

# Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of Human Respiratory Syncytial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus, and Coronavirus

Hans H. Hirsch,<sup>1,2</sup> Rodrigo Martino,<sup>3</sup> Katherine N. Ward,<sup>4</sup> Michael Boeckh,<sup>5</sup> Hermann Einsele,<sup>6</sup> and Per Ljungman<sup>7,8</sup>

<sup>1</sup>Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, <sup>2</sup>Transplantation and Clinical Virology, Department of Biomedicine, University of Basel, Switzerland; <sup>3</sup>Department of Hematology, Autonomous University of Barcelona, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; <sup>4</sup>Division of Infection and Immunity, University College London, United Kingdom; <sup>5</sup>Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; <sup>6</sup>Department of Internal Medicine II, Julius-Maximilians-University Würzburg, Germany; <sup>7</sup>Department of Hematology; Karolinska University Hospital, and <sup>8</sup>Division of Hematology, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden

Community-acquired respiratory virus (CARV) infections have been recognized as a significant cause of morbidity and mortality in patients with leukemia and those undergoing hematopoietic stem cell transplantation (HSCT). Progression to lower respiratory tract infection with clinical and radiological signs of pneumonia and respiratory failure appears to depend on the intrinsic virulence of the specific CARV as well as factors specific to the patient, the underlying disease, and its treatment. To better define the current state of knowledge of CARVs in leukemia and HSCT patients, and to improve CARV diagnosis and management, a working group of the Fourth European Conference on Infections in Leukaemia (ECIL-4) 2011 reviewed the literature on CARVs, graded the available quality of evidence, and made recommendations according to the Infectious Diseases Society of America grading system. Owing to differences in screening, clinical presentation, and therapy for influenza and adenovirus, ECIL-4 recommendations are summarized for CARVs other than influenza and adenovirus.

**Keywords.** respiratory virus; transplantation; leukemia; bone marrow transplantation; hematopoietic.

Community-acquired respiratory virus (CARV) infections include a variety of RNA viruses such as human orthomyxo-, paramyxo-, picorna-, and coronaviruses, and DNA viruses such as adeno-, boca-, and polyomaviruses [1, 2]. CARVs are detectable in the general

population throughout the year, but some CARVs show a pronounced seasonality in temperate climates that can exceed epidemic thresholds [1, 3]. CARV respiratory tract infections (RTIs) range from asymptomatic replication to significant disease that typically affects the very young and the very old populations, patients with chronic medical conditions, and those with inherited, acquired, or drug-induced immune dysfunction [1, 4]. In the past 2 decades, CARV RTIs have been recognized as a significant cause of morbidity and mortality in patients with leukemia and those undergoing hematopoietic stem cell transplantation (HSCT) [5–9]. These patients are at increased risk for progression to lower RTI (LRTI) with clinical and radiological signs of pneumonia, respiratory failure, and fatal outcome. The risk

Received 6 August 2012; accepted 18 September 2012; electronically published 28 September 2012.

Correspondence: Hans H. Hirsch, MSc, Transplantation and Clinical Virology, Dept of Biomedicine, Building Petersplatz, University of Basel, Petersplatz 10, CH-4003 Basel, Switzerland (hans.hirsch@unibas.ch).

**Clinical Infectious Diseases** 2013;56(2):258–66

© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1093/cid/cis844

of LRTI and fatal outcome appears to reflect the intrinsic virulence of specific CARVs as well as factors specific to the patient, the underlying disease, and its treatment.

To better define the impact of CARVs in leukemia and HSCT patients, and to improve their diagnosis and management, a working group of the Fourth European Conference on Infections in Leukaemia (ECIL-4) 2011 reviewed the literature on CARVs, graded the available evidence, and made recommendations according to the Infectious Diseases Society of America grading system (Supplementary Table 1). Because several aspects regarding influenza virus and adenovirus differ substantially, including availability of vaccines and use of specific antivirals, and screening of high-risk patients for occurrence of gastrointestinal and disseminated disease, respectively, ECIL recommendations are summarized for CARVs other than influenza and adenovirus [10].

## METHODS

PubMed was searched using each of the following terms: respiratory virus, respiratory syncytial virus, metapneumovirus, parainfluenza, rhinovirus, enterovirus, picornavirus, coronavirus, polyomavirus, bocavirus; together with leukemia, or hematopoietic transplantation, or HSCT, or bone marrow transplantation, or cord blood. Published studies were identified and reviewed in August 2011. In June 2012, 5 additional papers and one paper in press were identified. The majority of publications are retrospective observational studies, while few prospective studies have been published dealing with this topic.

### CARV Diagnostic Considerations

The diagnosis of CARV RTI is dependent on the specimen and the laboratory assay(s) available. Potential specimens for diagnostic testing include nasopharyngeal aspirates, nasopharyngeal wash, swabs (preferably flocked for nasal sampling), tracheal aspirates, and bronchoalveolar lavage (BAL) [1, 11]. Pooling bilateral nasopharyngeal with throat swabs is often preferred over nasopharyngeal aspirates or nasopharyngeal wash for upper RTI (URTI), and BAL is preferred over tracheal aspirates for the diagnosis of LRTI. Laboratory tests include:

- Nucleic acid amplification testing (NAT), used as a generic term to describe molecular genetic tests such as polymerase chain reaction and others for the detection of viral DNA or RNA.
- Direct antigen detection (DAD), used as a generic term to describe direct detection of antigens in a specimen using specific antibodies in different assay formats (direct fluorescent antigen, enzyme-linked immunoassay, immune chromatography, etc).
- Virus isolation by cell culture (VIC), used as a generic term to describe cell culture for the isolation of infectious,

replicating viruses. VIC is performed using conventional and/or shell vial cell culture techniques that can be combined with DAD for agent identification.

VIC has a higher clinical specificity for disease but requires a dedicated virology laboratory, is less sensitive than NAT, and has a comparatively long turn-around time of 2–5 days. DAD has a good clinical specificity, and a short turn-around time of <4 hours, but has a lower sensitivity compared with VIC and NAT [12–20]. NAT is often preferred because of a higher sensitivity, an acceptable turn-around time of <24 hours, in addition to the potential of quantifying viral loads, multiplexing with other infectious agents, detecting genetic variants, and molecularly characterizing nosocomial outbreaks in specialized laboratories.

### Definitions of CARV Infection and Disease

The detection of CARV in asymptomatic patients is increased when using sensitive NAT [16, 21, 22]. As outlined elsewhere previously [23], it is therefore important to distinguish between patients with CARV infection and CARV infectious disease. To provide a case definition comparable to one proposed by the European Centre for Disease Prevention and Control for influenza virus, the working group agreed to its adaptation for other CARVs in leukemia and HSCT patients (Table 1).

- URTI was defined as the detection of CARVs above and including the larynx (eg, in samples from nose, pharynx, larynx, conjunctivae, or sinuses).
- URTI disease (URTID) was defined as the detection of CARVs in upper respiratory tract fluid specimens together with symptoms and/or signs and other causes excluded.
- LRTI was defined as the detection of CARVs below the larynx (eg, in samples from trachea, bronchus, bronchoalveolar sites).
- LRTI disease (LRTID) was defined as pathological sputum production, hypoxia, or pulmonary infiltrates together with identification of CARVs in respiratory secretions, preferentially in samples taken from the sites of involvement (Table 1).

### Characteristics of Specific CARVs

#### (Human) Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) falls into 2 distinct antigenic subgroups, A and B. Infections occur year-round but peak during the cold season, with increases in URTID (eg, sinusitis, rhinitis, and laryngitis) in young children, and LRTID (eg, bronchiolitis and pneumonia) in neonates [3, 24]. RSV RTI of patients with HSCT and/or other hematological diseases follow the community activity and reflect an increased risk of community-acquired, household, and nosocomial transmission [15, 25–27]. In the past, the standard diagnostic assays

**Table 1. Definitions of Community-Acquired Respiratory Virus Respiratory Tract Infectious Disease**

Case Classification
<ul style="list-style-type: none"><li>• Possible case: meeting the <i>clinical</i> criteria of RTID</li><li>• Probable case: meeting the <i>clinical</i> criteria of RTID together with an <i>epidemiological</i> link</li><li>• Confirmed case: meeting the <i>clinical</i> criteria of RTID and the <i>laboratory</i> criteria</li></ul>
Clinical criteria
<ul style="list-style-type: none"><li>• New onset of symptoms AND at least 1 of the following 4 respiratory symptoms:<ul style="list-style-type: none"><li>◦ Cough</li><li>◦ Sore throat</li><li>◦ Shortness of breath</li><li>◦ Coryza</li></ul></li><li>• AND the clinician's judgment that the illness is due to an infection</li></ul>
Epidemiological criteria
<ul style="list-style-type: none"><li>• An epidemiological link to human-to-human transmission (activity in the community, contact with visitor, another patient, or healthcare worker)</li></ul>
Laboratory criteria
<ul style="list-style-type: none"><li>• Detection of CARV in a clinical specimen, preferably from the site of clinical involvement, by at least 1 of the following:<ul style="list-style-type: none"><li>◦ Virus isolation by cell culture</li><li>◦ Direct virus antigen detection</li><li>◦ Nucleic acid amplification testing</li></ul></li><li>• AND exclusion of a major role of other etiologies</li></ul>
Abbreviations: CARV, community-acquired respiratory virus; RTID, respiratory tract infectious disease.

have been DAD and VIC, but these techniques have been replaced or complemented by NAT in many centers [14, 28]. RSV infections occur in 0.3%–2.2% of pediatric patients with acute myeloid leukemia [29] and in 1%–12% of adult patients with hematological malignancy and HSCT [8, 30–36]. Infection in the first 100 days after myeloablative allogeneic HSCT has been associated with an increased risk of persistent air flow decline at 1 year after transplant [37]. Progression to LRTID is observed in 38% (mean; range, 0%–68%) of leukemia and HSCT patients, with an average mortality of 32% (range, 0%–70%), as reviewed elsewhere [14, 38]. Risk factors for LRTID include infection during preengraftment, lymphopenia, older age, allogeneic HSCT, and severe immunodeficiency due to a range of contributing factors (Table 2). Although the risk of a poor clinical outcome progressively increases with overall falling absolute lymphocyte counts [9], varying thresholds of lymphopenia have been reported in clinical studies (0.3 to  $0.1 \times 10^9/L$ ) [8, 31, 32, 39]. Rapid diagnostics, infection control measures, and deferral of chemotherapy and/or HSCT are important considerations [22]. Corticosteroid treatment is a risk factor in leukemia patients [30], but

**Table 2. Risk Factors of Respiratory Syncytial Virus–Associated Complications in Hematopoietic Stem Cell Transplantation Patients**

Progression to LRTID
<ul style="list-style-type: none"><li>• Lymphopenia <math>&lt;0.2 \times 10^9/L</math></li><li>• Older age</li><li>• Mismatched/unrelated donor</li><li>• Allogeneic HSCT <math>&lt;1</math> mo</li><li>• Neutropenia <math>&lt;500/\mu L</math></li><li>• No therapy with aerosolized ribavirin + IVIG</li></ul>
Mortality
<ul style="list-style-type: none"><li>• Preengraftment</li><li>• Lymphopenia <math>&lt;0.2 \times 10^9/L</math></li><li>• Allogeneic HSCT <math>&lt;1</math> mo</li><li>• Severe immunodeficiency</li><li>• Older age (<math>&gt;65</math> y)</li></ul>
Abbreviations: HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; LRTID, lower respiratory tract infectious disease.

the role of corticosteroids is controversial, since improving respiratory function has been seen despite increasing RSV loads and prolonged shedding [40, 41]. Currently, there is only limited evidence for effective treatments because of the lack of potent antiviral drugs and sufficiently powered, randomized controlled clinical trials (RCTs) [42, 43]. However, pooling of published studies suggests that treating URTID in HSCT and leukemia at risk for LRTID and treating manifest LRTID with ribavirin and intravenous immunoglobulin (IVIG) improves outcome [14, 33, 38]. It should be recognized that proper meta-analyses were not possible, and the results should therefore be interpreted with caution.

### Human Parainfluenza Virus

The human parainfluenza virus (HPIV) species -1, -2, -3, and -4 cause mild URTID throughout the year, but type-specific seasonal increases of URTID and LRTID with laryngotracheitis, bronchiolitis, and pneumonia are seen in 15% of infected children during autumn and spring [3, 44]. Diagnosis of HPIV infection has been largely made using DAD or VIC covering HPIV-1, -2, and -3, but is increasingly replaced by NAT also identifying HPIV-4. In adult and pediatric leukemia and HSCT patients, symptomatic HPIV infections have been reported to range from 2% to 7%, of which at least one-third are manifest as LRTID [9, 32, 45–49]. Among the pediatric patients, 90% of HPIV infections were deemed to be community-acquired. Given an estimated incubation period of 2.6 days (95% confidence interval [CI], 2.1–3.1) [50] and a high rate of 17.9% asymptomatic shedding [36], outpatient and nosocomial outbreaks are not infrequent, indicating the need for infection control strategies [18, 46–48, 51–56]. In HSCT recipients with URTID and LRTID, HPIV-3 is the most commonly

detected type in children as well as in leukemia and HSCT patients (80%–90%) followed by HPIV-1 and -2 [44, 45, 57, 58]. Nonmyeloablative conditioning has been associated with HPIV URTI after 30 days after transplant [48]. URTI has been associated with significant airflow decline in 40% of patients [37], which may progress to LRTID in 13%–37% and a fatal outcome in 10%–30% [45, 57]. Reported risk factors for LRTID are higher corticosteroid exposure, neutropenia, lymphopenia, infection early after allogeneic HSCT, a higher APACHE II score, and coinfections [32, 45, 47, 48, 57–60]. Treatment options are limited by the lack of effective agents and RCTs, although some centers consider treating HPIV URTID in patients with risk factors for LRTID and HPIV LRTID, with ribavirin and/or IVIG [8, 18, 31, 36, 37, 48, 61–64]. Bronchiolitis obliterans syndrome and obstructive airflow decline have been associated with HPIV infection within the first 3 months after allogeneic HSCT, which persisted at 1 year after transplant [37, 65].

#### **Human Metapneumovirus**

Human metapneumovirus (HMPV) is a paramyxovirus closely related to RSV, causing increases in URTID and tracheobronchitis in 5%–20% of children and adults during winter. HMPV infection is commonly diagnosed by NAT, and rates range from 2.5% to 9% during the first 2 years after allogeneic HSCT [32, 66–68]. Asymptomatic and prolonged shedding has been reported in HSCT patients [36, 69, 70]. HPMV URTID in HSCT patients can present with flu-like symptoms [66, 67]. In HSCT patients with pneumonia, HMPV is frequently codetected with other pathogens, including bacteria, fungi, and other CARVs, as well as cytomegalovirus, all which obscure the attributable morbidity [32, 66]. Recipient cytomegalovirus seropositivity was a risk factor in one study of HSCT patients [36]. Single cases of severe disease and fatal outcome have been reported [71, 72]. No general recommendation for treatment can currently be made, although some centers consider treating HMPV LRTID with ribavirin and/or IVIG despite the lack of supporting studies [19, 26, 32, 66, 67].

#### **Human Coronavirus**

Human coronaviruses (HCoVs) circulate throughout the year with a slight predominance in winter, presumably causing 10%–30% of cases of the “common cold.” HCoVs are divided into group 1–like (CoV-229E and -NL63) and group 2–like (CoV-OC43 and -HKU1) agents that are molecularly distinct. Although VIC and DAD are available, most centers use NAT in multiplex formats, reporting rates of 5.7% among acutely symptomatic patients. The incubation period has been estimated as 3.2 days (95% CI, 2.8–3.7) [50] followed by a median detectability of 2–3 weeks. URTID with rhinitis, pharyngitis, and laryngitis is the most common manifestation. Cases of

LRTID with bronchitis, bronchiolitis, and pneumonia have been reported in very young (age <1 year) and/or in immunodeficient patients [73–75]. In HSCT patients, HCoV has been detected in 6.7%–15.4%, but asymptomatic shedding may be as high as 41% [21]. In symptomatic HSCT patients, coinfections with other pathogens are frequent. LRTID and pneumonia with fatal outcome occur rarely [76]. General recommendations for treatment are limited in view of the largely benign course, the lack of effective antiviral agents, and appropriate clinical studies [21, 75, 77, 78].

#### **Human Rhinovirus**

Human rhinoviruses (HRhVs) belong to the Picornaviridae family and are divided into 3 species called A, B, and C encompassing >100 serotypes. HRhVs circulate throughout the year and are the most common cause of URTID (rhinorrhea, postnasal drip, cough) and occasionally (tracheo-)bronchitis [1]. The incubation period has been estimated as 1.9 days (95% CI, 1.4–2.4) [50]. Diagnosis largely depends on NAT, although DAD for rapid testing and VIC are performed in specialized laboratories. In allogeneic HSCT recipients, HRhVs have been identified as the most frequent CARVs, reaching a cumulative incidence as high as 22.3% by day 100 [21], with detection rates of up to 40% among symptomatic HSCT patients [34]. HRhV infection may be asymptomatic in 13% of HSCT patients, and prolonged shedding over 4 weeks is frequent, with coinfections with other CARVs occurring in 19% of patients [79]. One study reports that higher HRhV loads correlate with symptomatic presentations [80]. LRTID with frank pneumonia is rare and may occur in <10% of allogeneic HSCT infected with HRhV, usually in myeloablative conditioning, with an estimated mortality of <10% [32, 59, 79, 81]. The role of HRhV treatment is limited by the lack of agents and clinical trials.

#### **Other CARVs**

Human enteroviruses (HEnV), encompassing at least 66 serotypes, also belong to the Picornaviridae family. HEnVs are detected in <5% of hematological patients with URTID, which may progress to LRTID in 13% [9, 34, 79]. Although some HEnVs are identifiable by VIC, current laboratory diagnosis relies mostly on NAT, which may also be designed to detect other picornaviruses such as HRhV or parechoviruses. Lymphopenia of <500/ $\mu$ L is a risk factor for LRTID in HSCT patients.

Human bocavirus (HBoV) and human polyomavirus (HPyV) infections have been detected in patients with hematological malignancies or HSCT [82]. However, studies of cases with a well-documented clinical course and proven disease by histopathology are missing. Accordingly, risk factors for disease and the need for therapy are not well

defined. HBoV belongs to the Parvoviridae family and is detected in 5% of children with RTI. HBoV has been frequently codetected with other viral agents, preventing an unequivocal attribution to URTID or LRTID. In BAL from adult patients, HBoV was detected in 0%–3% of cases. Recent studies suggest that HBoV loads  $>5 \log_{10}$  copies/mL in respiratory fluids are more likely to indicate clinically significant replication [83]. Disseminated HBoV infection has been reported, but the clinical interpretation of NAT signals, even when found in blood or organ sites, may be difficult, since its prolonged persistence has been described akin to parvovirus B19 [84].

HPyV RTIs include KIPyV and WUPyV, which have been detected in 0.2% and 1.4% of children with acute URTID, respectively [85]. KIPyV has been detected more frequently in respiratory fluids of HSCT patients (17%) compared with other patients (5%) [86]. In symptomatic children with leukemia or HSCT, higher viral loads in BAL have been reported [87]. In a large prospective study of 222 HSCT patients, KIPyV and WUPyV showed a cumulative incidence of 26% and 8%, respectively, after 1 year, with no seasonal pattern, but an increased rate in patients  $<20$  years of age (hazard ratio, 4.4 and 4.6, respectively) [88]. Sputum production and wheezing were associated with KIPyV or WUPyV detection, but not with graft-vs-host disease, cytomegalovirus reactivation, neutropenia, lymphopenia, hospitalization, or death [88]. Pending further studies, routine testing for KIPyV and WUPyV cannot be recommended, and there are currently no data supporting the treatment of KIPyV or WUPyV LRTID [86].

#### ECIL-4 Recommendations on Prevention of CARV Infection

The working group recognizes that the person-to-person transmission of CARVs should lead to measures for their prevention through infection control measures (Table 3). These recommendations should be implemented at the level of patients, relatives, and healthcare workers, both inside and outside of medical institutions (Table 3).

Administration of IVIG preparations to HSCT and leukemia patients with hypogammaglobulinemia  $<4$  g/L may reduce the risk of morbidity or mortality secondary to CARV RTIDs (CIII). During RSV outbreaks in the community indicating an increased risk of exposure, the use of intravenous monoclonal antibody specific for the RSV-F protein (palivizumab) may be considered for pediatric patients aged  $<2$  years as monthly prophylaxis (CIII), but it is not indicated in other patient groups.

#### ECIL-4 Recommendations for Diagnosis of CARV Infection

To balance costs and clinical benefit, screening all patients for CARVs is currently not indicated unless indicated in the context of an infection control investigation of nosocomial transmission and prevention, and thus laboratory testing should focus on symptomatic patients (Table 4). Taking into

**Table 3. Recommendations on Prevention of Community-Acquired Respiratory Virus Infection**

- It is recommended that patients and contact persons should adhere to good personal hygiene, including frequent hand washing, covering the mouth when coughing and sneezing, and disposing safely of oral and nasal secretions (AII).
- Leukemia patients and HSCT patients should avoid contact with individuals with RTI in the hospital and in the community (AII).
- Young children should be restricted from visiting patients and wards because of the higher risk of CARV exposure, prolonged shedding, and ease of transmission (BII).
- All visitors and HCWs with RTI should be restricted from access to patients and wards (AII).
- Inside care facilities, infection control measures should be applied to leukemia and HSCT patients with RTI, including isolation rooms and application of strict protection measures (gloves, gowning, masks, eye protection) for HCWs and visitors (AII).
- Outpatients with RTI should be seen and treated in accordance with infection control measures, ie, in facilities and rooms separated from other HSCT and leukemia patients (AII).

See [Supplementary Table 1](#) for the Infectious Diseases Society of America grading system.

Abbreviations: CARV, community-acquired respiratory virus; HCW, healthcare worker; HSCT, hematopoietic stem cell transplantation; RTI, respiratory tract infection.

account the clinical impact of CARVs in HSCT and leukemia patients and the differences among centers in the technical and financial resources for comprehensive CARV diagnostics by multiplex NAT, the working group recommends prioritizing laboratory tests for specific CARVs such as influenza, RSV, and HPIV (Table 4).

#### ECIL-4 Treatment Recommendations for CARV Infection

Reflecting the clinical impact compared to other CARVs, the working group distinguishes the need of treatment for influenza A and B [10], RSV and HPIV, taking into account the higher risk for poor outcome in specific patient groups. The treatment of RSV and HPIV may involve the deferral of conditioning therapy, treatment with aerosolized ribavirin, or off-label use of systemic ribavirin, whereas no general recommendations for other CARVs can be made at this time (Table 5).

The corresponding modalities of RSV therapy and systemic ribavirin are summarized in [Tables 6 and 7](#), respectively. The working group is cautious about the use of intravenous monoclonal antibody specific for the RSV-F protein, because existing data outside of single case reports do not support its beneficial effect and the cost is very high. Therefore, only very young (age  $<2$  years) allogeneic HSCT patients with LRTID or at high risk for progression to RSV LRTID might be considered for treatment with intravenous monoclonal antibody specific for the RSV-F protein (eg, palivizumab 15 mg/kg body weight) (CIII; [Supplementary Table 1](#)), while this drug should not be considered in other patient groups.

**Table 4. Recommendations for Diagnosis of Community-Acquired Respiratory Virus Infection**

- HSCT candidates or HSCT recipients with URTID or LRTID should be tested for CARVs to guide infection control measures, treatment, and decisions regarding deferral of chemotherapy or HSCT (**AII**).
- Specimens should preferably be taken from the site of clinical involvement, preferably pooled swabs for URTID, or BAL for LRTID, (or tracheal aspirate if BAL is not available) (**BII**).
- First-line diagnostic testing should be performed for influenza A and B, RSV, and HPIV (**AII**).
- Testing for other CARVs<sup>a</sup> should be considered according to risk of exposure and the local epidemiology, or if testing for the first-line CARVs is negative (**BIII**).
- Patients with LRTID should be considered for BAL and broader diagnostic testing including lung biopsy as clinically indicated (**BII**).

See [Supplementary Table 1](#) for the Infectious Diseases Society of America grading system.

Abbreviations: BAL, bronchoalveolar lavage; CARV, community-acquired respiratory virus; HPIV, human parainfluenza virus; HSCT, hematopoietic stem cell transplantation; LRTID, lower respiratory tract infectious disease; RSV, respiratory syncytial virus; URTID, upper respiratory tract infectious disease.

<sup>a</sup> Including human enterovirus, human metapneumovirus, human rhinovirus, human coronavirus, and human adenovirus.

Withholding treatment for RSV infection might be considered for selected stable leukemia and HSCT patients after careful evaluation of risk factors for morbidity and mortality and the possibility of appropriate follow-up visits considering, for example, remission of underlying disease, absence of immunosuppressive drug treatment, absence of the risk factors

**Table 5. Recommendations for Community-Acquired Respiratory Virus Treatment in Hematopoietic Stem Cell Transplantation and Leukemia Patients**

- Deferral of conditioning therapy should be considered for patients with CARV RTID planned for allogeneic HSCT (**BII**).
- Deferral of conditioning/chemotherapy could be considered for patients with CARV RTID scheduled for chemotherapy of hemato-oncological diseases (**BIII**).
- Patients with RSV URTID undergoing allogeneic HSCT or recipients of allogeneic HSCT with risk factors for progression to RSV LRTID and death should be treated with aerosolized or systemic ribavirin and IVIG (**BII**).
- For allogeneic HSCT patients with HPIV LRTID, treatment with aerosolized or systemic ribavirin and IVIG may be considered (**BIII**).
- For allogeneic HSCT patients with CARV URTID or CARV LRTID other than RSV or HPIV, aerosolized or systemic ribavirin and IVIG treatment cannot be recommended (**CIII**).

See [Supplementary Table 1](#) for the Infectious Diseases Society of America grading system.

Abbreviations: CARV, community-acquired respiratory virus; HPIV, human parainfluenza virus; HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; LRTID, lower respiratory tract infectious disease; RSV, respiratory syncytial virus; RTID, respiratory tract infectious disease; URTID, upper respiratory tract infectious disease.

**Table 6. Recommendations for Respiratory Syncytial Virus Treatment in Hematological Patients**

- For treatment of RSV, aerosolized ribavirin can be administered as 2 g for 2 h every 8 h or as 6 g over 18 h/d for 7–10 d (**BII**).
- For treatments using aerosolized ribavirin, appropriate precautions should be applied to avoid environmental exposure and thereby potentially teratogenic effects in pregnant healthcare workers and visitors (**AII**).
- Patients on aerosolized ribavirin should be monitored and treated for adverse events including claustrophobia, bronchospasm, nausea, conjunctivitis, and declining pulmonary function (**BII**).
- For treatment of RSV, systemic ribavirin can be administered orally (**BIII**) or intravenously for patients unable to take oral medication (10–30 mg/kg body weight in 3 divided doses) (**CIII**).
- Patients on systemic ribavirin should be monitored and treated for adverse events including hemolysis, abnormal liver function tests, and declining renal function (**BIII**).
- For allogeneic HSCT patients with RSV LRTID or at high risk for RSV LRTID, aerosolized or systemic ribavirin therapy may be combined with IVIG or anti-RSV-enriched antibody preparations (**BIII**).

See [Supplementary Table 1](#) for the Infectious Diseases Society of America grading system.

Abbreviations: HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; LRTID, lower respiratory tract infectious disease; RSV, respiratory syncytial virus.

associated with LRTID, or mortality (**CIII**). Although some centers would treat patients with HPIV URTID and risk factors listed in [Table 3](#), treatment of HPIV URTID is not generally recommended given the clinically undefined risk and benefit ratio (**CIII**).

Overall, the evidence is more limited for patients with autologous HSCT and/or hemato-oncological disease.

Infection control measures should be applied to patients undergoing autologous HSCT or chemotherapy for hemato-oncological diseases with CARV URTID or LRTID (**BIII**).

Deferral of conditioning/chemotherapy should be considered for patients with CARV-RTID scheduled for autologous HSCT or chemotherapy for hemato-oncological diseases (**BIII**). Treatment of CARV RTID other than influenza is not generally recommended for patients undergoing autologous HSCT or chemotherapy for hemato-oncological diseases (**CIII**).

## DISCUSSION AND OUTLOOK

The working group acknowledges that despite the growing awareness of infections by CARVs in HSCT and leukemia patients, well-designed studies are largely lacking that evaluate diagnostic and therapeutic strategies for CARV. On the diagnostic level, studies are needed to identify the most appropriate diagnostic test and specimen from the upper and lower respiratory tracts. The detection of CARVs in peripheral blood has been associated with significant LRTID, disseminated disease, and poor outcome, but requires evaluation by specifically

**Table 7. Use of Systemic Ribavirin for Respiratory Syncytial Virus or Human Parainfluenza Virus Respiratory Tract Infectious Diseases<sup>a</sup>**

Oral or intravenous ribavirin maximal dosing 10 mg/kg body weight every 8 h for adults	
Day 1: Start with 600 mg loading dose, then 200 mg every 8 h	
Day 2: 400 mg every 8 h	
Day 3: Increase the dose to a maximum of 10 mg/kg body weight every 8 h	
In case of adverse events:	Decrease dose or discontinue ribavirin
Creatinine clearance:	Oral or intravenous administration
30–50 mL/min	Maximal 200 mg every 8 h
10–30 mL/min	No recommendation can be given <sup>b</sup>

<sup>a</sup> Modified after [14].

<sup>b</sup> Some experts use 200 mg once daily under close clinical and laboratory monitoring.

designed studies. There is interest to identify and confirm risk factors of severe disease and poor outcome and to evaluate laboratory markers of virus-specific immunity as surrogate markers of disease and recovery. The recent attempts to use RSV loads as a virological surrogate marker of antiviral treatment by small interfering RNA and/or clinical outcome may have a pacemaker role for other CARVs [89]. Importantly, the currently available treatments for CARV URTID and LRTID lack rigorous evaluation in appropriately sized, prospective randomized controlled trials. This is needed for comparing aerosolized ribavirin with systemic (oral) ribavirin; for evaluating the role of expensive IVIG preparations in combination with ribavirin; and for determining the use of intravenous monoclonal antibody specific for the RSV-F protein (palivizumab, motavizumab) as postexposure prophylaxis for high-risk patients as well as therapy for RSV URTID and LRTID. The development of vaccines is seen as an important area of research. Finally, a better understanding of the indirect alloimmune pathology of CARVs on clinical outcome is important [65], but also depends on a better definition of the direct viral impact.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online ([http://www.oxfordjournals.org/our\\_journals/cid/](http://www.oxfordjournals.org/our_journals/cid/)). 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.

## Note

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Turner RB. Upper respiratory tract infections section B. In: Mandell DaBs, ed. Principles and practice of infectious diseases. 7th ed. Philadelphia: Elsevier, 2010: 809–13.
2. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet* 2011; 377:1264–75.
3. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med* 2001; 344:1917–28.
4. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. *Am J Med* 1997; 102:2–9; discussion 25–6.
5. Whimbey E, Englund JA, Couch RB. Community respiratory virus infections in immunocompromised patients with cancer. *Am J Med* 1997; 102:10–8; discussion 25–6.
6. Boeckh M. The challenge of respiratory virus infections in hematopoietic cell transplant recipients. *Br J Haematol* 2008; 143:455–67.
7. Ison MG. Respiratory syncytial virus and other respiratory viruses in the setting of bone marrow transplantation. *Curr Opin Oncol* 2009; 21:171–6.
8. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. *Medicine (Baltimore)* 2006; 85:278–87.
9. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2001; 28:479–84.
10. European Group for Blood and Marrow Transplantation. 2011 Updates of ECIL. [http://www.ebmt.org/Contents/Resources/Library/ECIL/\\_layouts/mobile/view.aspx?List=9c1d8b11-2538-4794-a3d1-0320e97fe76c&View=f8038554-db71-45ae-ba17-5439cb906493](http://www.ebmt.org/Contents/Resources/Library/ECIL/_layouts/mobile/view.aspx?List=9c1d8b11-2538-4794-a3d1-0320e97fe76c&View=f8038554-db71-45ae-ba17-5439cb906493). Accessed 8 October 2012.
11. Weigt SS, Gregson AL, Deng JC, Lynch JP 3rd, Belperio JA. Respiratory viral infections in hematopoietic stem cell and solid organ transplant recipients. *Semin Respir Crit Care Med* 2011; 32:471–93.
12. Bredius RG, Templeton KE, Scheltinga SA, Claas EC, Kroes AC, Vossen JM. Prospective study of respiratory viral infections in pediatric hemopoietic stem cell transplantation patients. *Pediatr Infect Dis J* 2004; 23:518–22.
13. Kuypers J, Campbell AP, Cent A, Corey L, Boeckh M. Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients. *Transpl Infect Dis* 2009; 11:298–303.
14. Khanna N, Widmer AF, Decker M, et al. Respiratory syncytial virus infection in patients with hematological diseases: single-center study and review of the literature. *Clin Infect Dis* 2008; 46:402–12.
15. Kassis C, Champlin RE, Hachem RY, et al. Detection and control of a nosocomial respiratory syncytial virus outbreak in a stem cell transplantation unit: the role of palivizumab. *Biol Blood Marrow Transplant* 2010; 16:1265–71.
16. van Kraaij MG, van Elden LJ, van Loon AM, et al. Frequent detection of respiratory viruses in adult recipients of stem cell transplants with the use of real-time polymerase chain reaction, compared with viral culture. *Clin Infect Dis* 2005; 40:662–9.
17. van Elden LJ, van Kraaij MG, Nijhuis M, et al. Polymerase chain reaction is more sensitive than viral culture and antigen testing for the

- detection of respiratory viruses in adults with hematological cancer and pneumonia. *Clin Infect Dis* **2002**; 34:177–83.
18. Piralla A, Percivalle E, Di Cesare-Merlone A, Locatelli F, Gerna G. Multicenter nosocomial outbreak of parainfluenza virus type 3 infection in a pediatric oncohematology unit: a phylogenetic study. *Haematologica* **2009**; 94:833–9.
  19. Campbell AP, Chien JW, Kuypers J, et al. Respiratory virus pneumonia after hematopoietic cell transplantation (HCT): associations between viral load in bronchoalveolar lavage samples, viral RNA detection in serum samples, and clinical outcomes of HCT. *J Infect Dis* **2010**; 201:1404–13.
  20. Lee JH, Jang JH, Lee SH, et al. Respiratory viral infections during the first 28 days after transplantation in pediatric hematopoietic stem cell transplant recipients [published online ahead of print 4 March 2012]. *Clin Transplant* **2012**; doi:10.1111/j.1399-0012.2012.01607.x.
  21. Milano F, Campbell AP, Guthrie KA, et al. Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. *Blood* **2010**; 115:2088–94.
  22. Peck AJ, Corey L, Boeckh M. Pretransplantation respiratory syncytial virus infection: impact of a strategy to delay transplantation. *Clin Infect Dis* **2004**; 39:673–80.
  23. Relman DA, Falkow S. Microbial pathogenesis section A. In: Mandell DaBs, ed. Principles and practice of infectious diseases. 7th ed. Philadelphia: Elsevier, **2010**: 3–13.
  24. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* **2010**; 375:1545–55.
  25. Abdallah A, Rowland KE, Schepetiuk SK, To LB, Bardy P. An outbreak of respiratory syncytial virus infection in a bone marrow transplant unit: effect on engraftment and outcome of pneumonia without specific antiviral treatment. *Bone Marrow Transplant* **2003**; 32:195–203.
  26. Machado AF, Sallum MA, Vilas Boas LS, Tateno AF, Machado CM. Molecular characterization of strains of respiratory syncytial virus identified in a hematopoietic stem cell transplant outpatient unit over 2 years: community or nosocomial infection?. *Biol Blood Marrow Transplant* **2008**; 14:1348–55.
  27. Lavergne V, Ghannoum M, Weiss K, Roy J, Beliveau C. Successful prevention of respiratory syncytial virus nosocomial transmission following an enhanced seasonal infection control program. *Bone Marrow Transplant* **2011**; 46:137–42.
  28. Kuypers J, Wright N, Ferrenberg J, et al. Comparison of real-time PCR assays with fluorescent-antibody assays for diagnosis of respiratory virus infections in children. *J Clin Microbiol* **2006**; 44:2382–8.
  29. Sung L, Alonzo TA, Gerbing RB, et al. Respiratory syncytial virus infections in children with acute myeloid leukemia: a report from the Children's Oncology Group. *Pediatr Blood Cancer* **2008**; 51:784–6.
  30. Torres HA, Aguilera EA, Mattiuzzi GN, et al. Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia. *Haematologica* **2007**; 92:1216–23.
  31. Nichols WG, Gooley T, Boeckh M. Community-acquired respiratory syncytial virus and parainfluenza virus infections after hematopoietic stem cell transplantation: the Fred Hutchinson Cancer Research Center experience. *Biol Blood Marrow Transplant* **2001**; 7(suppl): 11S–5S.
  32. Martino R, Porras RP, Rabella N, et al. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. *Biol Blood Marrow Transplant* **2005**; 11:781–96.
  33. Avetisyan G, Mattsson J, Sparrelid E, Ljungman P. Respiratory syncytial virus infection in recipients of allogeneic stem-cell transplantation: a retrospective study of the incidence, clinical features, and outcome. *Transplantation* **2009**; 88:1222–6.
  34. Hassan IA, Chopra R, Swindell R, Mutton KJ. Respiratory viral infections after bone marrow/peripheral stem-cell transplantation: the Christie hospital experience. *Bone Marrow Transplant* **2003**; 32:73–7.
  35. McCarthy AJ, Kingman HM, Kelly C, et al. The outcome of 26 patients with respiratory syncytial virus infection following allogeneic stem cell transplantation. *Bone Marrow Transplant* **1999**; 24:1315–22.
  36. Peck AJ, Englund JA, Kuypers J, et al. Respiratory virus infection among hematopoietic cell transplant recipients: evidence for asymptomatic parainfluenza virus infection. *Blood* **2007**; 110:1681–8.
  37. Erard V, Chien JW, Kim HW, et al. Airflow decline after myeloablative allogeneic hematopoietic cell transplantation: the role of community respiratory viruses. *J Infect Dis* **2006**; 193:1619–25.
  38. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. *Blood* **2011**; 117:2755–63.
  39. Khanna N, Hirsch HH. Respiratory syncytial virus infection in immunocompromised patients revisited. *Clin Infect Dis* **2008**; 46:1934–5.
  40. Buckingham SC, Jafri HS, Bush AJ, et al. A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: effects on RSV quantity and clinical outcome. *J Infect Dis* **2002**; 185:1222–8.
  41. Liu V, Dhillon GS, Weill D. A multi-drug regimen for respiratory syncytial virus and parainfluenza virus infections in adult lung and heart-lung transplant recipients. *Transpl Infect Dis* **2010**; 12:38–44.
  42. Hynicka LM, Ensor CR. Prophylaxis and treatment of respiratory syncytial virus in adult immunocompromised patients. *Ann Pharmacother* **2012**; 46:558–66.
  43. Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. *Clin Infect Dis* **2007**; 44:245–9.
  44. Laurichesse H, Dedman D, Watson JM, Zambon MC. Epidemiological features of parainfluenza virus infections: laboratory surveillance in England and Wales, 1975–1997. *Eur J Epidemiol* **1999**; 15:475–84.
  45. Chemaly RF, Hanmod SS, Rathod DB, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. *Blood* **2012**; 119:2738–45; quiz 969.
  46. Srinivasan A, Wang C, Yang J, et al. Parainfluenza virus infections in children with hematologic malignancies. *Pediatr Infect Dis J* **2011**; 30:855–9.
  47. Srinivasan A, Wang C, Yang J, Shenep JL, Leung WH, Hayden RT. Symptomatic parainfluenza virus infections in children undergoing hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* **2011**; 17:1520–7.
  48. Ustun C, Slaby J, Shanley RM, et al. Human parainfluenza virus infection after hematopoietic stem cell transplantation: risk factors, management, mortality, and changes over time. *Biol Blood Marrow Transplant* **2012**; 18:1580–8.
  49. Lewis VA, Champlin R, Englund J, et al. Respiratory disease due to parainfluenza virus in adult bone marrow transplant recipients. *Clin Infect Dis* **1996**; 23:1033–7.
  50. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis* **2009**; 9:291–300.
  51. McCann S, Byrne JL, Rovira M, et al. Outbreaks of infectious diseases in stem cell transplant units: a silent cause of death for patients and transplant programmes. *Bone Marrow Transplant* **2004**; 33:519–29.
  52. Cortez KJ, Erdman DD, Peret TC, et al. Outbreak of human parainfluenza virus 3 infections in a hematopoietic stem cell transplant population. *J Infect Dis* **2001**; 184:1093–7.
  53. Hohenthal U, Nikoskelainen J, Vainionpaa R, et al. Parainfluenza virus type 3 infections in a hematopoietic unit. *Bone Marrow Transplant* **2001**; 27:295–300.

54. Sydnor ER, Greer A, Budd AP, et al. An outbreak of human parainfluenza virus 3 infection in an outpatient hematopoietic stem cell transplantation clinic. *Am J Infect Control* **2012**; 40:601–5.
55. Maziart RT, Sridharan P, Slater S, et al. Control of an outbreak of human parainfluenza virus 3 in hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* **2010**; 16:192–8.
56. Zambon M, Bull T, Sadler CJ, Goldman JM, Ward KN. Molecular epidemiology of two consecutive outbreaks of parainfluenza 3 in a bone marrow transplant unit. *J Clin Microbiol* **1998**; 36:2289–93.
57. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. *Blood* **2001**; 98:573–8.
58. Marcolini JA, Malik S, Suki D, Whimbey E, Bodey GP. Respiratory disease due to parainfluenza virus in adult leukemia patients. *Eur J Clin Microbiol Infect Dis* **2003**; 22:79–84.
59. Schiffer JT, Kirby K, Sandmaier B, Storb R, Corey L, Boeckh M. Timing and severity of community acquired respiratory virus infections after myeloablative versus non-myeloablative hematopoietic stem cell transplantation. *Haematologica* **2009**; 94:1101–8.
60. Hodson A, Kasliwal M, Streetly M, Macmahon E, Raj K. A parainfluenza-3 outbreak in a SCT unit: sepsis with multi-organ failure and multiple co-pathogens are associated with increased mortality. *Bone Marrow Transplant* **2011**; 46:1545–50.
61. Chakrabarti S, Collingham KE, Holder K, Oyaide S, Pillay D, Milligan DW. Parainfluenza virus type 3 infections in hematopoietic stem cell transplant recipients: response to ribavirin therapy. *Clin Infect Dis* **2000**; 31:1516–8.
62. Shima T, Yoshimoto G, Nonami A, et al. Successful treatment of parainfluenza virus 3 pneumonia with oral ribavirin and methylprednisolone in a bone marrow transplant recipient. *Int J Hematol* **2008**; 88:336–40.
63. Stankova J, Carret AS, Moore D, et al. Long-term therapy with aerosolized ribavirin for parainfluenza 3 virus respiratory tract infection in an infant with severe combined immunodeficiency. *Pediatr Transplant* **2007**; 11:209–13.
64. Sparrelid E, Ljungman P, Ekelof-Andstrom E, et al. Ribavirin therapy in bone marrow transplant recipients with viral respiratory tract infections. *Bone Marrow Transplant* **1997**; 19:905–8.
65. Versluys AB, Rossen JW, van Ewijk B, Schuurman R, Bierings MB, Boelens JJ. Strong association between respiratory viral infection early after hematopoietic stem cell transplantation and the development of life-threatening acute and chronic alloimmune lung syndromes. *Biol Blood Marrow Transplant* **2010**; 16:782–91.
66. Debur MC, Vidal LR, Stroparo E, et al. Human metapneumovirus infection in hematopoietic stem cell transplant recipients. *Transpl Infect Dis* **2010**; 12:173–9.
67. Williams JV, Martino R, Rabella N, et al. A prospective study comparing human metapneumovirus with other respiratory viruses in adults with hematologic malignancies and respiratory tract infections. *J Infect Dis* **2005**; 192:1061–5.
68. Oliveira R, Machado A, Tateno A, Boas LV, Pannuti C, Machado C. Frequency of human metapneumovirus infection in hematopoietic SCT recipients during 3 consecutive years. *Bone Marrow Transplant* **2008**; 42:265–9.
69. Debiaggi M, Canducci F, Sampaolo M, et al. Persistent symptomless human metapneumovirus infection in hematopoietic stem cell transplant recipients. *J Infect Dis* **2006**; 194:474–8.
70. Debiaggi M, Canducci F, Terulla C, et al. Long-term study on symptomless human metapneumovirus infection in hematopoietic stem cell transplant recipients. *New Microbiol* **2007**; 30:255–8.
71. Raza K, Ismailjee SB, Crespo M, et al. Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. *J Heart Lung Transplant* **2007**; 26:862–4.
72. Englund JA, Boeckh M, Kuypers J, et al. Brief communication: fatal human metapneumovirus infection in stem-cell transplant recipients. *Ann Intern Med* **2006**; 144:344–9.
73. Gerna G, Campanini G, Rovida F, et al. Genetic variability of human coronavirus OC43-, 229E-, and NL63-like strains and their association with lower respiratory tract infections of hospitalized infants and immunocompromised patients. *J Med Virol* **2006**; 78:938–49.
74. Folz RJ, Elkordy MA. Coronavirus pneumonia following autologous bone marrow transplantation for breast cancer. *Chest* **1999**; 115:901–5.
75. Pene F, Merlat A, Vabret A, et al. Coronavirus 229E-related pneumonia in immunocompromised patients. *Clin Infect Dis* **2003**; 37:929–32.
76. Uhlenhaut C, Cohen JI, Pavletic S, et al. Use of a novel virus detection assay to identify coronavirus HKU1 in the lungs of a hematopoietic stem cell transplant recipient with fatal pneumonia. *Transpl Infect Dis* **2011**; 14:79–85.
77. Gerna G, Campanini G, Rognoni V, et al. Correlation of viral load as determined by real-time RT-PCR and clinical characteristics of respiratory syncytial virus lower respiratory tract infections in early infancy. *J Clin Virol* **2008**; 41:45–8.
78. Oosterhof L, Christensen CB, Sengelov H. Fatal lower respiratory tract disease with human corona virus NL63 in an adult haematopoietic cell transplant recipient. *Bone Marrow Transplant* **2010**; 45:1115–6.
79. Parody R, Rabella N, Martino R, et al. Upper and lower respiratory tract infections by human enterovirus and rhinovirus in adult patients with hematological malignancies. *Am J Hematol* **2007**; 82:807–11.
80. Gerna G, Piralla A, Rovida F, et al. Correlation of rhinovirus load in the respiratory tract and clinical symptoms in hospitalized immunocompetent and immunocompromised patients. *J Med Virol* **2009**; 81:1498–507.
81. Gutman JA, Peck AJ, Kuypers J, Boeckh M. Rhinovirus as a cause of fatal lower respiratory tract infection in adult stem cell transplantation patients: a report of two cases. *Bone Marrow Transplant* **2007**; 40:809–11.
82. Schenk T, Strahm B, Kontny U, Hufnagel M, Neumann-Haefelin D, Falcone V. Disseminated bocavirus infection after stem cell transplant. *Emerg Infect Dis* **2007**; 13:1425–7.
83. Gerna G, Piralla A, Campanini G, Marchi A, Stronati M, Rovida F. The human bocavirus role in acute respiratory tract infections of pediatric patients as defined by viral load quantification. *New Microbiol* **2007**; 30:383–92.
84. Schenk T, Maier B, Hufnagel M, et al. Persistence of human bocavirus DNA in immunocompromised children. *Pediatr Infect Dis J* **2010**; 30:82–4.
85. Debiaggi M, Canducci F, Berra R, et al. Molecular epidemiology of KI and WU polyomaviruses in infants with acute respiratory disease and in adult hematopoietic stem cell transplant recipients. *J Med Virol* **2010**; 82:153–6.
86. Mourez T, Bergeron A, Ribaud P, et al. Polyomaviruses KI and WU in immunocompromised patients with respiratory disease. *Emerg Infect Dis* **2009**; 15:107–9.
87. Rao S, Garcea RL, Robinson CC, Simoes EA. WU and KI polyomavirus infections in pediatric hematology/oncology patients with acute respiratory tract illness. *J Clin Virol* **2011**; 52:28–32.
88. Kuypers J, Campbell AP, Guthrie KA, et al. WU and KI polyomaviruses in respiratory samples from allogeneic hematopoietic cell transplantation recipients. *Emerg Infect Dis* **2012**; 18:1580–8.
89. Zamora MR, Budev M, Rolfe M, et al. RNA interference therapy in lung transplant patients infected with respiratory syncytial virus. *Am J Respir Crit Care Med* **2011**; 183:531–8.