SUPPLEMENT ARTICLE

Management of Respiratory Viral Infections in Hematopoietic Cell Transplant Recipients and Patients With Hematologic Malignancies

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Despite preventive strategies and increased awareness, a high incidence of respiratory viral infections still occur in patients with hematologic malignancies (HMs) and in recipients of hematopoietic cell transplant (HCT). Progression of these viral infections to lower respiratory tract may prove fatal, especially in HCT recipients. Increasing evidence on the successful use of ribavirin (alone or in combination with immunomodulators) for the treatment of respiratory syncytial virus infections in HM patients and HCT recipients is available from retrospective studies; however, prospective clinical trials are necessary to establish its efficacy with confidence. The impact on progression to pneumonitis and/or mortality of treating parainfluenza virus infections with available (ribavirin) or investigational (DAS181) antiviral agents still needs to be determined. Influenza infections have been successfully treated with neuraminidase inhibitors (oseltamivir or zanamivir); however, the efficacy of these agents for influenza pneumonia has not been established, and immunocompromised patients are highly susceptible to emergence of antiviral drug resistance, most probably due to prolonged viral shedding. Infection control measures and an appreciation of the complications following respiratory viral infections in immunocompromised patients remain crucial for reducing transmission. Future studies should focus on strategies to identify patients at high risk for increased morbidity and mortality from these infections and to determine the efficacy of novel or available antiviral drugs.

Keywords. RSV; cancer; immunocompromised host; antiviral therapy; infection prevention.

Patients with hematological malignancies (HMs) and recipients of hematopoietic cell transplant (HCT) remain particularly susceptible to clinically severe viral infections, owing to their compromised immune system. Respiratory syncytial virus (RSV), influenza virus, parainfluenza virus (PIV), and human metapneumovirus (hMPV) are responsible for the majority of virologically diagnosed respiratory tract infections encountered in this patient population. Incidence of each virus can vary each season (Supplementary Figure 1); however, RSV has a higher incidence (2%–17%) in HCT recipients than do influenza (1.3%–2.6%), PIV (4%–7%), or hMPV (3%–9%) [1, 2] (Table 1). Factors associated with the acquisition of these infections include male sex, allogeneic HCT especially from an unrelated donor, cytomegalovirus seropositivity, CD4 lymphopenia in T-cell–depleted patients, and lack of engraftment [3–5].

CLINICAL SYNDROMES

RSV and influenza are seasonal viruses with the highest incidence during the winter months, whereas PIV has the highest incidence during the summer season. A large proportion of immunosuppressed patients experience upper respiratory tract infections (URTIs) with any combination of symptoms (eg, cough, rhinorrhea, nasal congestion, sinusitis, fever, headache, otitis media,

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Table 1. Respiratory Viral Infections in Patients With Leukemia, Lymphoma, and Hematopoietic Cell Transplant Recipients at the University of Texas MD Anderson Cancer Center Since 2009

	Leukemia		Lymphoma		HCT		Total	
Infection	Total	Nosocomial	Total	Nosocomial	Total	Nosocomial	Total	Nosocomial
Respiratory syncytial virus								
2009	4	0	18	1 (6)	50	7 (14)	72	8 (11)
2010	17	0	13	1 (8)	55	5 (10)	85	6 (7)
2011	19	0	3	0	49	5 (10)	71	5 (7)
2012	14	0	10	0	30	1 (3)	54	1 (2)
2013	16	1 (6)	12	1 (8)	51	4 (8)	79	6 (8)
2014	26	1 (4)	17	0	23	1 (4)	66	2 (3)
Total	96	2 (2)	73	3 (4)	258	23 (9)	427	28 (7)
Influenza								
2009	5	0	12	0	33	1 (3)	50	1 (2)
2010	17	1 (6)	11	0	33	1 (3)	61	2 (3)
2011	23	1 (4)	27	0	29	0	79	1 (1)
2012	18	0	8	0	19	0	45	0
2013	29	3 (10)	27	1 (4)	67	2 (3)	123	6 (5)
2014	32	1 (3)	28	0	54	2 (4)	114	3 (3)
Total	124	6 (5)	113	1 (1)	235	6 (3)	472	13 (3)
Parainfluenza								
2009	11	2 (18)	8	0	45	7 (16)	64	9 (14)
2010	21	0	11	0	54	7 (13)	86	7 (8)
2011	34	5 (15)	14	4 (29)	63	11 (17)	111	20 (18)
2012	26	5 (19)	6	0	42	5 (12)	74	10 (14)
2013	40	5 (13)	33	5 (15)	84	9 (11)	157	19 (12)
2014	4	0	10	0	14	1 (7)	28	1 (4)
Total	136	17 (13)	82	9 (11)	302	40 (13)	520	66 (13)

Data are presented as No. of nosocomial infections (%).

wheezing, sore throat, fatigue, malaise, and myalgia), whereas others may develop lower respiratory tract infections (LRTIs) and present with dyspnea, hypoxemia, and new or changing pulmonary infiltrates on chest radiography.

CLINICAL DIAGNOSIS

Specific viral diagnosis can only be made by laboratory confirmation, as all respiratory viral infections have overlapping clinical presentations. Direct immunofluorescence antigen testing is a rapid and inexpensive method available for diagnosing these viral infections, but it has variable sensitivity, ranging from 50% to 93% [6, 7]. A viral culture has been traditionally considered to be the gold standard for diagnosing common respiratory viruses; however, it may require up to a week to become positive. This is especially important in immunocompromised patients, for whom prompt diagnosis and treatment may prevent serious complications from these infections [8, 9]. Due to its high sensitivity and specificity, real-time polymerase chain reaction (PCR) assay is the preferred method for diagnosing viral infections [10, 11]. Multiplex PCR viral panels can efficiently test for multiple viruses at the same time. Furthermore, an automated nested multiplex PCR (FilmArray system) can detect 94.5% of viral pathogens with an average turnaround time of 75 minutes [12, 13].

RISK FACTORS FOR PROGRESSION TO LRTI AND DEATH

Influenza, RSV, PIV, and hMPV can cause LRTI (incidence ranging from 5% to 50%) and death (incidence ranging from 10% to 50%) in HCT recipients and patients with HM [1, 2]. Patients infected with RSV, PIV, or hMPV may also develop other late complications such as airflow obstruction or bronchiolitis obliterans [14–16]. According to Erard et al, 29% of allogeneic HCT recipients with community respiratory virus infections during 100 days post-HCT developed airflow decline within 1 year. The incidence of airflow decline was significantly higher in patients progressing to RSV LRTI (55%) and PIV LRTI (86%) [15]. Risk factors for progression to RSV LRTI or PIV LRTI include older age, smoking history, receipt of

allogeneic HCT, myeloablative regimen, neutropenia, lymphocytopenia, mismatched or unrelated donor transplant, use of marrow or cord blood compared with peripheral blood as a graft source, graft-vs-host disease (GVHD), preengraftment status or early posttransplant period, systemic corticosteroid use, high Acute Physiology and Chronic Health Evaluation II score at presentation, pulmonary coinfections, supplemental oxygen requirement at diagnosis, and detection of viral RNA in the serum [3, 4, 8, 17–22]. Insufficient data are available to comment on the risk factors for progression of hMPV infections.

Progression to LRTI increases the likelihood of a fatal outcome; therefore, prompt diagnosis and early intervention at the URTI stage is a plausible strategy for reducing the impact of these pathogens on patient outcome [23].

MANAGEMENT OF RESPIRATORY VIRAL INFECTIONS

RSV

Management of respiratory viral infections consists of supportive care and, when available, antiviral therapy, especially in patients at high risk of developing LRTIs. Ribavirin is a broad-spectrum nucleoside analogue with activity against DNA and RNA viruses. Based on our systematic review of retrospective studies, we identified that any form of ribavirin-based therapy (alone or in combination with immunomodulators) was effective in preventing URTI from progressing to LRTI (from 45% to 16%) and mortality (from 70% to 35%) in adult HCT recipients compared with no antiviral therapy [23]. A recent, retrospective study with the largest cohort to date of allogeneic HCT recipients with RSV infection (n = 280) identified that receiving ribavirin-based antiviral therapy at the URTI stage was the single most protective factor against progression to LRTI and death [20]. Similar findings have been reported in other studies, in which a lack of aerosolized ribavirin increased the risk of mortality in HCT recipients with RSV lower respiratory tract disease [18, 22] (Figure 1). A small case series described the tolerability and success of intravenous ribavirin in the treatment of 6 pediatric HCT recipients in preventing LRTI and mortality following RSV infection [24]. Similarly, intravenous and oral ribavirin were efficacious in preventing RSV LRTI in 10 adult HCT recipients with severe lymphocytopenia [25]. A very similar finding of higher rates of progression to LRTI in the absence of ribavirin therapy at the URTI stage also was observed in RSV-infected leukemia patients [19]. Furthermore, in a recent randomized clinical trial of HCT recipients and patients with HM, continuous (6 g over 18 hours daily) and intermittent (2 g over 3 hours every 8 hours daily) schedules of aerosolized ribavirin were equally effective in preventing progression to RSV LRTI [26].

Regarding the pipeline of potentially effective investigational drugs, ALN-RSV01 (Alnylam Pharmaceuticals, Cambridge, MA) is a small interfering RNA (siRNA) directed against the messenger RNA of the RSV nucleocapsid protein that has shown some promising results in 2 clinical trials [27, 28]. In the first randomized, double-blind, placebo-controlled trial, nasal spray of ALN-RSV01 was used for prophylaxis before experimental inoculation of healthy adults with wild-type RSV, and this strategy demonstrated a 38% decrease in number of infections. This effect was identified to be independent of preexisting RSV-neutralizing antibodies or intranasal cytokine levels in these individuals [28]. In addition, aerosolized ALN-RSV01 was given to adult lung transplant recipients with confirmed RSV infection and showed a significant reduction in the cumulative daily symptom scores and incidence of progressive bronchiolitis obliterans syndrome compared with placebo [27].

MDT-637 (MicroDose Therapeutx, Inc and Gilead Sciences) is an antiviral fusion inhibitor, which is delivered using the proprietary dry inhalation powder and is undergoing phase 2 trial (available at: http://clinicaltrials.gov/show/NCT01355016). Another compound, GS-5806 (Gilead Sciences), is an oral drug undergoing a randomized, double-blind, placebo-controlled, phase 2 trial evaluating its safety, efficacy, and tolerability in healthy volunteers infected with RSV-A Memphis 37b strain (available at: http://clinicaltrials.gov/show/NCT01756482).

Passive immunoprophylaxis with RSV intravenous immunoglobulin (IVIG) for high-risk HCT recipients failed to show efficacy [29]. The use of palivizumab (monoclonal antibody against RSV) for RSV prophylaxis in young children undergoing HCT was recommended in the 2009 international guidelines for preventing infectious complications in HCT recipients [30], but a lack of strong evidence about efficacy and its high cost make this strategy less attractive. Interestingly, palivizumab was successful in controlling an outbreak of nosocomial transmission of RSV in an HCT unit and is well tolerated in immunocompromised patients [31, 32]. RI-001 (ADMA Biologics, Inc, Ramsey, NJ), an intravenous IVIG isolated from healthy adults with high RSV titers, has shown some promising results when administered to 3 immunocompromised adults with documented RSV LRTI [33].

Dysfunctional cell-mediated immunity with respect to lymphocytopenia and associated immune defect seem to play key roles in the pathogenesis of RSV disease [20, 21]. Therefore, at the University of Texas MD Anderson Cancer Center (UTMDACC), we have developed an immunodeficiency scoring index that accounts for the number and magnitude of these risk factors to identify HCT recipients who are at high risk for progression to RSV LRTI and RSV-based mortality as guidance for prognosis and timely management of this infection [34]. Age, neutropenia, lymphocytopenia, GVHD, myeloablative conditioning regimen, corticosteroids, recent HCT, or

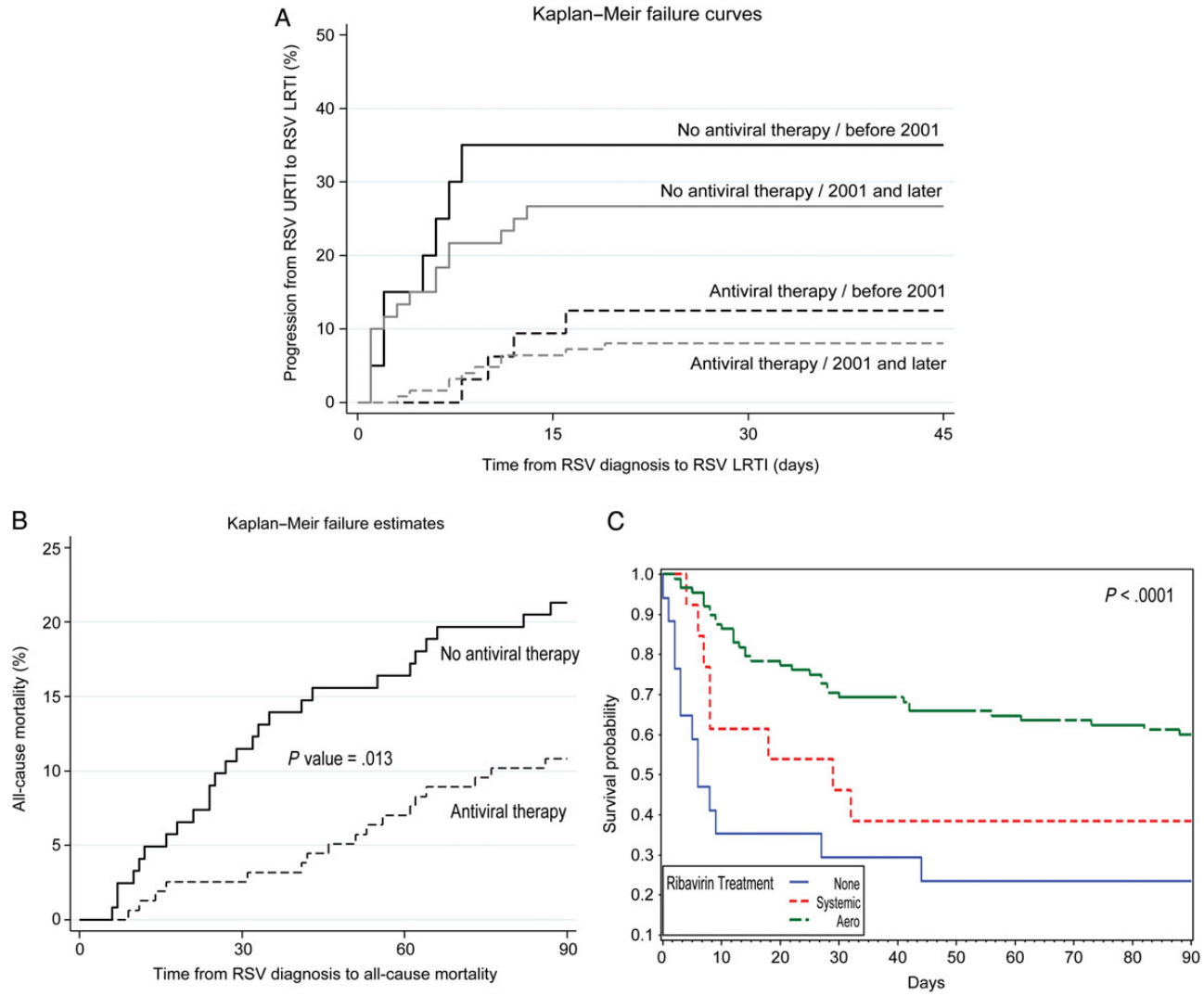

Figure 1. Effect of ribavirin (aerosolized or systemic) therapy on respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) and RSV-associated mortality in allogeneic hematopoietic cell transplant (HCT) recipients from retrospective studies at The University of Texas MD Anderson Cancer Center (UTMDACC; n = 280) and Fred Hutchinson Cancer Research Center (FHCRC; n = 118). *A* and *B*, Effect of administering aerosolized ribavirin therapy at upper respiratory tract infection stage on RSV LRTI ($P < .05$) and RSV-associated mortality ($P < .001$) in 280 allogeneic HCT recipients at UTMDACC [20]. *C*, Effect of aerosolized or systemic ribavirin administered at lower respiratory tract disease stage on pulmonary deaths ($P < .0001$) in 118 allogeneic HCT recipients at FHCRC [22]. Figure 1 was reproduced from articles by Shah et al [20] and Waghmare et al [22] with permission of Oxford University Press. Abbreviations: LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection.

preengraftment are the main risk factors that are weighed in this scoring index to categorize each patient into 3 prognostic risk categories: low, moderate, and high. This scoring index should be validated in a multi-institutional study.

PIV

Ribavirin has not been proven efficacious in HCT recipients in retrospective studies [14, 17, 35]. Furthermore, a large case series reported that it had no effect on viral shedding, symptom duration, hospital stay, progression to LRTI, or mortality following PIV infections in HCT recipients [17, 35]. Interestingly, in a recent study, ribavirin showed some benefit associated with overall mortality but not with deaths due to respiratory failure or in patients with bronchoalveolar lavage–confirmed PIV LRTI [36]. Aerosolized ribavirin has no proven benefit and is usually not recommended for the treatment of PIV infection. When patients progress to pneumonia, the use of IVIG, along with intensification of the antimicrobial regimen for possible superimposed bacterial and/or fungal infections, is usually recommended at UTMDACC [17]. The impact of IVIG on overall outcome following PIV infection still needs to be determined, but in theory it works by decreasing the anti-inflammatory

responses in the lungs, as mainly documented for RSV in cotton rat models [37, 38]. Very few novel antiviral drugs have shown promising results for treating PIV infection in this patient population. DAS181 (Ansun BioPharma, Inc, San Diego, California) is a sialidase catalytic domain/amphiregulin glycosaminoglycan binding sequence fusion protein that enzymatically removes the sialic acid residues from the respiratory epithelial cell surface that are essential for viral entry and infection [39, 40]. It has shown efficacy against PIV in vitro, in a cotton rat infection model, and in 3 immunocompromised patients with respiratory infections, including 2 HCT recipients [40–42]. Nebulized DAS181 was successful in clearing the infection from 2 HCT recipients with severe PIV LRTI requiring mechanical ventilation; however 1 of the patients developed recurrent PIV infection at the end of treatment and died [43]. An open-label study to examine the safety and efficacy of DAS181 administered by dry powder inhaler or nebulized formulation in immunocompromised patients with PIV infection is under way. Other compounds, such as BCX2798 and BCX2855, have been found to have antiviral activity against PIV-3, significantly reducing pulmonary viral titers and mortality in rats when given intranasally within 24 hours of infection [44]; however, no human studies are available to date. Finally, other treatment options, such as the use of interferon alfa-2b, have been reported in individual patients [45].

hMPV

Very few data are available for antiviral agents against hMPV. It can cause persistent viral infection and may result in fulminant respiratory decompensation and shock following transplant [16].

Influenza Virus

Changes in the susceptibility patterns of influenza virus strains dictate the recommendations for first-line therapy. With the increasing resistance against M2 inhibitors (amantadine and rimantadine), the neuraminidase inhibitor oseltamivir is the most widely used anti-influenza drug in these patients. A delay in initiation of antiviral therapy (24 hours after onset of symptoms) may lead to unfavorable complications such as progression to LRTI and death in HCT recipients; however, the beneficial effect of antiviral therapy is still observed even with a delayed start from symptom onset [8, 9]. Antiviral drug resistance is more common in immunocompromised patients due to continued viral replication despite antiviral therapy [46]. Pandemic 2009/H1N1 virus with H275Y mutation confer oseltamivir resistance [47], and triple combination therapy (oseltamivir, amantadine, and ribavirin) has been suggested to prevent emergence of this resistance [48, 49].

DAS181 (now undergoing phase 2 trials) was also active against influenza strains that were resistant to oseltamivir and zanamivir in vitro and in mouse models [50–53]. Development of resistance against DAS181 was minimal and unstable, as shown by extensive passaging of influenza virus strains (B/Maryland/1/59 and A/Victoria/3/75 [H3N2]), which resulted in reduced fitness of the viral strains [53]. DAS181 also showed broad-spectrum activity by blocking infection from highly pathogenic H5N1 (A/Vietnam/3046/2004) virus in ex vivo human lung tissue culture and primary pneumocytes [54]. Studies are needed to evaluate DAS181 for influenza treatment.

The intravenous route is preferred for antiviral agents in patients with gastrointestinal GVHD or LRTI, on mechanical ventilation, or requiring bilevel positive airway pressure to circumvent the bioavailability issues; hence, intravenous neuraminidase inhibitors (nitazoxanide, oseltamivir, and zanamivir) are undergoing phase 3 clinical trials [55–57]. Intravenous zanamivir was safe and effective in reducing viral load in hospitalized patients with severe or progressive laboratory-confirmed influenza during an open-label, multicenter, noncontrolled, phase 2 study, thus warranting further investigation [58]. Favipiravir (T-705) showed activity against lethal avian influenza A (H5N1), drug-resistant, and pandemic 2009 H1N1 viruses during in vitro and animal experiments [59–62]. In a large randomized, double-blind, noninferiority clinical trial, laninamivir octanoate (and its pro-drug CS-8958) caused significant illness alleviation in adults with influenza [63]. It also showed significant efficacy against oseltamivir-resistant influenza strains in mouse models [64, 65]. Adjunctive therapy with corticosteroids may decrease inflammation and thus prevent LRTI, but at the cost of prolonging viral shedding in immunocompromised patients [9].

During outbreaks, daily chemoprophylaxis with strain-specific anti-influenza antiviral drug has been recommended in HCT recipients (within 24 months after transplant, with GVHD or taking immunosuppressive therapy) by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices [30, 66]. In a randomized, double-blind, placebo-controlled trial, prophylaxis with oseltamivir was effective in reducing influenza burden by 75% in high-risk transplant recipients [67]. However, this strategy may lead to the selection of resistant influenza strains, as seen during the 2009/H1N1 pandemic [47, 68]. At our institutions, we recommend treating empirically all HCT recipients presenting with respiratory symptoms during the winter season when influenza virus is circulating in the community with oseltamivir until the diagnosis is confirmed or ruled out by a negative direct fluorescent antigen/culture test or multiplex PCR.

Preventive Strategies

The high cost of antiviral therapy, combined with a lack of clear evidence of drug efficacy in this patient population and the associated high morbidity and mortality, underscore the need for effective vaccines against these respiratory viruses. As per the

Infectious Diseases Society of America 2013 guidelines, an annual intramuscular (inactivated) influenza virus vaccine is recommended for all immunocompromised HM patients and HCT recipients who are 6 months or older [69]. The main exceptions are those patients who have received intensive chemotherapy, anti–B-cell antibodies, or HCT in the past 6 months due to the low immune response to the influenza vaccine (50% less than healthy adults) that can be observed in HCT recipients [69, 70]. In case of a community outbreak of influenza as defined by states and/or local health departments, vaccination is given at 4 months following HCT [69]. Live attenuated influenza vaccine should not be administered to immunocompromised patients or individuals who live in a household with an immunocompromised patient (ie, a patient in receipt of HCT in the past 2 months or with GVHD) [69].

Given the high morbidity and mortality and the lack of vaccines and specific antiviral therapy for most of these infections, preventive measures remain the best approach for decreasing the burden of viral infections in HM patients and HCT recipients. It is important to increase awareness among patients, caregivers, and healthcare personnel about the impact of these viruses on immunocompromised patients. At our institutions, healthcare workers with symptomatic respiratory tract infections are not allowed to work with immunosuppressed patients, as per the 2009 international guidelines for preventing infectious complications in HCT recipients [30]. Specifically at UTMDACC, staff members with mild respiratory symptoms must wear mask and gloves for direct patient contact, and those with fever and/or copious respiratory secretions are excused from direct patient care for at least 24 hours after becoming afebrile without the use of antipyretics. Because these infections may be acquired nosocomially, strict adherence to contact isolation, hand hygiene, and wearing masks and gloves, along with universal precautions, should be observed. Everyone involved in the management of immunocompromised patients as well as close family contacts should be encouraged to receive influenza vaccination.

SUMMARY

High incidence of respiratory viral infection along with resulting LRTI and mortality continues to be a major clinical problem in patients with HM and HCT recipients. Lack of directed antiviral therapy and vaccination against most of these viruses makes the matters worse. In the absence of randomized clinical trials, it is crucial to identify high-risk patients within this patient population who may benefit the most from preemptive antiviral therapy. Novel antiviral agents and potent vaccines are needed to prevent outbreaks and epidemics in the community. In addition, data are needed to describe the epidemiology, risk factors, and outcome characteristics of respiratory viruses that are now routinely detected by multiplex PCR assays, such as coronaviruses and human rhinoviruses. Infection control and awareness among healthcare workers and patients alike remain the mainstays for reducing the burden of these viral infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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