15 Respiratory Viruses and Other Relevant Viral Infections in the Lung Transplant Recipient

Ali Abedi, Reed Hall, and Deborah Jo Levine

Introduction

As advances occur in surgical technique, postoperative care, and immunosuppressive therapy, the rate of mortality in the early postoperative period following lung transplantation continues to decline [1].

With the improvements in immediate and early posttransplant mortality, infections and their sequel as well as rejection and chronic allograft dysfunction are increasingly a major cause of posttransplant mortality [2–5].

This chapter will focus on infections by respiratory viruses and other viral infections relevant to lung transplantation, including data regarding the link between viral infections and allograft dysfunction.

A. Abedi
Department of Pulmonary and Critical Care Medicine, University of Texas Health San Antonio, San Antonio, TX, USA

R. Hall
Pharmacy, University Hospital—University Health System, San Antonio, TX, USA
e-mail: Reed.hall@uhs-sa.com

D. J. Levine (✉)
Department of Pulmonary and Critical Care Medicine, University of Texas Health Science Center San Antonio, San Antonio, TX, USA
e-mail: levinedj@uthscsa.edu

Factors Related to Risk of Respiratory Viral Infections

Lungs are the most prone to infection of all solid organ transplantations [2, 4]. This reality is based on multiple factors related and unique to lung transplantation [1, 2]. The lungs are continually exposed to both new environmental pathogens and the colonized native upper airways. Furthermore, many of the natural defense mechanisms of the respiratory system are made ineffective by both the technical aspects of lung transplantation and the relatively increased degree of immunosuppression required to minimize high rates of acute and chronic rejection seen in lung transplantation compared to other solid organs [1, 2, 6, 7].

The usual physical barriers of the respiratory tract against infections include the presence of the mucociliary escalator that traps and expels infectious organisms. These mechanisms are facilitated by the integrity of the epithelium lining the trachea, bronchi, and small airways. The complete disruption of the bronchial circulation during lung transplantation can cause a loss of epithelium integrity and associated mucociliary action, which may not fully recover despite development of collateral flow in the future [1, 2, 6, 8, 9]. Additional compromise of the anatomical barrier to infection is created by the potential suppression of the cough reflex caused by denervation of the allograft [4, 7]. Disruption of the normal lymphatic flow of

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the lung during transplantation also increases the risk of infections by creating edema and stasis of interstitial fluids [4, 7].

The incidence of allograft dysfunction due to both acute and chronic rejection in lung transplantation is among the highest in solid transplantation, requiring relatively high levels of immunosuppression targeting multiple lines of immune cells and their associated cytokine pathways.

The use of induction and high levels of maintenance of immunosuppression creates a significant risk for development of viral infection, with higher tacrolimus levels having been specifically associated with increased rates of CARV infections [2]. Prevention and suppression of infection by respiratory viruses involves the activities of cellular and antibody-mediated immunity, which are impaired by immunosuppression targeting adaptive T-cell-mediated processes. This point is highlighted by relatively weak antibody response to vaccines directed against certain respiratory viruses in recipients of solid organ transplantation [3, 10–13].

The transmission of donor-harbored infections at the time of transplantation is another factor that increases the likelihood of viral infection in the LTR [1, 4, 5]. With many viruses, the highest risk for development active disease exists in circumstances when a recipient with no prior exposure or established humoral immunity to a virus is "mismatched" with a donor whose tissues harbor the active infection or latent form of the virus. Viral infections that have previously been documented as originating from donor lung tissue include CMV, Epstein-Barr virus, varicella-zoster, adenovirus, influenza, hepatitis B and C, and human immunodeficiency virus, in addition to others [2, 4, 14, 15]. Therefore, at most centers, the evaluation of a donor for lung transplantation routinely includes serologic screening for common viruses, as well as bronchoscopic assessment with PCR analysis of BAL samples for common respiratory viruses [1, 2].

Reactivation of latent virus previously introduced to the LTR following induction and maintenance of immunosuppressive therapy is another risk factor for clinically significant viral infection [16–18]. For this reason the initial pretransplant candidate evaluation process includes a thorough screening for many of the same viruses listed above. In addition to helping to determine a patient's candidacy for transplantation, this screening can help determine the need and duration of antiviral prophylaxis to specific viruses in the posttransplantation period [19, 20].

Infections with previously latent viruses in donor or recipient tissues are of significant concern early in the posttransplantation period. However, the period after several months posttransplantation represents its own risks for viral infection [2, 4, 5, 14, 15]. This phenomenon is related primarily to the return to community life by LTRs who have recovered from the initial surgical course and any subsequent physiologic or infectious insults. Evidence suggests LTRs who are greater than 1 year from surgery are five times more likely to present with CARV infections compared to those less than 1 year from transplantation [2, 14, 21].

Changing Epidemiology of Viral Infections in Lung Transplantation

Respiratory viruses and some members of the *Herpesviridae* family frequently cause clinically significant infections with potentially severe complications after solid organ transplantation (SOT).

Advancement in the field of diagnostic virology, primarily based on new molecular assays, has greatly improved the breadth and sensitivity of detection methods for viral infections. Multiplex PCR assays have now been available and FDA-approved for nearly a decade; they have provided a significantly larger number of small laboratories without expertise in viral culture techniques the opportunity to participate in real time diagnosis of a wide array of respiratory viral pathogens [22–24]. Furthermore, these new multiplex PCR-based assays are able to provide more rapid and sensitive identification of respiratory viruses than traditional viral culture and immunofluorescence testing [22, 25, 26].

Just in the last decade, several new viral respiratory tract pathogens have been identified, including human metapneumovirus (hMPV), human bocavirus (HBoV), new strains of human coronavirus (HCoV-NL63 and HCoV-HKU1), and new species of rhinovirus (HRV-C) [27, 28].

Respiratory and Other Viral Infections and Lung Allograft Dysfunction

The development of chronic lung allograft rejection (CLAD), encountered as bronchiolitis obliterans syndrome (BOS) or restrictive chronic lung allograft dysfunction (R-CLAD), continues to be the primary driver of mortality in LTR after the first 2 years following transplantation. Obliterative bronchiolitis, the hallmark of BOS, appears to be the pathologic end-stage of a process initially beginning with airway epithelial injury and leading to inflammatory reactions that promote airway obliteration. The inciting injury to the epithelium may be initiated as an exposure to toxic chemicals or drugs, infection including to viral agents, or an autoimmune process [3, 29, 30]. Airway inflammation and injury resulting from both the number and severity of episodes of acute rejection are also thought to play an important role in the development of CLAD [3, 30].

Viral infection as a process leading to allograft rejection has been previously documented in other solid organ transplants, such as renal allograft dysfunction caused by infections with BK virus and CMV. Similarly, multiple studies over the last two decades have indicated that respiratory viral infections play a major role in the development of acute rejection and chronic lung allograft dysfunction, manifested both as BOS and R-CLAD [3, 19, 29–37]. And these findings apply to both CMV and non-CMV respiratory viruses, with symptomatic or asymptomatic respiratory virus infection (RVI) [3, 19, 30, 32, 38–42].

In the past, remarkably high rates of pathologically documented graft changes suggestive of acute rejection have been reported in the setting of active respiratory viral infections. In some series as many as 62% of cases of respiratory virus infection in LTR were noted to have varying degrees of perivascular mononuclear cell infiltrates, as are seen in acute cellular rejection [3, 35, 36, 41, 43]. These findings are further supported by cohort studies where higher incidences of BOS have been noted in LTR who suffered CARV infections and have been reproduced in different settings where the acute and long-term outcomes of respiratory viral infection on declining allograft function have been documented [3, 33–35, 37, 39, 41, 42].

In cases where this relationship is seen, factors more likely to be associated with the development of graft dysfunction include respiratory virus infection involving the lower respiratory tract and infection with viruses known to cause more severe respiratory illness in general such as influenza and the paramyxoviruses [3, 33–35, 37, 39, 41].

The relationship between viral infection of the respiratory tract and development of allograft rejection would seem to be based on the similarity in pathogenesis of these processes. During the acute phase of a viral infection, as well as during the prolonged viral shedding often seen in the setting of lung transplantation, chemotactic cytokines released by injured parenchymal cells in the inflamed graft recruit alloreactive leukocytes. This process is further augmented by immune response specifically targeting the virus [44].

During this process, Th-1 and Th-2 CD4 T-cell subtypes and their associated cytokines interleukin (IL)-1, tumor necrosis factor, IL-6, and IL-8 are upregulated. The resulting alloreactive environment in the transplanted lung may lead to immune-mediated injury to the airway and subsequent rejection and graft dysfunction [45–51].

In recent lung transplant literature, the activity of the CXCR3 receptor expressed on the surface of activated lymphocytes provides further evidence supporting the role of viral infection in the development of lymphocyte-mediated allograft dysfunction [52, 53]. The CXCR3 receptor and its ligands, CXCL9-11, have roles both in the immune response to viruses and in the development of BOS [54–56]. In the setting of CARV infection in LTRs, the concentrations of each

CXCR3 ligand are increased and associated with larger decline in FEV^1 at 6 months [52].

In the case of CMV specifically, which is not a member of the CARV group, the interplay of viral-associated changes and host immune factors forms a pathophysiologic relationship that promotes development of allograft dysfunction. Here the cytokine cascades induced by the activity of CMV infection, as well as cytokines involved in the pathophysiology of rejection, promote the progression of one another [57–60].The release of tumor necrosis factor-alpha during allograft rejection, which acts as a key reactivation signal for latent CMV, facilitates viral replication and progression to active infection. Meanwhile the activity of CMV within the vascular endothelium and smooth muscle induces the upregulation of adhesion molecules which promote further proliferation and activity of inflammatory cells in the graft, leading to development of rejection. CMV has been thought to play an additional role in the development of rejection by the process of molecular mimicry, where the immune response against viral antigens leads to the production of anti-endothelial antibodies within the graft [2, 42, 57, 58, 60, 61].

Respiratory Viruses and Viral Infections Relevant to Lung Transplantation

Community-Acquired Respiratory Viruses (CARVs)

CARVs represent a diverse group of human pathogenic viruses, which belong to several distinct families. These include the *Paramyxoviridae* (RSV, hMPV, and PIV), *Orthomyxoviridae* (influenza A and B), *Picornaviridae* (rhinovirus and enteroviruses), *Adenoviridae* (adenovirus), and *Coronaviridae* (coronaviruses) [27, 28].

These viruses represent the most common causes of human respiratory infections and are most commonly acquired from contact with infected individuals or secretions left in the environment by an infected person [62–64].

Modes of transmission include contact with secretions followed by autoinoculation of mucosal membranes versus direct inoculation large droplets or aerosols.

Infection patterns for some of these organisms follow typical seasonal or temporal patterns and in these cases tend to mirror patterns in the general community. Healthcare-associated infections can also occur, even exhibiting cases of outbreaks within hospitals [65].

CARV infections can lead to serious complications in those with predisposing factors such as immunosuppression and altered pulmonary anatomical defense mechanisms, with LTR at particularly high risk of developing severe infections. Infections of the respiratory tract by CARVS in LTR can be further complicated by the occurrence of secondary bacterial infections and increased incidence of associated acute and chronic rejection [4, 21, 42, 64, 66, 67].

Picornaviruses, primarily RhV, are the most common viruses found in nasopharyngeal and BAL samples collected from LTR bit at routine screening and healthcare visits specifically for respiratory and infectious symptoms [14, 42, 67, 68]. Common CARVs and other RhV are much more likely to be isolated during emergency visits than routine screening, suggesting a higher incidence of symptomatic infection [14]. In general the LTR population can have as high as a 10% incidence of positive tests for CARV infection at surveillance screening without symptoms, with nearly double this rate when tested while presenting with symptoms of an acute respiratory illness [4, 14, 69].

The spectrum of disease severity for CARV infection in LTR varies significantly and does so depending on the specific infectious agent. RhV infections which are the most common of CARVs can often present with limited symptoms or be found on asymptomatic screening in one third of cases [14]. The most common symptoms of RhV infection include rhinorrhea and nasal congestion, with fevers and myalgias being relatively uncommon. Meanwhile, infections with influenza and paramyxoviruses (RSV and PIV) are almost always associated with symptoms and much more likely to be febrile illnesses [14, 67,

70]. Lower respiratory tract involvement with radiographic manifestation is typically rare except in the case of influenza. Infections with influenza and paramyxoviruses are also more than twice as likely to result in hospitalization compared with RhV and coronavirus, with nearly 50% of cases requiring admission [14, 21, 70].

In nearly all cases of symptomatic infection with CARVs, lower FEV_1 and FVC can be seen when compared to preinfection values for patients [14].

Respiratory Syncytial Virus (RSV)

RSV is an almost universally common respiratory tract infection of early childhood. It carries an incomplete pattern of natural immunity and frequent reinfections [45, 71]. It is the most charcterstic virus of the *Paramyxoviridae*. RSV is among the most commonly isolated CRVs and clinically ranges from mild upper respiratory infection symptoms such as rhinorrhea and cough to life-threatening lower respiratory tract infections with bronchiolitis and pneumonia similar to influenza. Risk factors for more severe disease include higher levels of immunosuppression, infection immediately following transplantation, and pre-existing pulmonary pathology. In LTR, RSV infection can cause significant morbidity and can be associated with acute and chronic graft dysfunction [72, 73]. RSV has been shown to significantly increase the risk of graft dysfunction, with as much as a mean FEV_1 decline of 30% in some series and associated mortality ranging from 10 to 15% [74–76].

Reverse transcription-polymerase chain reaction (RT- PCR)-based assays are the current mainstay of diagnosis with excellent sensitivity in symptomatic patients, while fluorescent antibody and serologic testing as well as viral culture can also be used to diagnose acute infection [76].

In the normal host, RSV infection primarily affects airway epithelial cells. The subsequent immune response, mediated in part by the IL-2-mediated T-helper 1 (Th1) activity, can clear the infection and prevent a prolonged inflammatory response leading to reactive airways disease [69, 77–80]. Th1 deficiency, meanwhile, can be associated with viral persistence and chronic airway inflammation, with a Th2-driven interleukin-10-associated response [81]. Suppression of the IL-2 pathway in LTR and the associated alterations in mucosal immunity may influence the pathogenesis of RSV infection in LTR and subsequent allograft dysfunction.

Prophylaxis and Treatment

Currently, there is no vaccine or antiviral prophylactic regimen for RSV, but there are multiple clinical trials assessing the effectiveness of innovative RSV vaccines. Pavilizumab is recommended for prophylaxis in children meeting treatment criteria, but the use of this medication for the prevention of RSV in older transplant recipients is not recommended [82].

There are limited data regarding the role of antiviral therapy to treat RSV in lung transplant recipients. Currently, the drug of choice is ribavirin with or without corticosteroids, which can be administered intravenous, orally, or inhaled (Table 15.1) [82, 83, 85–87]. Treatment decisions are commonly dependent on the severity of disease, and inhaled ribavirin is most often the route of choice for severe RSV infections. Inhaled ribavirin has many drawbacks: administration requires a hospital admission and an extended inhalation interval, and it can be teratogenic to women of child-bearing age. Because of these factors of the medication, appropriate precautions should be taken [82]. Intravenous ribavirin has reported success, although it is only available through compassionate use in the United States

Table 15.1 Ribavirin treatment regimens

Dosage form	Regimen	Duration
Inhaled ribavirin	6 g over 12–18 h	3–7 days
IV ribavirin [83, 84]	Day 1: 33 mg/kg in three divided doses (q8h) Maintenance: 20 mg/kg/day in three divided doses every 8 h	7 days + negative swab
PO ribavirin [84, 85]	400 mg three times daily ± loading dose Or 20 mg/kg/day divided every 8 h	5–10 days

Data from References [83–86]

[82, 83]. Adjunctive therapy using pavilizumab and intravenous immunoglobulin has been used, with little published efficacy [82, 88]. Lastly, presatovir and ALN-RSV01 are medications undergoing phase II clinical trials to assess the efficacy of these novel antiviral agents for the treatment of RSV infections in lung transplant patients [89].

Parainfluenza Virus (PIV)

The PIV family includes four major serotypes that have been found to cause human disease, with serotype 3 most commonly isolated from LTRs. Incidence of respiratory infection with parainfluenza virus ranges from 2 to 10% of all LTRs. As a community-acquired infection, the majority of cases occur more than 1 year following transplantation, with seasonal peaks in the warmer months of spring and summer [69, 90]. Parainfluenza virus infections have been associated with high rates acute cellular rejection, up to 82% in one series. Furthermore in this series, a significant portion, nearly one third of cases, progressed to develop BOS [90].

Prophylaxis and Treatment

There are no known vaccines or prophylactic antiviral medications known to prevent parainfluenza. Currently, there are no proven treatments for parainfluenza viral infections. Ribavirin, steroids, and IVIG have been used to treat parainfluenza infections in transplant recipients but have not been proven to provide benefit [91]. DAS181, a novel sialidase fusion protein, has been used through compassionate use and is currently in phase II trials for treatment of parainfluenza in immunocompromised patients [92, 93].

Human Metapneumovirus (hMPV)

hMPV is a relatively new addition to the paramyxovirus family. hMPV presents with a clinical spectrum of disease similar to RSV, albeit typically less severe. Disease severity can range from asymptomatic infection to severe lower respiratory tract infection [94, 95]. Current data do not support an association with hMPV infection and the development of persistent allograft dysfunction as is the case with RSV [96]. However, evidence of acute decline in lung function following hMPV infection does exist [69, 74, 75].

Influenza A and B Virus

Influenza A and B viruses are associated with seasonal infections, most common in the winter months and accounting for up to 5% of viral infections in LTRs [97]. Compared to normal hosts, where influenza infection is typically a self-limited upper respiratory syndrome with myalgias and fever, the risk of lower respiratory tract involvement is higher for LTRs and immunocompromised populations in general [35, 43].

Consequently, the Centers for Disease Control recommend annual influenza vaccination and chemoprophylaxis for the immunocompromised during community outbreaks [98].

In some series a majority of LTR patients with active influenza had concomitant acute allograft rejection, and seasonal increases in BOS have been suggested to have association with influenza outbreaks [36, 41, 99, 100]. Despite this, unlike paramyxovirus infections, serious influenza disease does not appear to be very common in LTR [72]. Rapid diagnostic methods using antigen-based assays or PCR amplification of target nucleic acid sequences can be performed on nasopharyngeal swabs or BAL samples.

Prophylaxis

The immunogenicity of the influenza vaccine in lung transplant recipients is unknown [82]. Even so, seasonal influenza vaccine is recommended for transplant patients [101]. Along with immunizing transplant patients themselves, herd immunity is a very important strategy when it comes to posttransplant patient care. Therefore, it is essential to ensure all close contacts of lung transplant recipients are also vaccinated. There are two types of influenza vaccines available: the intranasal live attenuated influenza vaccine and the intramuscular inactivated vaccine. Live attenuated vaccines are contraindicated in

transplant recipients; therefore, the inactivated vaccine is to be administered. Due to the intensity of immunosuppression directly posttransplant and concern of decreased immunogenicity, vaccinations are often withheld directly after transplantation. According to the American Society of Transplantation, a reasonable time frame is to wait at least 3 months after transplant before influenza vaccine administration [82] .

Postexposure prophylaxis with oseltamivir or zanamivir may be indicated in transplant recipients exposed to influenza, primarily if it is an exposure of someone living in their household [82]. Prophylaxis should be initiated if patient presents within 48 h of exposure for oseltamivir and 36 h of exposure for zanamivir [102, 103]. See Table 15.2 for prophylaxis dosing and duration.

Treatment

There are two classes of antivirals that have been used to treat influenza: the M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir). The neuraminidase inhibitors are preferred agents to treat influenza [82]. M2 inhibitors are no longer recommended due to increased resistance and inactivity to influenza A and B, respectively [82]. Oseltamivir is commercially available as a capsule and suspension; zanamivir is administered as an inhalation and peramivir as an infusion [102–104]. Currently, the IV formulation of zanamivir and oseltamivir are only available as an investigational use, and not commercially available. Oseltamivir is the most used antiviral to treat influenza in the lung transplant population; zanamivir and peramivir lack data for severe disease and for treatment of hospitalized patients [101, 105]. The usual duration of therapy for influenza A or B treatment is 5 days, although immunosuppressed patients, including lung transplant recipients, may have prolonged viral replication and also have an increased risk of developing antiviral resistance; therefore, longer duration of therapy can be considered [82, 105]. Dosing and duration of therapy is presented in Table 15.2.

Rhinoviruses (RhV)

RhVs are the most common cause of colds in adults and are members of the *Picornaviridae* family [66]. Much like in the general population, RhVs are increasingly recognized as the most common cause of respiratory viral illness in the LTR [66, 106–111]. In addition, as many as 50% of PCR-documented cases of RhV infections in transplant recipients have few to no symptoms at the time of surveillance testing [106, 108, 112]. The typical clinical presentation involves an afebrile upper respiratory illness with rhinorrhea and sinus congestion. It is sometimes associated with sore throat and cough. Coinfections with

Table 15.2 Dosing of anti-influenza medications

	CrCl (mL/min)	Treatment	Duration	Prophylaxis	Duration
Oseltamivir	≥60	75 mg twice daily	≥5 days	75 mg once daily	7–10 days
	30–60	30 mg twice daily		30 mg once daily	
	10–30	30 mg once daily		30 mg every other day	
	HD/CrCl<10	30 mg after each HD session	5 days	30 mg after every other HD cycle	
Zanamivir	N/A	Two inhalations (10 mg) twice daily	≥5 days	Two inhalations (10 mg) once daily	10 days
Peramivir (IV)	≥ 50	600 mg	Single dose	N/A	
	30–49	200 mg			
	10–29	100 mg			
	< 10/HD	Dose after dialysis, adjusted based on creatinine clearance			

Data from References [102–105]

other pathogens complicate many cases of RhV infection in LTR and may contribute significantly to the relatively high morbidity and mortality rates observed [110].

The incidence of RhV-associated lower respiratory tract infection in LTR has been documented in contrast to typically mild and self-limited disease in the general population. These events are associated with risk of both acute and chronic rejection and increased mortality [106, 110].

There a currently no specific prophylactic or treatment options available for RhV.

Adenovirus

Adenovirus is a non-enveloped DNA virus ubiquitous in the community. Adenovirus causes a primary infection in all individuals typically in the first few years of life and counts for about 10% of all childhood respiratory illness. From there the virus may remain in lymphoepithelial tissues in latent form and subsequently create disease by reactivation [70, 113].

The mode of transmission of adenovirus in general involves inhalation of aerosolized droplets, direct contact with conjunctival secretions, feco-oral contamination, or contact with infected blood [66]. In the immunocompromised, speculation exists regarding adenovirus disease as either a primary infection from the environment or the result of transmission from the donor tissue and reactivation of previously latent virus epithelia of the pharynx, intestinal tract, and urinary tract [13, 114, 115].

In the immune competent host, symptoms associated with infection are usually self-limited, including cough, pharyngitis, keratoconjunctivitis, gastroenteritis, and fevers.

Disease in the immunocompromised, including LTR, has a wide range of severity. Although asymptomatic infection is reported, severe disease with significant morbidity and mortality can also occur. Infection sites in the immunocompromised are typically comprised of the urinary tract, gastrointestinal tract, lung, and liver [116]. More severe disease and poorer outcomes can be predicted based on higher number of affected sites and organ systems involved, as well as pathologically determined invasive disease [116–118].

The more feared complications of adenovirus infection for the recipients of solid organ transplants include pneumonia and hepatitis, with mortality rates of up to 50% documented [70].

Severe pulmonary infections have specifically been documented in LTR, with many of these cases progressing to respiratory failure with high mortality rates. In these instances, pathologic assessments at autopsy have revealed necrotizing hemorrhagic pneumonia with diffuse alveolar damage, as well as invasive disease represented by basophilic inclusions within bronchial epithelial cell consistent with adenovirus infection [114]. These severe infections have been documented to occur both in the first few weeks following transplantation and less frequently years after returning to the community [114, 119].

Prophylaxis and Treatment

There are no vaccines or established chemoprophylaxis to prevent adenovirus in solid organ transplant recipients.

Currently, there are no randomized controlled trials regarding the treatment of severe adenovirus infections. The current preferred therapy for most centers is minimization of immunosuppression. If an antiviral is needed cidofovir can be considered [120]. This drug should be utilized with caution; cidofovir administration is associated with significant adverse reactions, primarily neutropenia and nephrotoxicity, both of which are pronounced with lung transplant [120, 121]. In order to mitigate nephrotoxicity caused by cidofovir, probenacid and hydration should be added to the regimen [121]. Probenacid is administered 3 h before, 3 h after, and 8 h after cidofovir, along with hydration with normal saline [120, 121]. As adjunct to reduced immunosuppression with or without cidofovir, immunoglobulin may be considered, primarily in patients with hypogammaglobinemia [120], although the benefits of IVIG in the setting of adenovirus infection with or without hypogammaglobinemia are still not clear. In the future, brincidofovir (CMX001), a

lipid conjugate of cidofovir which is currently in clinical trials, may be a viable option. Benefits of this dosage form may include an oral formulation, higher potency, and less nephrotoxicity.

Coronaviruses

Coronaviruses are a frequent cause of the common cold with currently an unclear role in infections affecting LTR [14, 21, 68]. New sensitive molecular assays for detection of coronavirus infection can help to detect this virus, which can range from simple upper respiratory illness to severe lower respiratory tract infections [122]. Severe infections in the immunocompromised can present as pneumonia and bronchiolitis [123, 124].

Similar to RhV infections, no current pharmacologic options for prophylaxis or treatment are available.

Human Bocavirus (HBoV)

HBoV, a recently identified member of the *Parvoviridae* family, can cause respiratory disease in humans with typically seasonal pattern in winter [125, 126]. Although a great deal of data regarding infections in the immunocompromised has not yet been compiled, case reports have documented severe respiratory and disseminated infections in the setting of lung transplantation [127].

β-Herpesviruses

The *Herpesviridae* are a heterogeneous family of morphologically similar double-stranded DNA viruses that can infect humans and other animals. Humans act as primary hosts for eight members of this virus family and are typically transmitted through direct person-to-person contact.

Cytomegalovirus (CMV)

CMV is the most common and important among the opportunistic infections that complicate lung transplantation. Its association to morbidity and mortality posttransplant has been well documented and increasingly shown to be mediated by elevated risk of acute and chronic allograft dysfunction [2, 32, 128–131].

CMV exposure and seropositivity are ubiquitous in the general population, ranging from 30 to 97% [59]. Exposure to and infection with the virus confer a life-long carrier status with risk of future reactivation in the setting of a compromised immune system [2, 69, 132]. The overall incidence of CMV infection in LTR has been reported as the highest among all solid organ transplants, with figures ranging from 30 to 86% of patients, in part due to the relatively higher-level immunosuppression required in the post-lung transplantation setting [57, 59]. The high incidence rates and associated complications of CMV infection exact a high price on the LTR population, with mortality rates reported at 2–12% [2, 57, 69].

Unlike community-acquired infections, the primary risk factor development of CMV infection appears to be a mismatch between the serostatus of donor and recipient [57, 59, 131]. The highest risk category is that of a seropositive donor with seronegative recipient, in which case the transplant recipient who lacks previously formulated immunity to CMV receives exposure to the virus harbored within the allograft at a time when immunosuppression is at its most aggressive [59]. The intensity of the immunosuppression regimen, both at induction and maintenance, is also an important risk factor for CMV infection, as are host factors such as age medical comorbidities [57, 59]. Other modes of infection include transfusion of blood products from a seropositive donor and reactivation of latent infection in a seropositive LTR.

Clinical Manifestations

CMV infection and disease are distinct clinical entities. Replication of CMV with or without symptoms is regarded as infection, while the presence of symptoms or physiologic changes attributable to CMV is required to meet a definition of disease. The hallmarks of CMV disease include fevers and malaise, myalgias and

arthralgias, leukopenia and thrombocytopenia, as well as tissue invasive manifestations [20, 59].

Tissue invasive disease most commonly manifests as a pneumonitis. This syndrome can present with subtle fevers, nonproductive cough, and dyspnea associated with decline in pulmonary function tests. Other manifestations of tissue invasive disease include incidences of hepatitis associated with abnormal liver function tests, and gastroenteritis and colitis typically presenting with nausea, vomiting, and diarrhea [20].

Diagnosis

Quantitative nucleic acid-based amplification assays utilizing polymerase chain reaction (PCR) technology for the identification of viremia have largely replaced previously used methods of diagnosis relying on antigen detection for viral particles. Monitoring and diagnosis of CMV infection is now used in the overwhelming majority of transplant center [133]. Despite this, there is no current consensus on threshold values of CMV viral load considered to be an indicator of infection. Viral culture performed on blood, urine, and BAL samples is no longer routinely recommended for detection of CMV [42].

The presence of cell-mediated immunity to CMV, as determined by quantiferon-CMV assay measuring the presence of a CD8 T-cell response to the virus, holds promise as a marker to determine risk of CMV disease. Patients with positive CMV interferon-gamma release assays have been shown to more frequently clear viremia without progression to clinical disease, while those with negative assays suffer higher rates of late onset CMV disease after discontinuation of prophylactic therapy [134, 135].

Treatment General

Intravenous ganciclovir has historically been the treatment of choice for the treatment of CMV [136]. The IV formulation is still the drug of choice for severe life-threatening disease and in patients who have severe diarrhea or cannot tolerate medications by mouth [137]. In 2007, the Victor Study group concluded that oral valganciclovir is also a treatment option in select solid organ transplant recipients with mild to moderate disease [138], although it should be noted that less than 10% of the patients in the Victor Study were lung transplant recipients, and these patients did not have severe disease [138]. Whether using intravenous ganciclovir or oral valganciclovir treatment should be continued for 14–21 days plus viral clearance [136]. If virus is not cleared after 21 days, there is a high risk for recurrent disease; therefore, longer duration may be necessary if resolution of viremia is not accomplished [136–138]. Table 15.3 outlines dosing guidelines adjusted for renal function for both ganciclovir and valganciclovir.

Prophylaxis

Chemoprophylaxis for CMV should be started as soon as possible, and always within 10 days after transplantation for those at risk for CMV [136]. Recommendations for prophylaxis of CMV disease in lung transplant recipients are based on donor and recipient IGG serostatus (Table 15.4). For patients at the highest risk for developing CMV disease, donor IGG positive and recipient IGG negative (D+/R−), prophylaxis with IV ganciclovir, valganciclovir, or a combination of both is recommended [136]. The duration of prophylaxis varies, but at least 12 months of prophylaxis is recommended, with some centers extending prophylaxis beyond 12 months [136, 142]. As adjunct to chemoprophylaxis, CMV immune globulin can also be considered for the D+/R− high-risk group of patients [136]. For moderate-risk recipient IGG seropositive recipients, IV ganciclovir or valganciclovir is recommended for 6–12 months [136, 142, 143]. For low-risk donor and recipient IGG seronegative negative patients, no CMV-specific prophylaxis is necessary [136, 142]. HSV prophylaxis with acyclovir is still indicated, but neither ganciclovir nor valganciclovir is required [35, 142, 144] (Table 15.4). Preemptive therapy, i.e., withholding valganciclovir or IV ganciclovir prophylaxis and monitoring patients on a weekly basis for CMV viremia then treating to prevent disease progression, is generally not recommended in lung transplant recipients [136].

Table 15.3 CMV treatment

	Valganciclovir			Ganciclovir	
Estimated CrCl	Prophylaxis/maintenance	Treatment/induction	Estimated CrCl	Prophylaxis/maintenance	Treatment/induction
CrCl ≥60 mL/min	900 mg daily	900 mg twice daily	CrCl ≥70 mL/min	5 mg/kg daily	5 mg/kg twice daily
CrCl 40–59 mL/min	450 mg daily	450 mg twice daily	CrCl 50–69 mL/min	2.5 mg/kg daily	2.5 mg/kg twice daily
CrCl 25–39 mL/min	450 mg every other day	450 mg daily	CrCl 25–49 mL/min	1.25 mg/kg daily	2.5 mg/kg daily
CrCl 10–24 mL/min	450 mg twice weekly	450 mg every other day	CrCl 10–24 mL/min	0.625 mg/kg daily	1.25 mg/kg daily
CrCl <10 mL/min	Use not recommended consider ganciclovir		CrCl <10 mL/min	0.625 mg/kg three times weekly following dialysis	1.25 mg/kg three times weekly following dialysis
Alternative dosing valganciclovir in dialysis	Solution 100 mg three times weekly following dialysis	Solution 200 mg three times weekly following dialysis			

Data from References [139–141]

Table 15.4 CMV prophylactic regimens

Risk level		Recommended medication therapy	Duration
High	**D+/R-**	IV ganciclovir Or Valganciclovir +/− CMV IVIG	At least 12 months
Moderate	**D+/R+** **D−/R+**	IV ganciclovir Or Valganciclovir	6–12 months
Low	**D−/R-**	CMV-specific chemoprophylaxis not recommended	

Data from References [136, 139, 140, 142]

Resistance

An emerging concern is the management of ganciclovir-resistant CMV disease. Ganciclovir resistance is associated with high morbidity and mortality, and there are few options when it comes to treatment [145]. Current drugs of choice are either foscarnet or cidofovir, both of which are highly toxic and require extended hospitalizations when initiating therapy. Resistance is usually due to a mutation of the UL97 gene and less commonly the UL54 gene [136, 145]. The UL97 mutation does not confer resistance to cidofovir or foscarnet, but the UL54 mutation may confer resistance to all three medications and is therefore more difficult to treat [136, 145]. Many times as adjunct to cidofovir or foscarnet transplant, centers consider discontinuation of the current antimetabolite and initiating leflunomide, which has both antiviral and antimetabolite properties [146, 147]. Future options for treatment of CMV include maribavir and brincidofovir (CMX001), both of which are currently in clinical trials and not available for use [148, 149]. No matter the situation, treatment of ganciclovir-resistant CMV should be undertaken with caution and on a case by case basis.

Epstein-Barr Virus (EBV)

EBV, an oncogenic virus, holds a strong association for the development of post-lymphoproliferative disease (PTLD). Encompassing a heterogeneous group of lymphoproliferative disorders, PTLD ranges from a reactive polyclonal lymphoid hyperplasia to aggressive non-Hodgkin's lymphomas. A deficient EBV-specific cellular immune response caused by immunosuppressant regimens is considered to be at the etiology of PTLD [68, 150]. In the setting of lung transplantation, the incidence of PTLD has been noted to range from 1 to 20%, with intense prolonged immunosuppression and EBV mismatch (EBV positive donor and EBV negative recipient) considered major risk factors [150–152]. In the setting of EBV mismatch, monitoring of viral load can be clinically useful as a continuous increase of EBV load may indicate pending development of PTLD [153].

Prophylaxis and Prevention

Overall immunosuppression plays a vital role in EBV and PTLD occurrence [154]. The use of lymphocyte-depleting therapy has been linked to increased PTLD cases [154]. This should be considered with discussing the use of lymphocyte-depleting induction and treatment approaches in order to prevent rejection and minimize the risk of PTLD [154]. Both acyclovir and ganciclovir have in vitro activity against EBV lytic replication and have been used as prophylaxis, although efficacy is not proven [154].

Another approach is monitoring of EBV viral load with serial PCRs during posttransplant follow up. This allows centers to preemptively add chemoprophylaxis, decrease immunosuppression, and trend the viral load. As with other prophylactic strategies, the efficacy of EBV monitoring and preemptive intervention to decreases the occurrence of PTLD posttransplant has is not established.

Treatment

Minimization of immunosuppression is a mainstay in management of EBV and PTLD. With reduced immunosuppression, the reconstituted cytotoxic T-Cell population is thought to control the EBV infected B-cell population [154]. The addition of antiviral medication in combination to reduced immunosuppression for patients with PTLD is controversial. This is primarily due to the majority of EBV within a PTLD mass not undergoing lytic infection; therefore, the utility of antiviral therapy is not well defined [154]. IVIG has also been considered as an adjunctive therapy to the treatment regimen, although the benefit of the addition of IVIG is not established.

Anti-CD20 treatment with rituximab with or without traditional chemotherapy is an option depending on severity of the disease and patients response to reduced immunosuppression [154]. Usual regimens are those similar to B-cell lymphoma, often requiring CHOP [154]. Even with treatment options, PTLD in lung transplant recipients remains a high cause of morbidity and mortality. Recently a single center reported approximately 50% of patients treated with a rituximab-based therapy had full remission of disease and 22% with no response to treatment and a 5-year survival of only 29% after PTLD diagnosis [155].

Due to the complexity of the transplant and severity of PTLD, a multidisciplinary approach is often beneficial. Patients, transplant care providers, along with a cancer treatment center can devise a plan that would best fit each individual patient and maximize outcome and quality of life.

Herpes Simplex Virus (HSV) 1 and 2 and Varicella-Zoster Virus (VZV)

HSV and VZV are members of the *Alphaherpesvirinae* which previously represented opportunistic infectious agents in first week post-lung transplantation. Infection with HSV in particular was a cause of severe pneumonitis in up to 10% LTR and associated with high mortality rates [4, 68]. However, severe HSV infection has since become a relatively rare complication with improved antiviral prophylaxis in the posttransplant setting.

Herpes zoster, caused by the reactivations of dormant VZV infection, presents with painful vesicular dermatomal skin lesions. Development of zoster in LTR bears a cumulative probability of approximately 20% after 5 years posttransplantation, with over 5% of cases progressing to disseminated cutaneous infection. Following occurrence of herpes zoster, the post-herpetic neuralgia syndrome can be observed in nearly one of five of those effected [151].

Prophylaxis

Prior to listing, transplant candidates should be evaluated for varicella seropositivity [156]. Seronegative patients are commonly considered for the varicella vaccine, administered least 14 days prior to transplantation [156]. The varicella vaccine is a live-attenuated vaccine and should not be administered after transplantation; therefore, every effort should be made to vaccinate appropriate patients prior to transplantation [156].

All lung transplant recipients should receive prophylaxis for herpes viruses directly after transplantation [156, 157]. Most patients will be receiving prophylaxis with valganciclovir for CMV; this is sufficient herpes virus prophylaxis [156, 157]. For patients who do not require CMV prophylaxis (donor and recipient are seronegative for CMV), acyclovir or valacyclovir is the drug of choice for prophylaxis [156, 157], although famciclovir is also acceptable (Table 15.5).

Treatment

Treatment as an outpatient with oral antivirals is appropriate for mucocutaneous and mild to moderate disease in lung transplant recipients. Patients with moderate to severe disease who are hospitalized require more aggressive therapy [156, 157]. For these transplant recipients, primarily those diagnosed with disseminated or

Table 15.5 Herpes simplex/herpes zoster (VZV) prophylaxis and treatment table

	Indication		
Medication	Prophylaxis	Treatment (outpatient) Duration: 7–14 days	Treatment (moderate to severe/CNS) Duration: 21 days
Acyclovir (PO)	400–800 mg 2× daily	HSV: 400 mg 3× daily VZV: 800 mg 5× daily	N/A
Valacyclovir (PO)	500 mg 2× daily	HSV: 1 g 2× daily VZV: 1 g 3× daily	N/A
Famciclovir (PO)	500 mg 2× daily	HSV: 500 mg 2× daily VZV: 500 mg 3× daily	N/A
Acyclovir (IV)	N/A	5 mg/kg 3× daily (if unable to tolerate PO)	10 mg/kg 3× daily

All medications are adjusted for renal function; refer to individual product labeling
Data from References [158–161]

CNS disease, intravenous acyclovir is the drug of choice (Table 15.5) [156, 157].

Duration of therapy ranges from 7 to 21 days depending on the severity of disease [156, 157]. For localized herpes zoster infections, therapy should be continued for at least 7 days *AND* until the lesions are crusted over [156]. It should be noted that a delay in lesion crusting is commonly seen in transplant recipients, which often extends the duration of therapy. In general, duration of treatment for mild to moderate HSV and VZV disease is recommended to for 7–14 days, and 21 days in severe and central nervous system infections [156, 157].

Human Herpes Virus (HHV) 6 and 7

HHV-6 and HHV-7 are lymphotropic viruses belonging to the same subfamily as CMV. They can cause primary infections during early childhood. Patients who have undergone solid organ transplantation have been noted to suffer reactivation of disease typically early in the posttransplantation period [162].

The clinical syndrome associated with HHV-6 can consist of skin rashes, hepatitis, bone marrow suppression, pneumonitis, and encephalopathy, although severity of infection varies and the majority of cases are thought to be asymptomatic [68, 162].

The clinical impact of HHV-7 is less well characterized.

Human Herpes Virus (HHV) 8

HHV-8 is the virus associated with the development of Kaposi's sarcoma (KS), which is a well-characterized entity following SOT in heart, renal, and liver transplant recipients. The incidence of KS after transplantation in the United States is approximately 0.4%, with the majority of cases occurring in renal transplant recipients. In about 60% of cases, KS lesions are confined to skin and mucosa of the oropharynx, while the remainder can exhibit involvement of internal organs and lymph nodes [163]. In the last few decades, a mounting number of cases of KS in LTR have brought recognition to HHV 8 as an important pathogen in the setting of lung transplantation [163, 164]. KS, considered a rare malignancy in LTR, can manifest with involvement of the allograft as bronchial and pleural disease, as well as cutaneous lesions or involvement of other viscera such as the gastric or intestinal tracts [163–166]. It should be considered in patients with characteristic skin lesions and pulmonary disease, including hemorrhagic pleural effusions that are typically rich in HHV-8 viral particles and DNA when tested [166]. Furthermore, an association between increasing HHV-8 viremia and progression of pulmonary KS has been previously described [163].

Although data on the management of this rare entity in LTR are limited, most cases appear to have full or partial response to reduction in immunosuppression, with small case series showing response to therapy with sirolimus

[163]. Other therapies traditionally used in the treatment of KS include conventional chemotherapies with bleomycin, vincristine, and doxorubicin in addition to radiation, although there are no data regarding these therapeutic modalities in the setting of lung transplantation.

HHV-8 is susceptible in vitro to the anti-*Herpesviridae* agents cidofovir, foscarnet, and ganciclovir, with data from the management of KS in the setting of HIV suggesting a reduced risk of developing KS [167–169]. However, data on the use of these agents in the management of KS following SOT are again limited.

Other Viruses

Several other viral infections have been documented to create complications in the course of lung transplantation. Although largely out of the scope of this chapter, a few examples are briefly discussed below.

BK Virus

BK virus is a member of the human polyomavirus family, almost universally infecting healthy adults with seroprevalence in up to 100%. Data from kidney transplant recipients provde the largest source of information regarding clinically infection with BK virus, where reactivation of BK virus occurs in up to 45% and may cause parenchymal and obstructive renal allograft disease. In the setting of lung transplantation, only rare cases of BK virus-associated nephropathy of native kidneys have been reported [170–172].

Prevention and Treatment

Standard of prevention and treatment of BK virus in lung transplantation is not well established. Although BK virus may be detected in the urine of over 25% of lung transplants, viuria has not shown to have an effect on renal function [170, 173, 174]. Therefore, decreasing immunosuppression or the use of other treatment modalities, such as leflunomide for BK virus in lung transplantation, is not established as a standard of care.

Parvovirus B19

Parvovirus B19 can cause pure red cell aplasia, more commonly seen in renal transplant recipients. It has been shown to occur as a very rare complication after lung transplantation, in isolated case reports [68, 175]. Despite the relative lack of data in the literature on this subject, the ubiquity of parvovirus exposure in the community warrants investigation of this possibility in cases of unexplained isolated anemia in LTRs [176, 177].

Summary

Chronic lung allograft dysfunction (CLAD) continues to be the major causes of morbidity and mortality after lung transplantation. Viruses, especially the community respiratory viruses (CRV), are common and have also been a major source of morbidity in lung transplant recipients. An important and newly intense area of focus for research has been the interface between respiratory viruses, the respiratory virome, and chronic rejection. With improved techniques to study the pathogenesis of all types of chronic rejection as well as recent advances in metagenomics, we are no doubt in a place now when we can move forward in not only understanding the relationship between viruses and lung allograft rejection but also being able to work toward a solution.

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