Review

Respiratory viral infections in transplant recipients

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A wide range of viruses affect the respiratory tract of transplant recipients, including adenovirus, influenza, human metapneumovirus, parainfluenza virus, respiratory syncytial virus (RSV) and rhinovirus. Prospective studies using contemporary diagnostic techniques have recently improved our understanding of the epidemiology and importance of these respiratory viruses among transplant recipients. From these studies, rhinovirus, in particular, has been shown to be one of the most common causes of infection in stem cell and lung transplant recipients. In addition to epidemiological data, recent studies have also advanced our understanding of management of influenza, adenovirus, and RSV infections among transplant recipients.

Introduction

Every year, the number of patients undergoing stem cell and solid organ transplantation to treat malignancy and end-organ failure increases. Despite advances in screening and prophylaxis strategies, infections remain a significant cause of morbidity and mortality among transplant recipients [1–3]. The respiratory viruses, including adenovirus, influenza virus, human metapneumovirus (hMPV), parainfluenza virus (PIV), respiratory syncytial virus (RSV) and rhinovirus (HRV), are increasingly recognized as contributing to significant morbidity and mortality among transplant recipients. Recent prospective studies have improved our understanding of the incidence of respiratory viral infections in addition to the most effective diagnostic and therapeutic strategies among haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients [4–11].

Until recently, most of the data on respiratory viral infections among HSCT and SOT recipients came from retrospective studies [12,13]. These studies typically had the same significant limitations: they were derived from patients admitted to the hospital with respiratory infections and used culture as the predominant diagnostic method. As a result, these study designs underestimated the true incidence of disease and overestimated the severity of illness as a result of their selection biases [12,13]. Despite these limitations, several generalizations, which have been confirmed in the contemporary, prospective studies, can be made:

(i) The seasonality of respiratory viral infections among transplant recipients usually follows that of the general population (Figure 1) [14].

(ii) No one virus is exclusively associated with one clinical syndrome (that is, influenza-like illness, croup, etc). As such, diagnostic strategies should initially be broad, attempting to screen for all recognized viruses [12,13,15].

(iii) Patients with compromised immunity often have atypical presentations of common conditions. As the result of medications and underlying conditions that prevent a normal inflammatory response, symptoms may be mild [12,13]. Lung transplant recipients, for example, might initially only have the subjective symptoms of shortness of breath or subtle changes in pulmonary function testing without more typical symptoms [16]. Fever can be absent in transplant recipients with pneumonia or can be the sole presenting sign or symptom [12,13].

(iv) Viral shedding can be prolonged among transplant recipients [12,13]. Influenza and rhinovirus are the best studied viruses in this regard. In one study, patients who had undergone autologous HSCT shed influenza virus for an average of 6.7 days without therapy while allogeneic HSCT recipients shed virus for an average of 11.1 days [17]; longer durations of shedding have also been shown [5,18]. Shedding, likewise, might occur with minimal to no symptoms, which could contribute to outbreaks [5,7,8,10]. Prolonged shedding despite the use of antiviral compounds might also contribute to the emergence of resistant variants [18].

(v) Transplant recipients appear to be at high risk of infectious complications. In the older studies, initial evidence of progression to lower tract involvement with the virus occurred in >50% of patients in some studies

[12,13]. Viral pneumonia probably represents the most advanced form of progression of respiratory viral infection. In immunocompetent patients, viruses cause 1–23% of community-acquired pneumonia [19]. All of the respiratory viruses have now been recognized to cause lower tract disease and lower tract disease is associated with increased risk of adverse complications, as will be discussed later in the article. Respiratory viral infections are also a risk factor for subsequent development of fungal and bacterial pneumonia [20]. There is emerging data suggesting a bidirectional interaction between bacteria and the respiratory viruses which predispose to these severe infections. The virus induces local epithelial damage, alters airway function, upregulates and modifies expression of cell surface receptors, and alters the innate immune system, and bacteria can enhance the pathogenicity of the virus and enhance inflammation [21]. Other infections, such as cytomegalovirus (CMV) viraemia, might complicate respiratory viral infections as well.

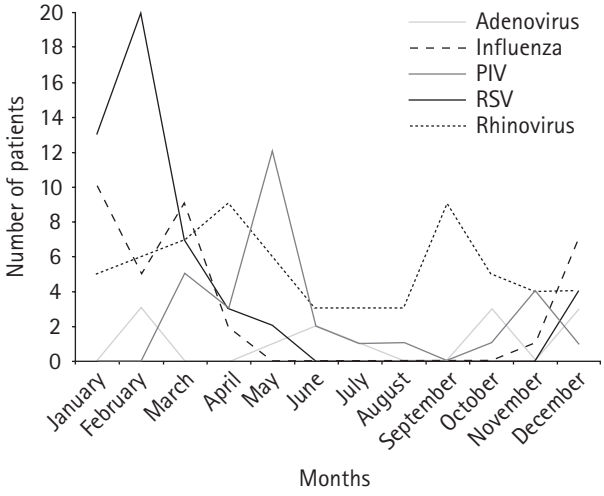
(vi) Lymphopenia is consistently a risk factor for more serious infections, progression to pneumonia and mortality, secondary to community respiratory viral infections [17,22]. Reconstitution of lymphocytes, especially virus-specific lymphocytes, appears to be associated with clinical and virological improvement. Reduction in immunosuppressive regimens is often a key part of management in serious infections.

(vii) Respiratory viral infections appear to be a risk factor for both acute and chronic rejection, with the greatest risk being in lung transplant recipients [7,11,16,23]. Concomitant acute rejection at the time of respiratory viral infection has been demonstrated in up to 82% of lung transplant recipients [12,13,24]. Among lung transplant recipients, bronchiolitis obliterans syndrome (BOS) or pathologically confirmed bronchiolitis obliterans (BO) occurs more commonly in individuals with documented lower tract infections with one of the respiratory viruses (hazard ratio [HR]: 2.0–4.3) [23]. Concurrent rejection and graft dysfunction has been documented with other SOT recipients as well, although at an lower frequency than in lung transplant recipients [13]. The pathogenesis of the link between respiratory viral infections and rejection is not clearly understood.

(viii) In general, there is increased risk of severe respiratory viral infection and its sequela among paediatric recipients, allogeneic HSCT recipients and lung transplant recipients as compared to adults, autologous HSCT recipients and other SOT recipients respectively. Likewise, infection early after transplant and in the presence of lymphopenia are predictors for a more progressive course [12,13].

More contemporary, prospective studies are providing a clearer picture of the true epidemiology of respiratory viral infections among transplant recipients

Figure 1. Seasonal distribution of respiratory viral infections by pathogen



Adapted with permission from [14], copyright Elsevier and the Association of Professors of Medicine. The figure shows the total number of transplant recipients with individual viruses over a 3 year period. PIV, parainfluenza vrus; RSV, respiratory syncytial virus.

[12,13]. In general, the strongest data come from stem cell and lung transplant recipients, although data in other transplant populations are emerging. These studies suggest that many of these respiratory viral infections are mild to asymptomatic and do not require admission [5,6,8,10]. Most of the newer studies have provided limited follow up of these patients to understand long-term sequelae, but most patients appeared to have minimal short-term effects from their infections and there were few deaths. From these studies, rhinovirus has emerged as the most prevalent virus among transplant recipients [5,6,8,10]. Lastly, recent data suggests that antiviral therapy, particularly for influenza, RSV and adenovirus, might prevent the progression to more severe disease and might decrease mortality [25–30]. Despite these advances, the current studies have tended to be small, single-centre studies with short follow-up periods. There is limited long-term follow up, particularly among lung transplant recipients, and very limited data in non-lung SOT populations. As a result, a prospective study with long-term follow up is needed to define the full epidemiology of respiratory viral infections among transplant recipients.

Diagnosis of respiratory viral infections

Diagnosis of the RNA respiratory viruses can be achieved by combinations of serology, virus culture, antigen detection, nucleic acid testing and histopathology; diagnosis of adenovirus is more complex and discussed in greater detail below. In general, serology is not useful for initial diagnosis of

Table 1. FDA-approved rapid diagnostic tests for influenza

Test	Company*	Viruses detected	CLIA waived	Sensitivity, %†	Specificity, %†	Specimen types
Directigen Flu A	Becton-Dickinson	A	No	67–96	88–100	
Directigen Flu A+B	Becton-Dickinson	A and B‡	No	71–100	90–100	NPW, NPA, NPS, NS, TS, BAL
Directigen EZ Flu A+B	Becton-Dickinson	A and B‡	No	69–86	86–100	NPW, NPA, TS
NOW Influenza A	Binax	A	Yes	78–82	92–94	NW, NA, NPS
NOW Influenza B	Binax	B	Yes	58–71	97	NW, NA, NPS
NOW Influenza A&B	Binax	A and B‡	Yes	93–100	93–100	NW, NA, NPS
OSOM Influenza A&B	Genzyme	A and B‡	No	56–74	92–98	NS
QuickVue Influenza Test	Quidel	A and B§	Yes	73–81	96–99	NS, NW, NA
QuickVue Influenza A+B Test	Quidel	A and B‡	Yes	62–94	89–99	NS, NPS, NA, NW
XPECT Flu A&B	Remel	A and B‡	No	92–98	100	
SAS Influenza A Test	SA Scientific	A	Yes	NA	NA	NPS, NA, NW
SAS Influenza B Test	SA Scientific	B	Yes	NA	NA	NPS, NA, NW
Flu OIA	Thermo-Biostar	A and B§	No	62–88	52–80	NA, NPS, TS, sputum
Flu OIA A/B	Thermo-Biostar	A and B‡	No	62–88	52–80	NA, NPS, TS, sputum
ZstatFlu	ZymeTx	A and B§	Yes	57–65	98–100	TS

*Company details are as follows: Becton-Dickinson, Franklin Lakes, NJ, USA; Binax, Scarborough, ME, USA; Thermo-Biostar Inc, Boulder, CO, USA; Genzyme, Cambridge, MA, USA; Quidel, San Diego, CA, USA; Remel, Lenexa, KS, USA; SA Scientific, San Antonio, TX, USA; ZymeTx, Oklahoma City, OK, USA. †Values according to product package insert; most data from immunocompetent patients. ‡This test is able to distinguish influenza A from influenza B. §This test can detect both A and B but does not differentiate the two. BAL, bronchoalveolar lavage; CLIA, Clinical Laboratory Improvement Amendments; FDA, Food and Drug Administration; NA, nasal aspirate; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal swab; NPW, nasopharyngeal wash; NS, nasal swab; OIA, optical immunoassay; TS, throat swab.

respiratory viral infections and has reduced sensitivity among transplant recipients. Virus isolation can be achieved for most of the common RNA viruses except for hMPV and coronaviruses; special cell lines and conditions are needed to grow these viruses and cultures tend to be inefficient [31,32]. As with other diagnostic strategies, yields of cultures are dependent on the site of sampling: greatest yield is from bronchoalveolar lavage (BAL) and nasal wash. Nasal swabs are less sensitive than nasal washes or nasopharyngeal aspirates for RSV; for other viruses sensitivities appear similar with the washes and aspirates having a slight advantage [33–35]. Traditionally, several individual cell lines are inoculated; cytopathic effect and/or heamadsorption can be detected from 3–21 days after inoculation and is dependent on the virus, viral inoculum, cell line and the growth conditions used, among other variables. Shell vial assays allow earlier detection of virus with the application of monoclonal or polyclonal antibodies used to detect the presence of virus after 24–48 h. Although these assays are more rapid, they may have a slightly lower sensitivity compared to traditional culture methods [36]. Recently, several fixed mixtures of cells (that is, R-Mix [Diagnostic Hybrids, Athens, OH, USA]) have become commercially available for traditional and shell vial techniques. In general, these mixed cell lines allow greater ease in setting up and monitoring viral cultures with similar sensitivity of individual cell lines [37,38].

Rapid antigen detection, using several different techniques, is available for influenza (Table 1), RSV (Table 2) and adenovirus; rapid testing for adenovirus is not commonly used among transplant recipients and there is limited data in this population. These different antigen detection platforms provide a diagnosis in about 15–30 min. Despite their speed, sensitivity can be lower than reported in licensing studies and can be substantially lower among immunocompromised patients, especially adults. In the case of RSV, one study documented a sensitivity with one test method of 15% for nasal wash specimens among immunocompromised patients; sensitivity is improved to 89% when BAL is used [39].

Several studies of direct fluorescent antibody (DFA) testing of primary patient specimens have documented sensitivity that approached that of PCR for certain viruses [10,40]. DFA testing is limited by lack of reagents for some of the viruses (hMPV, rhinovirus, coronavirus) [41] and appears to be less sensitive than PCR in detecting dual infections [40]. Like PCR, though, DFA testing can detect several viruses from a single specimen.

Several PCR-based assays are only available at a few specialized centres. Increasingly, though, reference laboratories are offering PCR-based assays commercially. In addition, research-only and analyte-specific reagents are now available for local laboratories to develop their own assays. Most of the available assays can be used to screen for a wide range of pathogens in tandem and many have been tested in transplant populations [7,10,11,40,42–47]. Nucleic acid amplification assays appear to be the most sensitive diagnostic tools available and most allow for simultaneous detection of a broad range of respiratory pathogens from a single sample. Several companies are currently working on systems based on Luminex's xMAP technology (Luminex

Table 2. FDA-approved rapid diagnostic tests for respiratory syncytial virus

Test	Company*	CLIA waived	Sensitivity†	Specificity†	Specimen types
Directigen RSV	Becton-Dickinson	No	93–97%	90–97%	NPW, NPA, NPS
Directigen EZ RSV	Becton-Dickinson	No	67–87%	86–95%	NPW, NPA, NPS
NOW RSV	Binax	Yes	74–98%‡	92–100%‡	NW, NPS
Fisher Sure-Vue RSV	Fisher Scientific	Yes	96%	94%	NPW, NPA, NPS
Quicklab RSV	Integrated Biotechnology	Yes	93–100%	87–98%	NW, NPS
Immuno*Card* STAT! RSV Plus	Meridian Bioscience	Yes	91%§	80%§	NPS, NPA
QuickVue RSV Test	Quidel	No	92–99%	92%	NPA, NPS
XPECT RSV	Remel	Yes	75–96%‡	94–98%‡	NA
SAS RSVAlert	SA Scientific	Yes	91%¶	NA	NPW, NPA, NS
OIA RSV	Thermo-Biostar	No	67–87%	83–96%	NW, NPS
Clearview RSV	Wampole Laboratories	Yes	93–100%	88–97%	NPS, NPW, NPA

*Company details are as follows: Becton-Dickinson, Franklin Lakes, NJ, USA; Binax, Scarborough, ME, USA; Thermo-Biostar Inc, Boulder, CO, USA; Fisher Scientific, Loughborough. UK; Integrated Biotechnology, Carmel, IN, USA; Meridian Bioscience, Cincinnati, OH, USA; Quidel, San Diego, CA, USA; Remel, Lenexa, KS, USA; SA Scientific, San Antonio, TX, USA; Wampole Laboratories, Princeton, NJ, USA. †Values according to product package insert; except for ‡[146], §[147], and ¶[148]; most data from immunocompetent patients. CLIA, Clinical Laboratory Improvement Amendments; FDA, Food and Drug Administration; NA, nasal aspirate; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal swab; NPW, nasopharyngeal wash; NS, nasal swab; OIA, optical immunoassay.

Corp, Austin, TX, USA). These systems allow for the simultaneous detection of all of the recognized respiratory viral pathogens[48] but, to date, there is limited available data about their sensitivity and they require a significant up-front investment in specialized equipment. Despite its limited availability, PCR is the preferred testing method for immunocompromised patients.

In general, all patients with presumed respiratory viral infection should have a nasopharyngeal swab, wash or aspirate performed and sent for rapid antigen testing, if available. Positive results for the test might be considered diagnostic, although false-positive test results do occur and negative results do not rule out infection. All negative rapid tests should trigger additional testing with PCR, DFA or culture, depending on which is available locally. If upper tract samples fail to document the cause of the respiratory illness or if there is clinical or radiological evidence of lower tract involvement, BAL should be considered and sent for the range of available tests.

Influenza

Epidemiology

Influenza A and B are typically associated with influenza-like illnesses in immunocompetent hosts, while influenza C is more commonly associated with milder, cold-like syndromes [49]. Rarely, influenza C has been associated with more severe disease [49]. Classically, influenza is associated with acute-onset febrile illness with associated cough, myalgias and arthralgias. In general, the attack rate of influenza probably depends on various factors including patient age (higher in children), likelihood of exposure (community versus nosocomial, contact with children), level of specific immunity (from prior infections and immunizations), degree of immune defects and nature of the epidemic (magnitude and antigenic type). Although many immunocompromised patients manifest influenza-like illness, less typical presentations can occur. Lung transplant recipients, for example, may only have alterations in pulmonary function testing; fever with few other symptoms has also been described among transplant recipients [12,13]. Immunocompromised patients tend to have prolonged shedding (among HSCT recipients, shedding lasts an average of 11.3 days without treatment and 9.7 days with the use of neuraminidase inhibitors) [17], which is associated with a long duration of symptoms, progression to viral pneumonia and emergences of resistant variants. Advanced underlying disease and lymphopenia are significant risk factors for progressive and fatal disease [17]. The available studies indicate that 1–5% of transplant recipients develop an influenza infection [17,50].

Prevention

Prevention of influenza depends on either vaccination or antiviral therapy [51]. There are currently two Food and Drug Administration (FDA)-approved formulations of influenza vaccination: an inactivated injectable vaccine and a live, attenuated intranasal vaccine [51]. Because of the concern of disease with the live vaccine, only the inactivated injectable vaccine is routinely recommended for use in immunocompromised patients [51]. Close contacts of transplant recipients, including family members, should also be vaccinated; inactivated injectable vaccine is preferred. If only live, attenuated intranasal vaccine is available, the close contacts to the patient should discuss the options with the transplant team before receiving vaccination. It is recommended that health care workers and visitors who have received a live, attenuated vaccine should avoid contact with severely immunocompromised patients for at least 7 days [51]. Unfortunately, influenza vaccination is less effective in

inducing an antibody response and in preventing influenza infections in transplant recipients than vaccination in healthy control subjects [12,13,52]. To overcome the limitations of vaccination, some experts recommend the use of antiviral agents to prevent influenza. Although both M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir) are approved for this indication, the widespread emergence of resistance to M2 inhibitors has resulted in the loss of this class for preventing or treating influenza [51,53]. The neuraminidase inhibitors have been documented to be 70–93% effective in preventing influenza in immunocompetent adults and children [54]. Limited data on the use of the neuraminidase inhibitors in immunosuppressed patients suggest significant protective efficacy [27,30]. A prospective study is in progress and will hopefully provide further details about the safety and efficacy of this practice.

Treatment

Patients with severe influenza should have doses of immune suppressive medications reduced as much as is felt safe by the transplant physician. Antiviral therapy appears to be associated with reduced morbidity and mortality of patients with documented influenza [12]. The frequent resistance to M2 inhibitors [51,53] favours the use of neuramindase inhibitors in transplant recipients [55]. Although data are limited, the early use of zanamivir and oseltamivir appears to be safe and use is associated with more rapid clearance of virus, reduced symptomatology, reduced progression to pneumonia and reduced mortality among HSCT recipients [17,28,29]. The dose and duration of oseltamivir and zanamivir are designated on the basis of data from immunocompetent ambulatory adults and children with uncomplicated influenza [54], and the optimal dose and duration of therapy have not been established for immunocompromised patients. The use of higher dose oseltamivir (150 mg twice daily in adults) might provide additional antiviral benefit without a significant increase in toxicity [12]. Because viral shedding is prolonged [17], therapy should be extended beyond the approved 5 days; many recommend monitoring viral shedding and continuing therapy until shedding has ceased. It is unclear whether culture, antigen detection or PCR is the best method to determine duration of therapy [12,13]. Additionally, there might be benefit in starting therapy well after symptom onset, in using higher than the approved doses, and in possibly using a drug combination [12,13,56,57]. Prospective studies are needed to address these issues.

Resistance

One major issue related to the use of antiviral agents in this population is the emergence of resistant variants [18,58–61]. M2 inhibitor resistance occurs from changes in the amino acids that constitute the protein and results in cross-resistance among all drugs in the class. M2 inhibitor resistance appears to be stable and persistent [53,58,62]. These features have contributed to the rapid and widespread emergence of M2 inhibitors that currently limits the effectiveness of this class of drugs [51,53,58]. On the other hand, neuraminidase inhibitor resistance can occur as the result of mutations in either the neuraminidase or haemagglutinin gene, does not always result in cross-resistance among all neuraminidase inhibitors and may be more transient [18,59,60,63]. Further work is needed to identify risk factors for the emergence of resistant variants, to develop more rapid methods of detection of resistant variants, to prevent resistance emergence and to more efficiently manage patients with infections caused by resistant variants [64].

hMPV

hMPV [31] has been increasingly recognized as a significant pathogen in both immunocompetent and immunocompromised patients. It appears to have a similar epidemiology and clinical course to RSV [9,65–73]; one study noted that up to 25% of lung transplant recipients had respiratory infections caused by hMPV, highlighting its importance [74]. Fatal infections have been noted [9,69,72,73,75] and the presence of copathogens, particularly RSV, appears to predispose to more severe disease [45,76]. Few studies have investigated therapeutic options for hMPV and none have studied preventative strategies. Reduction of immunosuppression is the cornerstone of any treatment intervention. Ribavirin, $NMSO_3$ and pooled immunoglobulin, but not palivizumab, inhibit hMPV *in vitro* [77,78] and data from a mouse model indicate that ribavirin reduces hMPV replication and global pulmonary inflammation [79]. As such, nebulized ribavirin with or without pooled intravenous immunoglobulin are reasonable considerations in patients with severe hMPV infection.

PIV

Unfortunately, there has been limited progress in our understanding of PIV infections in immunocompromised patients [12,13]. More recent prospective studies continue to suggest that PIV is a significant pathogen among transplant recipients and is associated with severe disease and increased risk of rejection [7,11–13,16,23,24,80]. Risk factors for progressive disease include being a child, presence of graft versus host disease (GVHD), anti-lymphocyte therapy, lymphopenia and steroid use [12,13,81], whereas lower tract disease (HR: 3.4), need for ventilatory

support (HR: 3.3), and presence of copathogens (HR: 2.8) were strongly associated with death [81]. Strict attention to infection control is the key to prevention of PIV infections as several nosocomial outbreaks have been documented [16,82,83]. The appropriate therapy for PIV, particularly in HSCT recipients, has yet to be established. Although aerosolized and intravenous ribavirin and immunoglobulin intravenous (IGIV) have been tried, neither has been shown to reduce viral titres or mortality in HSCT recipients [81,83]. Among lung transplant recipients, response to oral, aerosolized and intravenous ribavirin is more promising; notably, some patients with few to no symptoms have been treated with oral ribavirin with limited follow-up data [84,85]. Two new haemagglutinin–neuraminidase inhibitors, BCX2798 and BCX2855, show significant anti-PIV activity *in vitro* and *in vivo*, but they have not been tested in humans to date [86].

RSV

Epidemiology

Much like the case of PIV, there have been few recent advances in our understanding of the epidemiology and diagnosis of RSV infection in transplant recipients [12,13]. In contemporary prospective studies, RSV remains a pathogen associated with significant disease and is associated with prolonged replication, increased risk of infectious and non-infectious complications, and increased mortality (odds ratio [OR]: 1.6) among immunosuppressed patients [7,12,13,20,22,40,87–92]. There appears to be an increased risk of progression to lower tract disease among patients who have received lymphocyte-depleting therapies, have lymphopenia, have prior lung disease or experience onset prior to HSCT or to engraftment [12,13,22]. The risk of proceeding with HSCT in a patient diagnosed with RSV prior to conditioning is controversial; contributing to the controversy, risk may be related to underlying malignancy, the type of transplant to be performed and the conditioning regimen to be used. Patients who proceed with transplant frequently need oxygen therapy and progressive disease may occur [87], and there appears to be little risk of progressive malignancy when the transplant is delayed [93]. On the basis of this information, most centres defer stem cell transplant until RSV has been cleared.

Prevention

The cornerstone of prevention of RSV is strict infection control practices [94]. Once RSV begins to spread on a transplant unit, control is difficult [95]. Use of passive immunoprophylaxis with immunoglobulin (IGIV, RSV immune globulin [this product has limited availability] or palivizumab) might reduce the frequency and severity of RSV in immuncompromised patients [96], but there are limited data to support its routine use. [97–99]. Additionally, the high cost of these interventions in adults can limit their accessibility.

Treatment

Limited data exist on the management of RSV in transplant recipients. One prospective study in HSCT recipients with upper respiratory RSV infection who received preemptive aerosolized ribavirin found acceptable tolerance and a trend to reduction of viral load [25]. Retrospective reports suggest that aerosolized ribavirin is superior to intravenous ribavirin in stem cell transplant recipients [12,13]. The use of oral ribavirin has been studied in patients with RSV and appears to have some degree of efficacy [100], and some centres use oral ribavirin plus immunoglobulin preparations for the treatment of RSV. Further studies of oral ribavirin are needed. Addition of intravenous antibodies appears to have the greatest benefit in reducing mortality [12,13]. Although the retrospective data suggests that palivizumab is the preparation associated with the lowest mortality when combined with aerosolized ribavirin [101], RSV immunoglobulin and IGIV plus aerosolized ribavirin have improved mortality relative to aerosolized ribavirin alone [89,97,102–104]. There are insufficient data to prove that one antibody preparation is superior to the others. The use of donor lymphocyte infusions has been attempted rarely, but might improve survival [105].

Rhinovirus

HRVs are members of the *Picornaviridae* family and are the most common cause of colds in adults and children [106]. In the past, these viruses were under-recognized as a significant pathogen in immunocompromised patients but several recent prospective studies using nucleic acid testing have clearly demonstrated that rhinoviruses are probably the most common respiratory viral pathogens in transplant recipients [5,6,8,10,107,108]. Interestingly, some patients (9–52%) with detectable virus RNA had few to no symptoms at the time of testing [5,8,109]. Prolonged shedding was documented in many of those with either symptomatic or asymptomatic patients [5,6,8,10,108]. Many of the patients had coinfections with other pathogens which can contribute to the high morbidity and mortality of this infection [107]. Longer-term follow-up studies are needed to understand the clinical importance and infection control implications of this prolonged shedding.

Although most patients in these prospective studies have recovered well with mild and self-limited infections as would be seen in the general population [106,110], progression to the lower tract, other complications and death have also been documented in immuno-

compromised patients [5,107,109]. Two recent studies of patients with new lower respiratory tract disease, one in adult HSCT recipients and the other in lung transplant recipients [5,107], clearly document that HRV can cause lower tract disease. Lower airway involvement is associated with a high risk of both acute and chronic rejection and mortality is high. For both studies, though, the relative contributions of HRV and identified copathogens to this mortality are unclear [5,107].

Pleconaril was studied extensively in healthy adults with rhinoviral colds, was well tolerated and led to faster resolution of symptoms, to more rapid improvement in symptom scores and to clearance of virus from nasal mucous [111]. Pleconaril was not approved by the FDA and is therefore not commercially available. Because of its induction of the cytochrome P450 enzymes [111], interaction with common immunosuppressants should be expected. The compound has been reformulated into an intranasal formulation which is currently undergoing study; it is unclear what role this formulation would play in a patient with severe disease or if it can safely be nebulized to deliver drug to the lower respiratory tract. Several other novel antivirals are too early in development for their safety and efficacy to be determined [112]. In immunocompetent patients, serum-neutralizing antibodies correlate with protection and topical interferon might be efficacious in preventing and in moderating viral shedding and symptoms [113]; their role in transplant recipients has not been studied. Systemic interferon might predispose SOT rejection and should be used with extreme care.

Adenovirus

Epidemiology

Adenoviruses are non-enveloped, double-stranded DNA viruses that can be classified into one of six species (A–F) on the basis of haemagglutinin properties, DNA homology, oncogenic potential in rodents and clinical disease (Table 3) [114]. Adenoviruses cause mostly respiratory, gastrointestinal or conjunctival disease throughout the year without significant seasonal variation (Figure 1). Transmission can occur via inhalation of aerosolized droplets, direct conjunctival inoculation, foecal-oral spread or exposure to infected tissue or blood [115]. Latency, in the pharynx (tonsils and adenoids), intestine, urinary tract and lymphocytes, might occur and probably contributes to the frequency of post-transplant infections [116,117].

In HSCT recipients, the incidence of disease due to adenovirus ranges from 3 to 47% [114]. Available data suggest that adenoviral infections are more frequent in allogeneic stem cell transplant recipients compared to those receiving autologous grafts (8.5–30% vs 2–12%) [114]; children compared to adults (31–47% vs 13.6%) [114]; patients who receive T-cell depleted grafts or anti-T-cell agents (for example, anti-thymocyte globulin, alemtuzumab) (45% vs 11%) [118]; and patients with acute GVHD. [114]. Most retrospective studies have documented the onset of adenovirus disease primarily during the first 100 days (median: 36–90) following HSCT [114,118], although later infection has been described [118].

Table 3. Infections associated with adenovirus species and serotype

Species	Serotype	Major site of infection
A	12, 18, 31	Gastrointestinal tract
B	3, 7, 16, 21, 11, 14, 34, 35	Respiratory tract, urinary tract
C	1, 2, 5, 6	Respiratory tract
D	8 10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49	Eye, gastrointestinal tract
E	4	Respiratory tract
F	40, 41	Gastrointestinal tract

In HSCT recipients, adenovirus is commonly associated with upper and/or lower respiratory tract infection, gastrointestinal disease, hepatitis, nephritis and cystitis [114]. Haemorrhagic cystitis is a common manifestation of illness and can typically be treated with local therapy and rarely progresses to disseminated infection (10–20%) [114]. Coinfections or complicating infections occur frequently after adenovirus infections [114]. Untreated, the mortality for HSCT patients approaches 26% for all symptomatic patients while pneumonia and disseminated disease portend more ominous outcomes (50% and 80% mortality respectively) [114].

Adenovirus infection has been reported in all SOT populations [119], with invasive disease in up to 10% of patients [114]. Among SOT recipients, risk factors for adenovirus infection include renal or hepatic transplant, paediatric age group, T-cell depletion and serologic mismatch (transplant from an adenovirus-seropositive donor to an adenovirus-seronegative recipient) [114]. Haemorrhagic cystitis, nephritis, pneumonia, hepatitis, enterocolitis and disseminated disease have been described [114]. With the exception of haemorrhagic cystitis (the most common form of symptomatic disease in renal transplant recipients), the transplanted organ is typically the site of infection [15,40,114]. Enterocolitis might mimic rejection in small bowel recipients and should be screened for any time rejection is considered [120,121]. The detection of adenovirus in myocytes in heart transplant recipients appears to be predictive of adverse clinical outcomes including coronary vasculopathy and graft loss (OR: 4.7 compared with adenovirus-negative patients) [122]. Because latent adenovirus infection has been documented in 11% of donor hearts [123], a prospective study is needed to correlate the timing of detection with adverse effect.

Diagnosis

The diagnostic approach to patients with adenovirus disease is complex. It is important to have a low threshold to test for adenovirus as the virus can cause a variety of illnesses unique to each transplant type. Although adenovirus can be detected in the stool in most clinical syndromes, the site of infection should determine the type of sample to test (for example, stool for gastrointestinal disease, urine for genitourinary disease). Once disease is documented, quantitative vial load testing of blood should be considered as it may provide a marker for monitoring disease progression and treatment response [114].

Various diagnostic techniques, including serology, antigen detection methods, culture, nucleic acid testing and pathology, have been described. Definitive diagnosis is made by correlating histopathology with clinical course. Culture has traditionally been considered the gold standard, although PCR is more sensitive [124]. Traditional cultures can take several days to weeks to become positive and rapid shell vial techniques are limited by reduced sensitivity relative to traditional cultures. Nucleic acid testing methods are increasingly being used because of their ease and sensitivity. Several different techniques have been applied and there are several assays that detect multiple pathogens in a multiplex platform [114]. PCR applied to whole blood has emerged as a significant screening method with proven effect in paediatric HSCT recipients; its role in screening adult HSCT recipients has yet to be documented [125–127]. There is not a specific threshold above which quantitative adenoviraemia is predictive of disease, although higher viral DNA levels ($>1\times10^6$ copies/ml, in one study) have been associated with a greater likelihood of death among paediatric transplant recipients [128,129]. The overall trend of viral load over time and the degree of immune suppression, particularly the presence of lymphopenia, are probably more predictive of outcomes than actual values [125]. Reduction of immunosuppression and/or institution of cidofovir-based therapy in paediatric HSCT recipients with persistent adenoviraemia might reduce the frequency of morbidity and mortality [125]. Adenoviraemia is commonly found among adult SOT recipients and does not predict disease, so it should not be used to prospectively screen for disease, with the possible exception of small bowel transplant recipients [116]. Dynamic trends in adenovirus load in blood also appear to be a useful tool in monitoring response to therapy (see below) [26,114,130–132].

Despite these advantages, there are several drawbacks to nucleic acid testing for adenovirus. There is still significant genetic heterogeneity in the adenovirus genome (greater than 80% sequence dissimilarity between some species) [115], which presents challenges in designing a single robust assay to detect and quantify all types. Some assays that claim to detect all serotypes might be less efficient at detecting certain strains. The lack of assay standardization remains an important limitation, as most molecular testing for adenovirus is performed with user-developed assays. Furthermore, no universal quantitative standards exist to allow normalization between different tests. As such, caution must be exercised when comparing values from different laboratories, often using different techniques on different specimen types.

Treatment

There are limited options for therapy of adenovirus infection, and the optimal timing for therapeutic intervention during the course of illness is unclear [114]. Reduction of immune suppression, if possible, is recommended for all patients with adenovirus disease. Cidofovir appears to have the best *in vitro* and *in vivo* efficacy; unfortunately significant toxicity has so far limited its application to wider patient populations [26]. Not all patients have meaningful reductions of viral replication despite therapy. The available data suggests that a lack of reduction of viral load following the first two doses of cidofovir is predictive of a progressive clinical course [26]. In general, one of two dosing regimens are used: 5 mg/kg once a week for 2 weeks then every other week or 1 mg/kg three times a week [133,134]. Although the 1 mg/kg three times a week regimen is associated with less nephrotoxicity [133], the efficacies of the two regimens have not been directly compared. Notably, the 1 mg/kg three times a week regimen is associated with breakthrough CMV and HSV infections [135,136]. Lipid ester preparations of cidofovir appear to have increased *in vitro* efficacy against adenovirus and might have less toxicity [114]. Phase I testing of these agents has begun. Ribavirin has *in vitro* activity against only serogroup C viruses and does not appear to have significant activity in humans; it is not approved for use for treatment of adenovirus infections [130]. Other agents, including vidarabine, zalcitabine and ganciclovir, have documented *in vitro* activity but their clinical efficacy in managing adenoviral infections is less well studied [114]. Vidarabine has been used to treat haemorrhagic cystitis with some success but is currently only available in an ophthalmologic preparation and is associated with significant toxicity [137]. Zalcitabine has documented efficacy in a rat pneumonia model but no data in humans for the treatment of adenovirus [138]. Ganciclovir might reduce the frequency of adenoviral infections among HSCT recipients [139], but it does not appear to effect the frequency of adenoviraemia among SOT recipients [116]. Lymphocyte reconstitution plays a crucial role in the clearance of adenovirus [140]. As such, donor lymphocyte infusions might also have a role in the management of adenoviral infections, although experience with this method is limited [141,142].

New Viruses

In addition to these traditional respiratory viruses, a number of novel pathogens, including new respiratory coronaviruses NL-63 and HKU-1 and human bocavirus, have been discovered. Although our understanding of the epidemiology and management options for these viruses is limited, some have been associated with significant disease in transplant recipients [4,143–145].

Conclusion

Our understanding of the epidemiology of respiratory viral infections has advanced in recent years and most have been clearly associated with significant disease in transplant recipients. However, from the available data it seems that respiratory viruses remain common pathogens in transplant recipients. Although many recipients might have mild, transient infections, more severe disease for all recognized viruses has been described. Studies of the long-term consequences of these infections need to be undertaken as do prospective studies of prophylactic and therapeutic options. New antivirals are desperately needed as available therapy remains limited and is frequently associated with significant toxicity.

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