent individuals, they are at higher risk for severe infections. This higher risk likely can be attributed to poor viral clearance [153,154]. A recent systematic review in HSCT recipients and hematologic malignancy patients estimated the incidence of progression of HMPV-URTI to LRTI at 34% and an associated mortality rate of 6% [154]. Factors associated with this progression in HSCT recipients include early onset of infection after transplantation, steroid use, and a low lymphocyte count [155].

To date, treatment of HMPV infections has been mainly supportive. Researchers have investigated several treatment regimens. Standard immunoglobulin preparations have inhibited replication of HMPV *in vitro* [156], and approaches such as use of selective immunoglobulins and fusion inhibitors have demonstrated antiviral activity *in vitro* and in animal studies.

Administration of oral or aerosolized ribavirin with or without polyclonal IVIGs has been advocated for the treatment of severe HMPV infections and is currently used in some centers for high-risk patients [156–160], although most data are still anecdotal.

2.8.1. Antivirals in the pipeline

Fusion inhibitors target the initial steps of viral fusion and penetration into the human cell. Fusion inhibitors with sequence similarity with the HRA and HRB domains of the viral fusion protein have demonstrated important role in viral inhibition. BALB/c mice inoculated with lethal intranasal HMPV challenge were completely protected from clinical symptoms and mortality if they simultaneously received the HRA2 peptide [152]. HR-1 peptides also have demonstrated effectiveness as viral inhibitors [161].

Researchers developed MAb 338 (Medimmune, Gaithersburg, MD, USA) to target HMPV fusion proteins. It appeared to effectively neutralize HMPV in golden Syrian hamster models and reduce the pulmonary viral titers, thereby limiting severe acute manifestations and bronchial hyper-reactivity [162].

A human monoclonal antibody fragment (human Fab D57) with biological activity against the fusion protein of HMPV demonstrated prophylactic and therapeutic potential against severe HMPV infections when tested in cotton rats [163].

2.9. Coronavirus

Human coronavirus (HCoV) is a single-stranded, enveloped RNA virus belonging to the family Coronaviridae. In temperate climates, HCoV infection is transmitted primarily during the winter and is a well-recognized cause of URTIs during the respiratory viral season [164]. Usually mild in immunocompetent hosts, HCoV infection in immunocompromised populations may progress to LRTI [16]. Emerging HCOVs, such as severe acute respiratory syndrome-associated HCoV in 2002–2003 and the more recently identified Middle East Respiratory Syndrome in 2012–2013, have prompted a further impetus to develop therapeutics against this infection because current antiviral agents are lacking and treatment of it remains palliative. Discovery and *in vitro* evaluation of HCoV therapy is ongoing, including investigation of entry inhibitors, human monoclonal antibodies, and proteasome inhibitors [165–168].

3. Conclusion

Respiratory viral infections continue to be major clinical problems in immunocompromised patients. High clinical suspicion and the use of rapid diagnostic tests remain crucial, as early treatment is associated with improved outcomes and reduced transmission. Several advances in the prevention and treatments of influenza infection have occurred in recent decades. Inadequate efficacy of the influenza vaccine as well as the emergence of antiviral resistance, which appears to occur more commonly in immunocompromised patients than in healthy host, underline the difficulties in management of respiratory infections in immunocompromised individuals. RSV and PIV infections continue to be associated with high morbidity and mortality, and further advancements in prevention of and therapy for respiratory viral infections are needed. The impact of rhinovirus, coronavirus, and metapneumovirus infection in patients with compromised immune systems is becoming evident as new, widely available molecular testing improves the recognition of these viral infections.

4. Expert commentary

Over the past decade, important diagnostic advances, specifically, the use of rapid molecular testing has helped close the gap between clinical scenarios and pathogen identification and enhanced early diagnosis of viral infections and understanding of the role of prolonged shedding and viral loads. Respiratory viral infections can be complicated for both clinicians and immunocompromised patients. Future studies that identify and validate scoring systems to ascertaining patients at highest risk for complications of respiratory viral infections including LRTI, are of utmost importance. Also, identification of long-term complications after respiratory viral infections in immunocompromised patients and devising interventions for prevention will be of the utmost value. Last, advancement in novel antiviral therapeutics

with high-resistance thresholds and effective immunization for preventable infections in immunocompromised patients are needed.

5. Five-year view

To curtail the impact of respiratory viruses on our immunocompromised patients, we should focus on prevention of exposure and progression to worse outcomes. Multiple interventional modalities should be studied from stimulation of the innate immune system, response to immunizations, to new antiviral therapies, to avert infection and progression to lower tract respiratory infections. One of the main challenges for immunocompromised patients is the ability to clear infections with subsequent complications associated with worsening infections, prolonged shedding, risk of resistance and coinfections. Treatment targeting not only viral replication, but also the immune response to these infections may offer better outcomes. Last, understanding the role of the microbiome and virome, and its implications on transmission as well as development of infection will be key for development of new strategies.

Key issues

- Respiratory viruses are the most frequent cause of respiratory infections in immunocompromised patients, and are associated with higher rate of progression to pneumonia, respiratory failure and death.
- High prevalence of M2 inhibitors resistance detected in influenza A (H3N2) and 2009 H1N1 virus strains preclude their use for prophylaxis or empiric treatment of seasonal influenza
- Neuraminidase inhibitors are the first line agents for treatment of Influenza and treatment is most likely to provide the most benefit when initiated within the first 48 h of illness
- Zanamivir is currently the therapy of choice for the treatment of oseltamivir-resistant influenza infection
- An immunodeficiency scoring index for RSV, that accounts for the number of risk factors, can be used to identify HSCT recipients who are at high risk for progression to RSV LRTI and RSV associated mortality
- Ribavirin-based therapy (alone or in combination with immunomodulators) can be effective in preventing progression from URTI to LRTI and may improve mortality in highly immunosuppressed adult HSCT recipients
- The safety and efficacy of DAS181 in immunocompromised patients with PIV pneumonia, is currently being studied in an ongoing phase 2 double-blind, placebo-controlled trial.
- Vapendavir binds to the HRV capsid protein, preventing the release of viral RNA into the target cells and has demonstrated favorable results in asthmatic adults with HRV URTIs.
- Antiviral agents for HMPV and HCoV are still under study *in vitro* or in animal models

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