# 31

# Respiratory Syncytial Virus and Human Metapneumovirus Infection in Transplant Recipients

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## 31.1 Introduction

Respiratory viruses may cause serious morbidity and mortality in the immunocompromised host, and the transplant recipient appears particularly vulnerable. The impact of infection with respiratory viruses and the subsequent development of severe lower respiratory tract disease has been increasingly appreciated as respiratory viruses become more readily detectable. Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are among the best-documented respiratory viruses causing a wide range of respiratory disease in transplant recipients, ranging from asymptomatic shedding to fatal respiratory failure. Understanding the epidemiology and clinical characteristics of RSV and hMPV permits clinicians to intervene pretransplant, provide appropriate infection control and prevention measures, potentially treat patients, and manage immunosuppressive therapy.

Severe respiratory disease in the seriously immunocompromised host in the mid-twentieth century was originally attributed to infection with opportunistic pathogens such as gram-negative bacteria, fungi, *Pneumocystis jiroveci*, and mycobacteria, as well as cytomegalovirus (CMV) and adenovirus. In the later twentieth century, episodes of acute upper respiratory infection (URI) and LRTI without an identified etiology were often considered to be "idiopathic" pneumonia or attributed to regimen-related toxicity or acute respiratory distress syndrome (ARDS). In the classic 1982 study of 215 non-bacterial, non-fungal pneumonias in 525 allogeneic hematopoietic stem cell transplant (HSCT) recipients, 44% of the episodes of pneumonia remained undiagnosed. The overall mortality rate associated with idiopathic pneumonia in these HSCT recipients was 60%, a strikingly high figure [1]. The potential morbidity of RSV infections was first recognized in immunocompromised children in the 1970s, more than a decade earlier than in immunocompromised adults [2–6]. The recognition of respiratory viruses as an important clinical problem likely reflects the increasing number of severely immunodeficient patients, more aggressive attempts to identify the cause of respiratory illness in high-risk patients, and the increasing ability of clinical virology and pathology laboratories to identify respiratory viruses in clinical specimens.

Although uncommon or atypical pathogens may be responsible for respiratory disease in the transplant recipient, the same viruses that cause typically mild but acute respiratory illness in the general population are responsible for hospitalizations in persons of all ages with underlying medical conditions [7]. These same viruses are also a common cause of respiratory disease in transplant recipients [8–15]. With the widespread availability of sensitive and reliable molecular diagnostic methods, RSV and hMPV have been detected worldwide in transplant recipients and shown to be common causes of respiratory disease in the immunocompromised host [16, 17]. In both the general population as well as in transplant recipients, RSV and hMPV may produce a wide constellation of clinical syndromes ranging from the common cold to bronchiolitis to severe pneumonia, but in contrast to the general population, RSV and hMPV may significantly impact the morbidity and mortality of the transplant recipient.

## 31.2 Virology

RSV was first identified in 1956 and became appreciated as a major cause of epidemic bronchiolitis and pneumonia in young children in the 1960s [18, 19]. HMPV was first identified in 2001 by molecular techniques in symptomatic children by van den Hoogen et al. as a paramyxovirus causing bronchiolitis and URI in children [20]. Both viruses are classified within the Pneumovirinae subfamily of the Paramyxoviridae family of non-segmented, negative-strand, enveloped RNA viruses [21]. HMPV belongs to the Metapneumovirus genus whereas RSV is a member of the Pneumovirus genus. Both viruses are highly pleomorphic and their sizes vary from 150 to 600 nm. The RSV and hMPV genomes are approximately 13–15 kb in length and closely resemble each other, excluding a few differences in the order of the genes and the absence of the non-structural

genes (NS1 and NS2) from hMPV genome. The remaining eight genes code for nine proteins present in both viruses: the nucleoprotein (N protein), the phosphoprotein (P protein), the matrix protein (M protein), the fusion glycoprotein (F protein), the putative transcription factor (M2-1 protein), the RNA synthesis regulatory factor (the M2-2 protein), the small hydrophobic glycoprotein (SH protein), the attachment glycoprotein (G protein) and the viral polymerase (L protein). The RNA core of the virion is associated with P, N, L, M2-1, M2-2 proteins, surrounded by M protein and covered by a lipid envelope. F is the most highly conserved of the envelope glycoproteins within each virus and between RSV and hMPV. The fusion glycoprotein is essential in promoting attachment and fusion of the virus with the cell membrane during viral entry. The fusion protein is the target of many vaccines under development as well as that of monoclonal antibodies such as palivizumab, which is used to prevent RSV disease in preterm infants. By contrast, the G gene is the most variable. Whole genome analysis of both RSV and hMPV has shown the existence of two genotypes, A and B. In hMPV, those two major genetic groups are further divided into subgroups A1, A2, B1, B2 based upon the sequence variability of the G and F genes. Subgroup A2 is again divided into A2a and A2b.

RSV and hMPV infections produce both humoral and cellular immune responses. Humoral immunity protects against reinfection while cellular immunity controls established infection and terminates viral shedding. Protective immunity in immunocompetent hosts is thought to be relatively short-lived. Both viruses interfere with the host's innate immune system resulting into incomplete clearance and partial immunity.

## 31.3 Diagnosis

Prompt and accurate identification of respiratory viral pathogen is critically important in the transplant recipient because it enables specific infection control precautions to be instituted, the initiation of specific antiviral therapy, impacts the use of immunosuppressive therapy, and potentially affects whether transplantation should proceed [22–24]. Furthermore, identification of a respiratory viral pathogen can assist in avoiding unnecessary therapy, procedures, and surgical procedures (such as open lung biopsy), as well as assist in the identification of a potential cluster or epidemic of infections within the medical unit, hospital, or community. In hospitalized adults (both immunocompromised and immunocompetent), rapid viral diagnosis has been shown to reduce mortality and decrease the length of hospital stay and total cost [25, 26].

Laboratory diagnosis of respiratory viruses including RSV and hMPV has evolved considerably; adequate specimen collection is still essential for the successful identification of viruses in clinical samples. Newer types of nasopharyngeal swabs have shown improved viral diagnostic sensitivity compared to previous swabs, with similar sensitivity to nasal washes when using sensitive molecular methods in patients [27, 28]. For example, nylon flocked swabs and foam swabs increase cell capture within the swab and then release into the transport media, increasing viral recovery [29, 30]. Nasal wash or aspiration methods are superior for isolation of viruses by culture and increase the sensitivity of culture, antigenic assays and quantitative molecular assays [31]. Nasal washes are well tolerated in cooperative adults and offer the advantage of visualizing the quality of the specimen. Bronchoalveolar lavage remains the specimen of choice to diagnose lower respiratory tract infections because of the ability to simultaneously test for potential co-pathogens such as fungi, *Pneumocystis jiroveci*, and bacteria, as well as to document viral infection in the lower airways. Discordance in viral detection between upper and lower respiratory tract samples have been described with both viruses; negative upper tract and positive lower tract specimens in immunocompromised patients are possible but more discordance has been noted for hMPV compared with RSV.

Molecular diagnosis of RSV and hMPV is faster and more sensitive than viral culture or antigen detection, and most laboratories currently use commercial or in-house molecular assays to detect RSV and hMPV (Table 31-1). Many genes have been targeted to detect RSV, including the N, F and L genes, with similar genes also targeted to detect hMPV. Many rapid assays have been approved including some highly multiplexed respiratory panels allowing detection of RSV and hMPV as well as many other respiratory viruses and bacteria. Several different primer sets may be utilized simultaneously in the reaction mix, and the virus identified by the size of the amplicon or following hybridization with a virus-specific probe. Some commercial assays are very rapid and require minimal technical expertise, with only 1–2 h of turn around time [32, 33]. Some laboratories have developed quantitative assays using hydrolysis probe technology with standard curves to help understand the significance of positive results and to follow viral loads under therapeutic management [34–36]. No quantitative commercial assays are yet available. Molecular assays have also been used to detect viral RNA from blood/serum as a prognostic marker [37].

Unlike molecular methods, isolation of virus by culture confirms the presence of a complete infectious unit capable of further multiplication. Positive culture results may be obtained with as little as a single infectious virion, below the threshold of detection for most other detection methods, including some nucleic acid amplification test (NAAT) methods. Another advantage of viral culture is that multiple viruses may be identified from a single sample and viruses can grow independently of point mutations that could potentially create false negative results by NAAT. The major limitations of viral isolation include the time, expense, and expertise required for virus isolation.

TABLE 31-1. Diagnostic tests for common respiratory viruses

| Virus | RSV | HMPV | Test advantages |
|---|---|---|---|
| Specimen | Nasopharyngeal aspirate, nasal wash, nasal swab, bronchoalveolar lavage | | |
| Real time RT-PCR assays[a] | Widely available | Widely available | Sensitive, specific, and ability to be rapid (within 1 h); typing, determination of viral load, and sequencing possible |
| Enzyme-based Immunoassay (EIA[b]) | Widely available | Not available in the USA but available in Canada and Europe | Rapid but less sensitive (particularly for low viral loads); relatively inexpensive |
| Fluorescent antigen detection | Available | Available | Less expensive, rapid; assess quality of specimen; not as sensitive as RT-PCR |
| Culture (clinical lab) | Central labs only | Limited labs only | Becoming less available; results take time but enables typing and analysis of viral strains |

[a]Many viruses can be detected simultaneously by real-time PCR methods [32].
[b]EIA kits are available for RSV only in the USA but for hMPV outside the USA.

A variety of cell lines can be used to grow RSV (Hep-2, A549, RhMK) or hMPV (LLC-MK2, Vero), and detection by cell culture can also be accomplished using several types of cells together, such as the R-Mix cells (mixture of mink lung cells and A549 cells) [38] (Diagnostic Hybrids, Athens, OH). Centrifugation combined with viral antigen detection methods permits more rapid diagnosis [39]. RSV- and hMPV-specific monoclonal antibodies have been used for immunofluorescence (IFA) techniques either directly on respiratory specimens or in cell culture [40, 41]. The sensitivity of IFA is lower than that of NAAT for detection of RSV and hMPV. However, results can be reasonably fast, the method is relatively inexpensive, and importantly, this method also confirms that an appropriate specimen has been properly obtained by looking at ciliated epithelial cells. Sensitivity of IFA when performed by an experienced laboratory is as high as 70–90% of the samples positive by PCR—at least in children [34]. IFA can detect viruses that would be missed by NAAT because of point mutations. IFA positivity also has good clinical correlation while low grade NAAT positivity can be detected for longer periods of time with unclear significance and transmissibility.

Enzyme immunoassays (EIAs) and rapid antigenic diagnostic tests (RADTs) are commercially available for RSV and to a lesser extent for hMPV. These assays lack sensitivity and/or specificity and are not recommended in transplant populations. More than one diagnostic method should be used, since no method is perfect. Molecular assays have the greatest sensitivity—although perhaps at times can perhaps be too sensitive. Paradoxically, rare point mutations causing mismatches have been described causing false negative results of NAAT in transplant units. Viral cell culture requires time, is becoming less available in laboratories, and is more expensive and less sensitive, although it can catch those strains with mismatches and provide information on viral replicative nature while receiving treatment.

## 31.3.1 Strain Identification and Characterization

Further characterization of RSV and hMPV strains obtained from culture or directly from the clinical specimen is frequently desirable. Antigenic differences among virus strains isolated from different geographic locations or at different times may also be examined. Pools of monoclonal antibodies and "RNA fingerprinting" have been used in the analysis of RSV strains in nosocomial outbreaks [42, 43] but direct sequencing of the F and G glycoproteins is more commonly utilized [44, 45]. Next-generation sequencing is a very promising tool to characterize RSV or hMPV strains during severe infection. This could provide information on phylogenicity to identify outbreaks and also detect mutations that could be associated with antiviral or monoclonal resistance as well as increased virulence. Some human gene alleles in the human genome may increase RSV severity in infants, but little is known yet on these genomic variations in transplant recipients. Next-generation sequencing has the potential to provide information on the virus and the human genomes simultaneously.

# 31.4 Epidemiology

## 31.4.1 RSV Epidemiology

### 31.4.1.1 Hematopoetic Stem Cell Transplantation

RSV is well known to cause annual winter outbreaks in the community (Figure 31-1). Surveillance studies of respiratory viruses from transplant centers have established the high frequency and the significant clinical impact of respiratory viral infections in HSCT recipients overall [8–15, 46, 47] as well as the relative importance of RSV in terms of morbidity and mortality (Table 31-2). A 1988 retrospective review conducted at the Children's Hospital of Philadelphia revealed a

FIGURE 31-1. Seasonality of RSV and hMPV by number of cases/week in outpatient and hospitalized patients, Seattle, 2012–2015.
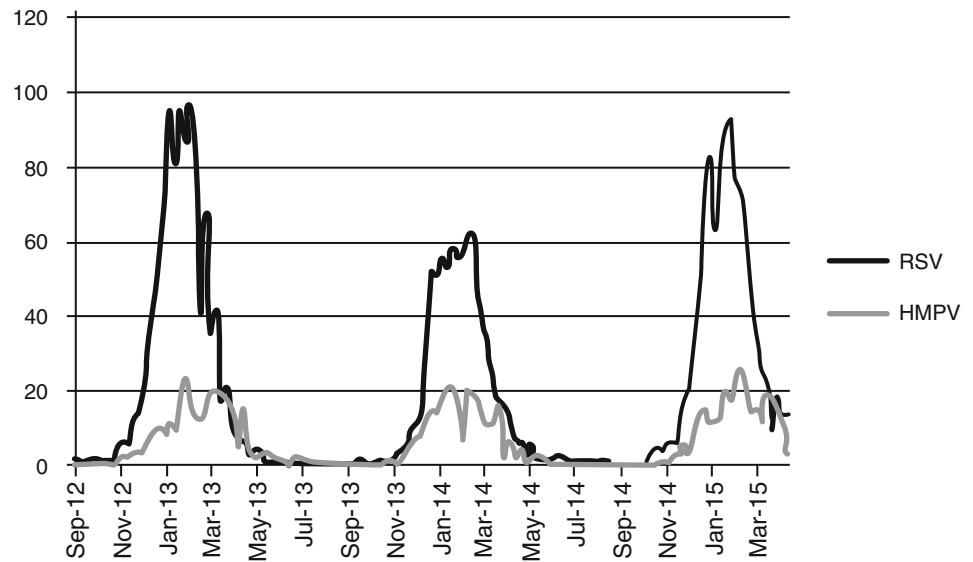


TABLE 31-2. Lower respiratory tract disease associated with RSV and hMPV in transplant recipients

| Virus | Incidence % | Progression to LRTI (%) | Deaths associated with LRTI (%) | Reference |
|---|---|---|---|---|
| HSCT: | | | | |
| RSV | 1–12 | 18–55 | 7–43 | [48, 49] |
| hMPV | 3–7 | 21–40 | 33–40 | [45, 48–50] |
| SOT: | | | | |
| RSV- | | | | [51–53] |
|   Lung TX -adults | 2–16% | ? | 10–20% | |
|   Liver Tx (peds) | 3–46% | ? | 12–20% | |
| | 46% | ? | ? | |
| hMPV- | | | | [54] |
|   Lung TX | 4% | ? | 33% | |

respiratory viral infection in 11 (12%) of 96 pediatric HSCT patients, with only one infection due to RSV [47]. One of the earliest studies demonstrated fatal RSV pneumonia in four of 11 immunocompromised adult HSCT and solid organ transplant recipients with RSV infection [5].

Most studies conducted in the twentieth century utilized classical virological methods that were relatively insensitive for the detection of RSV and/or did not detect recently described respiratory viruses such as hMPV. Thus, these studies likely underestimated the true frequency of RSV overall. Nonetheless, early studies from large transplant centers reported serious sequelae in small numbers of patients who developed pneumonia where RSV was detected [5, 9, 13]. At the Fred Hutchinson Cancer Research Center (Hutch), a prospective surveillance study conducted in 1987 documented respiratory viral infections in 15 (19%) of 78 immunocompromised patients who were followed until hospital discharge [13]; five (33%) patients developed pneumonia and two (13%) patients died (one with RSV, the other with adenovirus). A subsequent prospective surveillance study described 127 viral infections and revealed an overall frequency of viral infections of approximately 4% [11]; 49% of RSV isolates were from BAL. This study demonstrated the relatively high numbers of patients with RSV lower respiratory tract disease, which was higher than rates of LRTI caused by PIV (22%) influenza (10%), or rhinovirus (3%).

Results of viral surveillance in transplant units vary depending on the type of surveillance protocols utilized, time of year surveillance was conducted, type of clinical samples evaluated, and laboratory tests utilized. At the Huddinge University Hospital, Stockholm, a prospective surveillance study conducted among HSCT recipients between 1989 and 1996 detected 39 (7.1%) respiratory viral infections in 545 patients, including RSV in 21% [14]. At M.D. Anderson Cancer Center (MDACC), prospective surveillance conducted using culture techniques among hospitalized adult HSCT recipients during two 6-month winter periods detected 67 (31%) respiratory viral infections in 217 hospitalized patients with acute respiratory symptom. Nearly half of these were due to RSV (33 patients, 49%). The impact of these illnesses was considerable: 20 (61%) patients had RSV infection progressing to pneumonia, and

12 patients with RSV pneumonia died. During the winter period when community viruses were frequent and nosocomial transmission was high, the frequency and mortality of respiratory viral-associated pneumonias was more than four times as high as CMV-associated pneumonia.

Recent prospective studies conducted in transplant centers worldwide continue to demonstrate the importance of RSV and report incidence of infections and risk factors for fatal disease (Table 31-2). A 2005 study from Barcelona, Spain, described the 2-year incidence of symptomatic respiratory viral infections in over 400 patients followed for up to several years posttransplant. Altogether, 29% of allogeneic HSCT recipients and 14% of autologous HSCT recipients had respiratory viruses detected, with 19 patients (4.6%) receiving either autologous or allogeneic transplants having symptomatic RSV disease [55]. Risk factors associated with having a respiratory virus identified included close household contacts with children under the age of 12 years and chronic graft versus host disease. Lymphopenia was identified as a major risk for URI progression. Similar rates have been demonstrated in other centers in the USA [15], South America [56], and Europe [57].

### 31.4.1.2 Solid Organ Transplantation

Less data is available documenting the impact of RSV in SOT recipients (Table 31-2), RSV has been shown to cause lower respiratory tract disease and has been associated with other complications, such as organ rejection and bronchiolitis obliterans. Lung transplant recipients have the highest rates of RSV lower respiratory tract disease in diverse types of organ transplant. RSV infections in lung transplant recipients have also been associated with organ rejection and progressive bronchiolitis obliterans, both of which have been observed to be seasonally related [58, 59]. Adult renal transplant recipients have also been reported to develop RSV-associated lower respiratory tract disease. The mortality has been low, and most patients have recovered without specific antiviral therapy [5, 60]. RSV infections in pediatric liver transplant recipients have been associated with significant morbidity and some but relatively low mortality [51]. Among 483 pediatric liver transplant recipients cared for at the University of Pittsburgh between 1985 and 1991, 17 (3.4%) children developed RSV infections, three-quarters of which were nosocomially acquired. The majority of the children had lower respiratory tract involvement, and two (12%) children died. Specific antiviral therapy was not administered. The risk factors for more severe disease included onset of infection early after transplant, preexisting lung pathology, augmented immunosuppression prompted by rejection, and younger age. Infections occurring late after transplantation in the absence of rejection were usually not severe.

An intensive prospective approach to determining the incidence and risk factors for respiratory viruses was carried out at the Hutch among 122 HSCT recipients, who were prospectively enrolled between 2000–2004 and tested weekly through 100 days posttransplant using both culture and RT-PCR detection methods [50]. The cumulative incidence estimates of hMPV and RSV at day 100 were similar, at 6.2% and 5.8%, respectively. Multivariable analysis demonstrated that only recipient CMV seropositivity was associated with increased risk for acquisition of a respiratory virus (hazard ratio = 4.1, CI 1.7–10.1, $P$ = 0.002).

The frequency of RSV infections and associated morbidity and mortality differs substantially, potentially accounting for the variability reported by different institutions. These differences reflect the intensity of viral surveillances, the time of surveillance, the viruses prevalent in the community, the degree of immunosuppression of the patients, infection control policies, the inclusion of potential as well as actual transplant recipients, surveillance in outpatients as well as inpatients, the types of laboratory assays utilized, and the case definition utilized (i.e., both clinical and laboratory definitions).

## 31.4.2 HMPV Epidemiology

### 31.4.2.1 Hematopoietic Stem Cell Transplantation

HMPV has been detected worldwide with a seasonal distribution. Community outbreaks occur yearly mainly in winter and spring (January to May in the northern hemisphere; June to July in the southern hemisphere) (Figure 31-1). Often hMPV outbreaks will be concomitant with or subsequent to RSV outbreaks. HMPV most commonly affects young children less than 2 years old and is second only to RSV as a cause of bronchiolitis. Seroprevalence studies have shown a high percentage of children have contracted the virus by age 5–10 years. However, reinfection can occur later secondary to insufficient immunity or infection with different genotypes. Predominant hMPV strains can vary from location to location and from year to year. Vicente et al. have reported higher virulence by genotype A [61], while Papenburg et al. reported higher virulence by genotype B [62]. However, the interaction or impact of hMPV with other viruses or bacteria remains unclear, particularly in immunocompromised patients.

The importance of hMPV in transplant recipients has not been as well studied as RSV (Table 31-2). It was first reported shortly after the detection of hMPV by Boivin et al. [17]. An early prospective longitudinal study from Spain documented hMPV in both autologous and allogeneic HSCT recipients, with the incidence and clinical impact of hMPV and RSV disease documented to be quite similar [55]. One early prospective study documented hMPV infections in 22 adults with hematologic malignancies that progressed from upper respiratory infection to pneumonia, with a case- fatality rate close to 14% [63]. Lower respiratory tract disease and pneumonia due to hMPV infection in HSCT recipients has been reported to have an overall incidence of 1–4% [48, 55, 64, 65]. A single case series described hMPV-positive nasal

aspirate samples in 86% of 21 adults following HSCT, many of whom were asymptomatic [66]. This study demonstrated very high rates of genetically similar viruses and differs from most other studies due to high rates of genetically identical viruses. These authors suggested that these hMPV infections may have originated in the hospital nosocomially; nonetheless, this study is an outlier compared to other reports of hMPV in transplant centers.

Pneumonia rates following hMPV infection have been reported at 20–28% with mortality rates of 0–4% [67–69]. Among 163 HSCT recipients who underwent BAL for investigation of lower respiratory tract disease with pulmonary infiltrates by radiographic imaging, hMPV was detected in BAL samples from 5 of 163 (3%) patients; four of these five died with acute respiratory failure highlighting the potential severity of hMPV pneumonia [64]. A retrospective cohort study at the Hutch described a high mortality rate of 43% among patients with hMPV pneumonia, a rate similar to RSV pneumonia mortality [49]. Studies from other transplant units continue to document the potential of hMPV to cause severe lower respiratory tract disease, with clinical presentations and outcomes generally similar to RSV [49, 70].

### 31.4.2.2   Solid Organ Transplantation

The significance of hMPV infection in SOT recipients remains less well defined, with the exception of hMPV disease in lung transplant recipients [70]. Case reports of severe disease have been described following liver and renal transplantation [71, 72]. Rates of hMPV infection in lung transplant recipients have been reported to be similar to those seen in studies of HSCT recipients, varying from 4–6% [57, 73]. In most of these patients, hMPV appears to frequently be the sole pathogen detected. Detection of hMPV in lung transplant recipients may not necessarily signify disease, as was noted in a study of 93 lung transplant recipients undergoing BAL mainly for surveillance purposes; four cases of hMPV was detected in asymptomatic patients [74]. HMPV infection has been found in 4–6% of lung transplant recipients, but prevalence may be higher during nosocomial outbreaks [39, 75]. One study in the setting of a community outbreak identified hMPV in BAL samples from 9 of 26 (35%) patients; their clinical presentation varied from asymptomatic infection to severe disease [39].

Acute allograft rejection was more frequent in the hMPV-infected group than in the non-hMPV-infected group (33% vs. 6%, respectively; $P=0.0257$); and overall mortality was also higher (33% vs. 0%, respectively; $P<0.0025$) [39]. Another prospective study found hMPV infection as frequent as RSV after lung transplantation, and to cause as much pneumonia and acute allograft dysfunction (63% vs. 72%, respectively), but only RSV was associated with chronic allograft dysfunction at 6 months [76]. In another study, 25% of hMPV infections in lung transplant recipients

were associated with acute allograft dysfunction compared with 88% for RSV [49]. A meta-analysis of hMPV respiratory infections and allograft rejection, among lung transplantation recipients indicated that detection of hMPV from airway secretions may be a significant posttransplantation occurrence. A total of 2883 samples from 1007 lung transplant recipients, were analyzed for virus detection; 337 samples had viruses identified and 57 (17%) were positive for hMPV. Twenty of these 57 (35%) cases of hMPV had acute rejection within 3 months of viral detection. There were five (9.4%) cases of chronic rejection in association with hMPV. All studies included in the meta-analysis, with the exception of one, identified rejection within 3 months. Another study has also described cases of chronic rejection within 6 months [77].

## 31.5   Clinical Manifestations

### 31.5.1   RSV in Transplant Recipients

Disease manifestations of RSV are dependent on many factors including the immunity and immune competence of the host, the time of infection related to transplant, the type of transplant, the age and underlying health of the patient, and the degree and duration of immunodeficiency. RSV infections in HSCT recipients typically follow the same clinical sequence as RSV infections in previously healthy children: signs and symptoms of a URI such as rhinorrhea, sinus congestion, sore throat, or otitis media frequently precede signs of lower respiratory tract disease including cough, wheezing, hypoxia, and pneumonia [5, 6, 9] (Tables 31-3 and 31-4). The presence of wheezing with respiratory symptoms during the respiratory virus season may provide the clue that RSV may be present. Progression of URI to LRI has been associated with patients who are early (<1 month) posttransplant,

TABLE 31-3. Clinical symptoms associated with RSV and hMPV infections in transplant recipients

| |
| --- |
| Upper respiratory tract symptoms: |
|    Rhinorrhea, congestion |
|    Sneezing |
|    Sore throat |
|    Sinus congestion, sinusitis |
|    Otitis media |
| Lower respiratory tract symptoms: |
|    Cough |
|    Wheeze |
|    Shortness of breath, chest tightness |
| Systemic symptoms: |
|    Fever |
|    Headache |
|    Myalgia |
|    Hypotension |

TABLE 31-4. Signs, symptoms and viral shedding associated with RSV and hMPV infection in HSCT recipients in a prospective single center institution[a]

| Virus | Number of separate clinical episodes | N (%) No respiratory symptoms | N (%) No systemic symptoms | Viral shedding (median days) | Viral shedding (range, days) |
|---|---|---|---|---|---|
| RSV | 34 | 1 (3) | 7 (21) | 11 | 2–76 |
| MPV | 21 | 0 | 4 (19) | 24 | 5–100 |

[a]Boeckh M, Campbell A, Xie H, Kuypers J, Leisenring WM, Chien J, Jerome KR, and Englund JA. Progression, Shedding Patterns, and Clinical Disease Associated with Respiratory Virus Infections after Allogeneic Hematopoietic Cell Transplantation. Presented at American Society of Hematology Annual Meeting, New Orleans, LA; December 7–10, 2013 (Abstract 3278).

those with lymphopenia, or those who are more severely immunosuppressed. In HSCT patients who have recently engrafted, the frequency of progression to LRI tract disease ranges from 25% to 40% [78, 79] (Table 31-2) Pneumonia following RSV infection may be primarily viral, bacterial, fungal, or mixed in origin. Once RSV disease has progressed to respiratory failure, however, the mortality remains high despite the use of antiviral therapy, immunotherapy, or decreased immunosuppressive therapy. Fatality rates of RSV pneumonia range from 20% in more recent case series to over 80% in earlier studies.

Risk factors for the progression of RSV upper respiratory disease to lower tract disease or pneumonia and factors relating to fatal disease have been evaluated. The most common risk factor described in multiple centers using different methods of case ascertainment and viral detection remains lymphopenia. In a prospective multicenter study carried out by the European Group for Blood and Marrow Transplantation, lymphopenia but not neutropenia significantly increased the risk for lower respiratory tract disease [80]. Older age and donor status are also significant risk factors in some studies, whereas CMV serostatus, acute graft versus host disease, time relative to engraftment, and pre-emptive aerosolized ribavirin at a low dose of 2 h daily were not significant [81]. Investigators from MDACC have demonstrated that season of year, relapse of malignancy, presence of graft versus host disease, increasing age, and lack of engraftment are inpatient risk factors for the development of RSV pneumonia [9, 12, 22, 82]. Recently, large retrospective studies have identified graft source including cord or marrow (adjusted hazard ratio (HR), 4.1, 95% CI 1.8–9.0) and oxygen requirement (adjusted HR 3.3, 98% CI, 15–6.7) to be independently associated with death due to respiratory failure in HSCT recipients [83]. Smoking history, conditioning with high-dose total body irradiation, and an absolute lymphocyte count < 100/mm^{3} at the time of URI onset are also significantly associated with disease progression [84].

Since initiation of therapy hinges on prompt diagnosis, the possibility of false negative laboratory tests must be considered in individual patients and the diagnosis should be aggressively pursued by other means, such as BAL. Regardless of the therapeutic intervention, high rates of mortality due to RSV pneumonia are documented in seriously immunocompromised patients when therapy has been initiated after the development of respiratory failure (Figure 31-2a). Survival rates remain low for severely immunosuppressed patients who are intubated due to progressive RSV pneumonia unrelated to super-imposed pulmonary hemorrhage, pulmonary edema, or bacterial superinfection [5, 50, 55, 81, 83].

## 31.5.2 HMPV in Transplant Recipients

HMPV may cause upper or lower respiratory tract infections in HSCT recipients. Asymptomatic shedding from upper respiratory tract has been reported, indicating that not all hMPV infections result in severe lower tract disease [50, 66, 85]. HSCT recipients with hMPV disease in the immediately posttransplant period typically present with respiratory symptoms including nasal congestion, sore throat, cough, or fever. Once lower respiratory tract disease develops, rapidly progressive pulmonary infiltrates frequently accompanied by hypotension, septic shock, or both may be present [64] (Figure 31-2b and c). In a prospective viral surveillance in HSCT recipients where samples for respiratory viruses were obtained weekly, regardless of the presence of respiratory symptoms, a cumulative incidence estimate of hMPV of 6.2% (95% CI, 1.3–11.2) over 1 year was determined; all cases of hMPV had clinical respiratory symptoms identified ranging from mild to more severe disease with single or multiple symptoms [50] (Table 31-4). Among 15 HSCT recipients with hMPV detected by RT-PCR in BAL, 10 (67%) had positive hMPV RT-PCR in nasal wash sampled within 11 days prior to or following the BAL [49]. Viral RNA was detected in the serum of one of these severely immunocompromised HSCT recipients at two time points, 4 days apart, with a viral load of ~8 Log10 copies/ml in each sample. This patient died of severe respiratory disease. In assessing risk factors associated with overall mortality at day 100 posttransplant, the use of bone marrow as the stem cell source, steroid treatment and oxygen use have been associated with overall mortality [49].

Radiographic findings associated with hMPV infection in the HSCT recipient may consist of centrilobular nodules, ground glass opacities, tree-in-bud to diffuse bilateral alveolar infiltrates [86, 87] (Figure 31-2b–f). Centrilobular nodules have been associated with less mechanical ventilation while ground glass opacities tended to be associated with
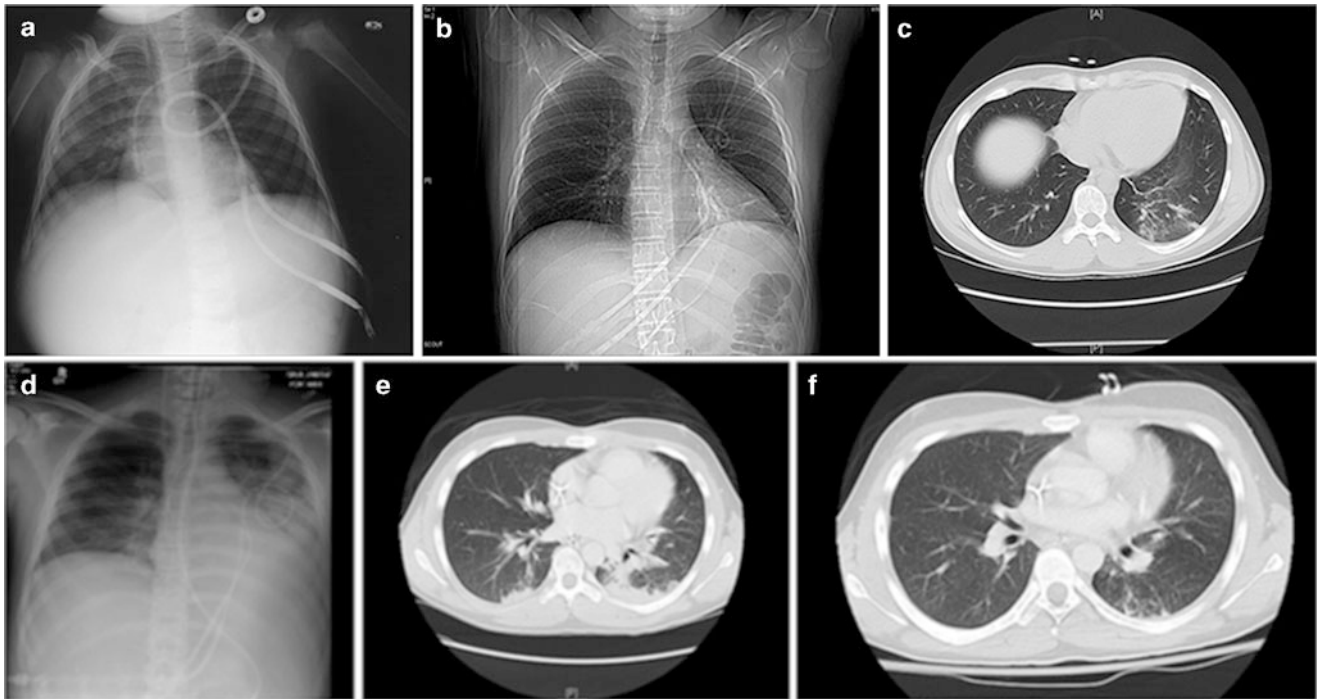
FIGURE 31-2. Chest radiographs of transplant recipients with RSV and hMPV lower respiratory tract disease. (**a**) Three-year-old with RSV pneumonia developing 1 week post HSCT, which proved to be fatal within 2 weeks despite antiviral therapy with aerosolized ribavirin. (**b**) HMPV Lower respiratory tract disease in a 16-year-old boy with ALL and hMPV disease diagnosed day 5 after a matched related BMT. He was diagnosed with hMPV infection on day #5 posttransplant, with clinical findings of mild respiratory distress with cough and abnormal chest radiograph showing interstitial infiltrates. Aerosolized ribavirin and IVIG therapy was initiated. (**c**) Posttransplant day #9: He required intubation due to respiratory failure and acute respiratory distress syndrome, with left sided pneumonia and increasing pleural effusion. He required mechanical ventilation and $50\%$ $FiO_2$. (**d**) Post Tx day #11: Worsening of left lower basilar consolidation with small left pleural effusion, but oxygen requirement down to 35% $FiO_2$; not yet engrafted and continued on ribavirin. (**e**) Day #16: Now engrafted and ribavirin discontinued. He was able to be extubated and relatively quickly weaned to room air. (**f**) Patient with improvement post engraftment on day #16 posttransplant. Chest CT shows interval improvement in bilateral patchy groundglass opacities and in left lower lobe consolidation. He received supportive care and 10 days of aerosolized ribavirin therapy, which did not substantially impact viral load, but he improved clinically concomitant with engraftment. He was subsequently extubated and discharged several weeks later.

increased rates of hypoxemia [49]. Alveolar consolidation corresponds to more extensive damage on histological examination. Histological evaluation has also shown hyaline membrane formation, foci of bronchiolitis obliterans and organizing pneumonia and diffuse alveolar hemorrhage.

Variable disease severity has been reported following hMPV infection in SOT recipients. In one study of 114 lung transplant recipients, hMPV was detected in four symptomatic and one asymptomatic patients (4.3%), but viral infection was not persistent and resolved without major complications [88]. In another study, nine lung transplant recipients with hMPV were compared with 17 transplant recipients without hMPV infection; hMPV infection was associated with signs of acute graft rejection and increase overall mortality (three of nine with hMPV-infected patients died and none died in the hMPV-negative group) [54].

### 31.5.3 Outbreaks

Outbreaks of respiratory viruses occur annually in the community, with potential for patients, families, or health care workers to become infected following exposure outside the hospital. However, nosocomial transmission within the hospital setting becomes a serious concern because of the high rates of morbidity and mortality in immunocompromised patients documented in nosocomial outbreaks. Hospital-based oubreaks of RSV infection in HSCT recipients can occur through introduction of circulating community strains as well as transmission of identical viral strains among patients [42, 44]. Outbreaks of RSV have been associated with high mortality rates ranging up to 45% of infected patients [89, 90]. The transmission of identical strains of RSV within the outpatient setting into the hospital setting

has also been shown [91], demonstrating the importance of infection control measures in both the inpatient and outpatient setting. Nosocomial transmission of hMPV can also occur, with outbreaks possible in both inpatient and outpatient units. In one study, 15 patients were diagnosed with hMPV within 7 weeks in a tertiary care cancer unit [92]. Molecular subtyping revealed infection with genotype A2a virus, implicating nosocomial transmission. Four patients (26.6%) died from hMPV-associated pneumonia and consequent multi-organ failure.

## 31.6 Treatment and Prevention Strategies

### 31.6.1 RSV Treatment

Current options for the antiviral therapy of RSV disease in immunocompromised hosts are limited. Large, controlled, therapeutic trials for RSV pneumonia or lower tract disease in immunocompromised patients have not been conducted. Aerosolized ribavirin, licensed in the USA for the therapy of RSV bronchiolitis and pneumonia in infants and young children in 1986, is the antiviral agent currently utilized for the treatment of RSV disease in immunocompromised patients. In general, ribavirin is given as an inhaled aerosolized solution via a face mask in a protective environment, such as a "scavenging tent," to protect health care workers from potential drug contamination. Ribavirin was initially licensed for use when given for 12–18 h/day, but the use of intermittent aerosolized ribavirin given over 2 h, three times daily, was found to have similar effectiveness to 12–16 h/day continuous infusion ribavirin in healthy children [93–95] and has been utilized in adults because of ease of administration and enhanced tolerability. A randomized trial in HSCT patients at risk for LRTI evaluated intermittent dosing of ribavirin given over 2 h three times daily versus continuous ribavirin administration using an adaptive randomized trial design in 50 HSCT patients, with the authors concluding that the intermittent schedule was preferable because of ease of administration and evidence of higher efficacy [96].

Only one randomized, controlled, multicenter clinical trial of aerosolized ribavirin for the prevention of RSV disease progression to LRI has been conducted in HSCT recipients early posttransplant, and despite an enrollment period of several years, only 15 patients were enrolled [97]. None of the ten patients randomized to high dose, short duration aerosolized ribavirin (administered as 2 g/100 ml water given over 2 h three times daily) had disease progression compared to 2/5 control patients, a trend that was not statistically significant ($P=0.08$). Viral loads appeared to be reduced during the ribavirin treatment, but did rebound after cessation of therapy. Data demonstrating effectiveness of ribavirin is mainly retrospective. In an open trial in adult HSCT recipients with "RSV-induced acute lung injury," monotherapy with aerosolized ribavirin was reported to be of benefit if initiated prior to the development of radiographic infiltrates [6]. In another open trial in adult HSCT recipients with radiographically proven RSV pneumonia, combination therapy with aerosolized ribavirin and high RSV-titered IVIG was reported to be of benefit only if initiated prior to the onset of respiratory failure [8, 98]. A retrospective MDACC study of confirmed RSV infections in 280 allogeneic HSCT recipients from 1996 to 2009 utilized multivariable logistic regression to demonstrate that lack of ribavirin aerosol therapy at the upper respiratory tract disease stage was an important risk factor associated with RSV LRTI and all-cause mortality [99]. In a retrospective study of HSCT recipients with confirmed lower respiratory tract RSV infection based on analysis of bronchoalveolar lavage fluid at the Hutch, viral RNA detection in the blood was detected in 30% of 92 patients at a median of 2 days following diagnosis of lower respiratory tract disease [37]. Neutropenia, thrombocytopenia, and mechanical ventilation increased the risk of RSV RNA detection in the plasma or serum but lymphopenia and steroid use did not. The detection of RSV RNA in the serum or plasma increased the risk of overall mortality with an adjusted hazard ratio (AHR) of 2.09 ($P=0.02$).

Data in solid organ transplant recipients is even more limited. Favorable responses have been reported in an open trial of lung transplant recipients with lower respiratory tract disease who received monotherapy with aerosolized ribavirin [58], as well as open trials with oral ribavirin [100–102], although controlled studies have not been performed. Oral ribavirin was found to be well-tolerated, result in less hospitalization, and be less expensive than intravenous or inhaled ribavirin in a retrospective study of 52 lung transplant recipients [102].

The treatment of RSV disease with a combination of antiviral therapy and passively administered immunoglobulin has been investigated in animal models and in children [103–106]. Therapy with IVIG containing high levels of RSV-specific antibodies alone does not seem to be effective in placebo-controlled trials in children who were not immunocompromised [104, 107]. In small open trials at MDACC, combination therapy with aerosolized ribavirin (18 h/day) and high RSV-titered IVIG (0.5 g/kg every other day) was associated with a favorable response in adult HSCT recipients and patients undergoing induction chemotherapy for leukemia who had RSV lower respiratory tract disease in whom therapy was initiated prior to respiratory failure [8, 98]. At the Dana Farber Cancer Institute, combination therapy with aerosolized ribavirin (18 h/day) and RSV-IVIG (1.5 g/kg for one dose) was similarly associated with a favorable response in 2 HSCT recipients with clinically severe RSV pneumonia occurring early following transplant [105]. In subsequent years, MDACC has utilized a combined regimen with similar response, although standard IVIG in frequent and large doses (500 mg/kg QOD) has been substituted for high-titered IVIG.

Other therapeutic options for the treatment of RSV include the use of oral ribavirin, which has been studied in HSCT recipients and found to be safe and less expensive than intravenous or aerosolized ribavirin [100, 108, 109], and is recommended as an option in addition to intravenous and inhaled ribavirin by the European Conference on Infections in Leukemia [94]. Other options include IV ribavirin (an investigational drug, ICN) and topical immunoglobulins administered with aerosolized or intravenous ribavirin [105, 110, 111]. The relative ease of administration of IV ribavirin is attractive, but high rates of mortality (80%) and significant cases of hemolytic anemia (20%) make this option currently problematic. Although the European experience with combination aerosolized/intravenous ribavirin has been favorable [112] and intravenous ribavirin is relatively simple to administer, the high rates of mortality and significant cases of hemolytic anemia make this approach controversial. Monotherapy with IV ribavirin may be more toxic in these patients than has been previously reported in patients with hemorrhagic fevers [113, 114].

The decision to initiate therapy with aerosolized ribavirin with or without immunotherapy for a RSV-URI must take into consideration many factors, including the patient's risk of developing serious lower respiratory tract disease (and specifically, the degree of anticipated lymphopenia), the potential exposure of health care workers to the medication, the psychological and physical discomfort to the patients of aerosol therapy, the adverse effects of aerosolized ribavirin such as bronchospasm, the high cost of these drugs as well as the intensive respiratory therapy needed to safely administer aerosolized ribavirin, and the need for hospitalization with more frequent or prolonged ribavirin dosing regimens.

In patients who have already undergone conditioning therapy and stem cell infusion but have not yet engrafted, the initiation of antiviral therapy at the URI stage may be beneficial. Early studies conducted in the 1990s were small and uncontrolled. One study conducted at FHCRC treated 25 HSCT recipients with upper tract RSV disease with low dose aerosolized ribavirin administered at a high concentration (60 mg/ml) for 2 h each day (total: 2 g/day [8]). Unfortunately, 8/25 patients developed pneumonia, and seven of these died. Another study evaluated combination therapy with aerosolized ribavirin and 500 mg/kg IVIG every other day in 12 patients, two of whom developed pneumonia and died [8, 115]. This "preemptive" strategy, similar to that used in the prevention of CMV disease and CMV pneumonia, is used at some transplant centers for those patients at highest risk of RSV disease progression, such as pre-engrafted patients with RSV detected in the first weeks following transplantation. Other options for preemptive therapy include immunotherapy with IVIG or RSV-specific monoclonal antibodies, although little data on efficacy of immunotherapy is available.

### 31.6.2   HMPV Treatment

No antivirals for the therapy of hMPV are currently available or routinely utilized. Ribavirin is active in vitro and in vivo against hMPV, although there are no controlled studies or evidence from large retrospective reviews for the treatment of hMPV pneumonia in humans and no drug has yet demonstrated clinical effectiveness in humans [116, 117]. Intravenous, oral or inhaled ribavirin alone or in combination with IVIG has been reported as potentially successful therapeutic options. A retrospective analysis compared the outcome between 13 immunocompromised patients with hMPV pneumonia treated with ribavirin±IVIG and ten untreated patients. Ribavirin treatment was associated with more hypoxemia and similar mortality, possibly related to late initiation of therapy [49]. A Seattle study describing hMPV lower respiratory tract disease in 55 immunocompromised children, including nine undergoing HSCT and eight SOT recipients, demonstrated that HSCT recipients had more evidence of severe disease [91]. Five of eight HSCT recipients but no SOT recipients had lower tract disease and were treated with aerosolized ribavirin; three had been diagnosed with hMPV pretransplant and during the posttransplant period received both ribavirin and IVIG. Two additional children received aerosolized ribavirin only. Ribavirin was generally administered at a dose of 2 g given three times daily for 5–11 days. Two of the three patients diagnosed with hMPV pretransplant who received ribavirin and IVIG died [91].

### 31.6.3   Infection Prevention Measures for RSV and hMPV

An aggressive infection control strategy can be effective in reducing the nosocomial acquisition of RSV by transplant recipients [91, 118]. Infection control strategies play a crucial role in the prevention of respiratory viral infection [89, 118–120]. An effective strategy is based on understanding the potential seriousness of these infections in transplant recipients, knowledge of the viruses circulating in the community, and ongoing surveillance in high-risk patients. Continuing education of patients, family members, visitors, and staff regarding the potential seriousness of these infections must be repeatedly emphasized. Frequent and routine clinical screening of high-risk patients for acute upper and/or lower respiratory tract illness or flu-like illness must be conducted, with sampling of respiratory secretions from symptomatic high-risk patients routinely performed both pretransplant and posttransplant. Each health care-acquired infection should be viewed as a sentinel event warranting an investigation and reaffirmation or modification of the preventative strategy.

Infection control strategies should be designed to prevent spread by multiple modes of transmission [90, 91]. Multiple

respiratory viruses may circulate in the community concurrently and can be spread by different means. Infection control measures may need to be intensified during community or hospital outbreaks, and the intensity and duration of infection control measures should be tailored to the risk of serious disease in different subsets of transplant recipients, and to what works in the "real world." Guidelines for the prevention of opportunistic infections among HSCT recipients have been issued by the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America, and European and American Societies for Blood and Marrow Transplantation. The guidelines clearly present evidence-based recommendations rated by the strength of the recommendation and the quality of the supporting evidence, similar to guidelines previously issued for the prevention of opportunistic infections in those with human immunodeficiency virus [120]. Preventive strategies for HSCT recipients, their household contacts and other close contacts, and health care workers are clearly outlined in this document.

The prevention of nosocomial acquisition of respiratory viral infections in HSCT recipients has been demonstrated in one prospective study comparing rates of infection in patients cared for in a "protected environment" with patients cared for on a transplant unit where infection control measures were strongly encouraged, but not rigidly enforced [9]. The effectiveness of infection control interventions has also been demonstrated by the dramatic decline in the frequency of nosocomial CRV infections among HSCT recipients cared for in this transplant unit after the implementation of an aggressive, multifaceted infection control strategy [118]. Although this intensive multifaceted approach has been effective, modified versions of this strategy have also been effective. For instance, the Seattle Cancer Care Alliance (SCCA) adult inpatient transplant unit uses a similar strategy with the exception that health care workers and other visitors do not wear masks when entering the patient room [91]. However, these workers are intensively screened for signs and symptoms of respiratory illnesses prior to entering the unit, and restricted from entering the unit if they are symptomatic. Similarly, HSCT recipients with respiratory symptoms are not transferred to other units, but are cared for on the transplant unit using modified droplet precautions with all persons entering the room wear gloves, gown, and mask, and the door to the room is kept closed. It may not be feasible to so intensively protect patients for the duration of increased susceptibility to respiratory viral diseases. Protective strategies are costly and cumbersome, and pose unpleasant restrictions on the freedom and quality of life of the patient and their families. This problem is further compounded by the growing trend to discharge patients early from the hospital and to perform outpatient HSCT or posttransplant care. Transplant recipients residing in the community and followed frequently in the outpatient setting are another group in which infection control practices must become priority [91].

The prevention of exposure to respiratory viruses is particularly challenging among high-risk transplant recipients living in the community because respiratory infections are so prevalent and so contagious. Examples of protective measures for outpatients include washing hands frequently and thoroughly, avoiding close contact with individuals suffering from respiratory illnesses, and encouraging close contacts to vigorously practice respiratory hygiene. In many cases, such as individuals living with children, such efforts may be nearly impossible. Consideration of removing day care exposures for young children or decreasing exposure to transplant recipients to children (including siblings), can and should be discussed with families. The rigor and duration of prophylactic measures need to be individualized based on the immunologic status of the patient and the risk for serious disease, the needs of the patient, and quality-of-life issues.

## 31.6.4 Passive Immunoprophylaxis

Passive immunization with immunoglobulin, immunoglobulin products, and humanized monoclonal antibodies have been actively studied in the pediatric infant population. Palivizumab, a humanized monoclonal antibody directed against the RSV F protein, is licensed for the prevention of RSV disease in premature infants and infants with congenital heart disease, and is administered as a monthly injection during the 4–5 months of RSV season. The cost of this therapy has led to new guidelines for use in the pediatric population [121]. Similar interventions have been utilized to attempt to decrease the morbidity of serious RSV disease in HSCT recipients but direct proof of effectiveness has not yet been demonstrated [115]. For example, passive immunoprophylaxis in immunocompromised patients has been evaluated in an open trial conducted [122] using high-titered human RSVIG. In this adult study, significant antibody titer increases to other respiratory viruses were extremely variable, although the subset of patients with the lowest titers appeared to receive the greatest increase in viral-specific antibody. The cost of this potential therapy remains quite high. The monoclonal RSV antibody palivizumab (Synagis) has been studied in an open label study in adult HSCT recipients [123]. Immunoprophylaxis with monoclonal RSV antibodies would be prohibitively expensive in older children and adults, but may have the potential to protect against RSV infection, based on pediatric studies.

New antibody products, including long-lasting monoclonal antibodies with enhanced activity against RSV, are under development and if available at a less expensive price, could potentially provide protection against RSV for patients in the pretransplant and immediate posttransplant phase. Newer monoclonal antibodies that have the potential to neutralize against both RSV and hMPV have also been described, offering hope for newer preventive modalities that may protect against both these viruses [124].

## 31.6.5 Pretransplant Screening

Screening of transplant recipients for respiratory viruses prior to transplant is not routinely recommended based on current US and international transplant guidelines [94, 125]. However, the assessment of viral shedding or infection in symptomatic transplant candidates prior to transplant is recommended. Delay of transplant based on detection of RSV or hMPV may be warranted depending on the evaluation of the risk and benefits of continuing on with transplantation. Consequences of postponing transplantation should be considered, including progression of underlying malignancy, logistical issues regarding the donor availability, and accessibility of services for the patient. An early study of RSV diagnosed prior to HSCT demonstrated that delaying transplant reduced the risk of pneumonia following transplant [23]. More recently, a large prospective study conducted in 458 patients at the Hutch demonstrated that nearly 25% of subjects had respiratory viruses detected pretransplant [24]. Overall, patients with a virus detected prior to transplant had fewer days alive and lower survival at day 100 (AHR 2.4; 95% CI 1.3–4.5) compared with patients who did not have viruses. In HSCT recipients who had respiratory symptoms and a virus detected prior to transplant (mainly adults), an increased overall mortality was seen compared with patients without respiratory viruses detected. Higher rates of pretransplant infection and sequelae of infection were seen in pediatric patients. Detection of respiratory viruses in asymptomatic patients was not associated with increased mortality. This data strengthens current guidelines that recommend patients with respiratory symptoms prior to transplant should be tested for respiratory viruses and transplant delayed, when feasible. However, this study was performed chiefly in adults. The higher rates of respiratory viruses documented in children pretransplant make routine screening of pediatric patients worthy of further investigation.

## 31.6.6 New Antivirals

Experimental approaches to the therapy of RSV antiviral therapy include novel fusion inhibitors [126], nucleoside agents, small RNA inhibitory molecules [109], and high-titered monoclonal antibody preparations. Two promising RSV antivirals that have shown efficacy in challenge studies in healthy adults include the Alios compound AL8176 (Alios Biopharma, South San Francisco, CA), an oral anti-RSV nucleoside designed to inhibit RSV replication by acting on the viral polymerase, and the Gilead Sciences compound GS5806 (Gilead Sciences, Foster City, CA), an orally bioavailable RSV fusion inhibitor [126, 127]. Clinical trials of these agents in healthy young children with RSV have been proposed [128]. An international multicenter, placebo-controlled clinical trial of GS5806 was initiated in July 2014, and remains ongoing in adult HSCT recipients with documented RSV infections (Clinicaltrials.gov identifier NCT02135614). Other antiviral agents are under development.

## 31.6.7 Vaccines

No RSV or hMPV vaccine is currently available. In general, active immunization of transplant recipients will be unlikely to prevent severe disease seen in the first several months posttransplant. However, prevention of RSV infection in families, staff, and nosocomial spread of virus by the use of vaccines holds true promise to benefit transplant recipients themselves. Promising advances in new vaccines directed against both RSV and hMPV have been reported over the past decade, with progress evident in both RSV fusion-protein based vaccines and live attenuated vaccines. Advances in the understanding of the pre- and post-fusion nature of the RSV F protein [129] has led to increased work in developing protein-based vaccines appropriate for older children, adults, and pregnant women.

Advances in technology and better molecular understanding of RSV and hMPV have resulted in new potential RSV candidate vaccines [130]. At least 12 RSV vaccines are in clinical studies in phase 1 or 2 clinical studies, with one RSV F vaccine under study in pregnant women. Examples of live RSV vaccine candidates under study include live-attenuated vaccines relying on genetic manipulation of the RSV genome [131], vectored virus vaccines utilizing the chimpanzee adenovirus or vaccinia virus Ankara [132], or chimeric viruses containing a backbone of attenuated parainfluenza with the F gene of RSV added [133, 134]. A chimeric hMPV vaccine containing a backbone of avian hMPV and F genes of the hMPV [135]. Although live viral vaccines are unlikely to be given to transplant recipients pretransplant or early post-transplant, they offer hope for the potential control of RSV and hMPV disease in family members and health care workers the future.

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