



# Posttransplant Complications and Comorbidities

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### Abstract

Infectious complications cause significant acute morbidity and mortality after pediatric lung transplantation. With the lung graft in direct communication with the environment, it is susceptible to a variety of bacterial, fungal, and viral pathogens. Appreciation for pre-transplant risk factors in addition to perioperative and posttransplant exposures is necessary to anticipate, diagnose, and treat infections in this population. Further, epidemiologic associations between infection and chronic allograft dysfunction have been reported and suggest consequences of infectious events may have substantial impact.

### Keywords

Bacteria · Cytomegalovirus · Infectious complication · Nontubercular mycobacteria · Pediatric lung transplantation · Respiratory virus

## Bacterial Infections

### General Epidemiology

Bacteria account for about 50% of infections post lung transplant with pneumonia being most frequent. Other sites include nosocomial central line-associated bacteremia, urinary tract, and surgical site infections. The greatest risk is within the first year after transplantation, particularly in the first 3–6 months. Donor infection and recipient airway colonization are also risk factors (Speich and van der Bij 2001; Aguilar-Guisado et al. 2007; Parada et al. 2010; Burguete et al. 2013; Yun et al. 2015).

One of the largest studies of primarily adults found that 75% of infections occurred within the first year posttransplant and 42% occurred within the first 3 months. The majority, 48%, was bacterial (Parada et al. 2010; Burguete et al. 2013). Another study showed similar results but found that bacteremia, both primary and catheter associated, was the most common infection in the first month after transplant with pneumonia becoming most frequent after 2 months. Multidrug-resistant bacteria including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and carbapenem-resistant or extended-spectrum beta-lactamase producing gram-negative bacilli were involved in 66% of infections. Bacterial infections were significantly more common in those colonized with multidrug-resistant gram-negative bacilli than those who were not (Yun et al. 2015).

A pediatric study of 42 children and 49 lung transplants found that half of the infections were bacterial with 42% occurring within 3 months after transplant and 80% in the first year. The lung was the most common site (72%) and *Pseudomonas aeruginosa* was the most common organism. Bacterial infections were felt to contribute to pulmonary dysfunction (bronchiolitis obliterans) but were not the primary cause of death (Metras et al. 1999). Recent data from the registry of the International Society for Heart and Lung Transplantation reported that non-cytomegalovirus infection was the cause of death in 24% of lung transplant recipients in the first year after transplant (Benden et al. 2013).

One of the largest studies of pneumonia in 236 lung transplant recipients (Aguilar-Guisado et al. 2007) found that the most common etiology was bacterial in 83%. Gram-negative bacilli accounted for 60% with *Pseudomonas*

*aeruginosa* being the most frequent isolate in 25%, followed by *Acinetobacter baumannii* in 14%. *Staphylococcus aureus* was the etiology in 14%. The probability of 1-year survival was significantly higher in those recipients who did not have an episode of pneumonia (Aguilar-Guisado et al. 2007). Late-onset community-acquired pneumonia with *Streptococcus pneumoniae* also occurs (de Bruyn et al. 2004).

### Chronic Lung Allograft Dysfunction

Survival after lung transplantation is limited by the high incidence of chronic lung allograft dysfunction (CLAD) that has two forms: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). The role of infection in the development of CLAD has recently been reviewed (Martin-Gandul et al. 2015; Gregson 2016). While acute infection with community-acquired respiratory viruses is recognized as a risk, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are increasingly recognized as well. One study of lung transplant recipients with cystic fibrosis found that loss of colonization with *Pseudomonas* was protective against the development of BOS (Gottlieb et al. 2009). Two further studies found that infections due to gram-positive bacteria, primarily *Staphylococcus aureus*, increased the hazard risk for BOS (Gupta et al. 2009; Valentine et al. 2009). The underlying allograft inflammatory state in the setting of infection also appears to be important in determining the development of CLAD (Gregson 2016).

### Cystic Fibrosis-Related Pathogens

Cystic fibrosis (CF) is a common, underlying diagnosis in children who undergo lung transplantation. The registry of the International Society for Heart and Lung Transplantation reported that half of children <10 years of age and 70% of children aged 11 through 17 years had CF (Benden et al. 2013). CF-specific bacterial pathogens including multidrug-resistant (MDR) or

pan-resistant bacteria persist in the paranasal sinuses and upper airways and can be a cause of posttransplant pneumonia. *Pseudomonas aeruginosa* is most common, but other organisms include *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia cepacia* complex (Shoham and Shah 2013). In lung transplant recipients, there is increasing resistance in gram-negative bacilli including extended-spectrum beta-lactamase, AmpC beta-lactamase, and carbapenemase (Shoham and Shah 2013; van Duin and van Delden 2013).

*Pseudomonas aeruginosa* infection occurs in up to 80% of patients with CF and bronchiectatic lung disease, and pretransplant colonization is a significant risk factor for infection after transplant. MDR *P. aeruginosa* has a prevalence rate from 10% to 45% in patients with CF (Shoham and Shah 2013). Survival posttransplant in patients colonized with pan-resistant *P. aeruginosa* before transplant was similar to those with sensitive organisms at 1 year (88% vs. 96%) but lower at 3 years (63 vs. 91%) (Hadjiliadis et al. 2007; Shoham and Shah 2013). However, the 2006 update of the International Guidelines for the Selection of Lung Transplant Candidates stated that colonization with multidrug or pan-resistant *P. aeruginosa* was not a contraindication because it has not been shown to significantly affect short-term survival (Orens et al. 2006). A recent study in lung transplant recipients with CF reported that infection with pan-resistant *Achromobacter xylosoxidans* and *Stenotrophomonas maltophilia* also did not reduce survival after lung transplantation (Lobo et al. 2015).

*Burkholderia cepacia* complex (BCC) is comprised of several different species that colonize the respiratory tract in 15–22% of patients with CF. Most infections are caused by *B. cenocepacia* (genomovar III) and *B. multivorans* (genomovar II). Pretransplant colonization with *B. cenocepacia* has been associated with increased posttransplant mortality (relative risk 8.4) with one study reporting 1-year survival of 29% compared to 92% in those uninfected and is considered by many centers as a contraindication to transplant (Shoham and Shah 2013). Recipients colonized with *B. multivorans* did not have

decreased survival while *B. gladioli* had an increased mortality risk but not as high as *B. cenocepacia*. BCC has an 80% prevalence of multidrug resistance (Shoham and Shah 2013).

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly recognized as a significant bacterial pathogen post lung transplantation. A study of lung transplant recipients found that 18% had *S. aureus* infection in the first 90 days with 62% being methicillin sensitive (MSSA) and 35% being MRSA. The site of infection was pneumonia 48%, tracheobronchitis 26%, and bacteremia 12%. Colonization before transplant with MRSA was a risk factor for MRSA infection posttransplant but was not associated with increased mortality at 30 and 90 days post onset of infection (Shields et al. 2012). A second study had a calculated incidence rate of MRSA of 76 cases per 1000 transplant years with the median onset of 3 months posttransplant. The most common site was the lower respiratory tract and 31% of MRSA infections were associated with bacteremia. The direct mortality after MRSA infection was 17.6% (Manuel et al. 2009).

## Nontuberculous Mycobacteria

Nontuberculous Mycobacteria (NTM) are ubiquitous bacteria found in environmental sources including water, soil, plants, and animals. Exposure is felt to be from the environment but more recently patient-to-patient transmission has been proposed for *M. abscessus* complex (Bryant et al. 2013). Pretransplant infection is confined primarily to the lungs, with abnormal parenchyma such as cystic fibrosis or bronchiectasis being a risk factor. Posttransplant infection can involve asymptomatic colonization, invasive lung disease, skin and soft tissue infection, and central line-associated bacteremia (Griffith et al. 2007; Keating and Daly 2013; Smibert et al. 2016).

NTM isolation from respiratory cultures in lung transplant candidates is common particularly in those with cystic fibrosis. One study (Chalermkulrat et al. 2006) reported a 20% colonization rate with 45% of isolates being

*M. avium* complex (MAC) and 41% *M. abscessus*. Isolation after transplant is also common from 13 to 22% with MAC accounting for about 70%. Invasive disease after transplant is much less common, however, occurring in fewer than 5% of lung transplant recipients (Chalermkulrat et al. 2006; Chernenko et al. 2006; Huang et al. 2011; Knoll et al. 2012). Pretransplant colonization has been associated with an increased risk of posttransplant NTM infection as well as invasive disease but only for *M. abscessus* (Chalermkulrat et al. 2006). While NTM isolation and disease particularly with *M. abscessus* is associated with increased complications post lung transplant, it has not been associated with increased mortality and is not considered an absolute contraindication to transplantation (Chalermkulrat et al. 2006; Knoll et al. 2012; Qvist et al. 2013). Case reports of two adolescents with cystic fibrosis and pretransplant *M. abscessus* infection showed that when antibiotic therapy led to AFB stain negativity at the time of transplant, the outcome was favorable even in the face of positive cultures (Zaidi et al. 2009).

Diagnosis of NTM disease is based on criteria published by the American Thoracic Society/ Infectious Diseases Society of America that include clinical and microbiological criteria (Griffith et al. 2007). Compatible symptoms and radiological changes consistent with NTM infection with other etiologies excluded must be accompanied by: positive culture from at least two sputum samples, positive culture from one bronchial lavage or wash, or lung biopsy with consistent pathology and positive culture. Treatment depends on accurate identification and susceptibility testing of the organism. Guidelines are available and consultation with an infectious disease expert is recommended (Griffith et al. 2007; Keating and Daly 2013).

## Treatment and Perioperative Antibiotic Management

Obtaining cultures of respiratory, blood, urine, and wound samples with accurate identification and determination of drug sensitivity is critical in

the treatment of bacterial infection post lung transplant. Consultation with a transplant infectious diseases physician and pharmacist is recommended when designing antibiotic therapy for multi- and pan drug-resistant organisms to maximize effectiveness and minimize toxicity. Removal of sources of infection such as central venous lines and drainage of focal fluid collections should be undertaken when feasible.

There are no well-conducted studies that have addressed the optimal choice of agent, duration, and efficacy of antibiotic prophylaxis for lung transplantation. In the absence of positive cultures from the donor or recipient, prophylactic regimens of 48–72 h and no longer than 7 days are recommended (Bratzler et al. 2013). In recipients with CF, broad-spectrum antibiotics are administered at the time of transplant and are selected to cover the pretransplant bacterial pathogens and associated resistance patterns (Hirche et al. 2014). Most centers treat recipients with a history of *P. aeruginosa* infection with two-drug anti-pseudomonal therapy for 2–3 weeks postoperatively to reduce the risk of pneumonia and colonization of the allograft (Shoham and Shah 2013).

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## Fungal Infections

Invasive fungal infections occur frequently in about 8–16% of adult lung transplant recipients (Chong et al. 2015; Vazquez et al. 2015; Peghin et al. 2016; Doligalski et al. 2014) and result in up to 60% mortality (Alexander and Tapson 2001; Marino and Gallagher 2010). Contributing factors in lung transplant may include the high degree of immunosuppression, impairment of mucociliary clearance, allograft denervation, and communication of the organ with the environment. Invasive fungal infections can present as invasive pulmonary disease, tracheobronchitis, anastomotic infection, or disseminated disease as defined by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group of the National Institutes of Health (EORTC/MSG) and the International Society for Heart and Lung Transplantation (Ascioglu et al. 2002; Husain et al. 2011). A

large multicenter prospective studies of adult SOT recipients reported that the most common fungal organisms in lung recipients were *Aspergillus* (63%), *Candida* (23%), and other molds (10%) while zygomycosis, cryptococcosis, and endemic fungi were uncommon (Neofytos et al. 2010). More recent data suggest an emergence of non-*Aspergillus* mold infections (Neofytos et al. 2013; Chong et al. 2015).

## Pediatric-Specific Studies

Pediatric studies have reported an incidence of pulmonary fungal infection from 10.5 to 20%, with *Aspergillus* being the most common organism in two studies (Danziger-Isakov et al. 2008; Liu et al. 2009b). A single center study of 55 lung transplant recipients (Liu et al. 2009b) found a higher incidence of posttransplant fungal colonization (60%) compared to adult patients (30–40%). However, posttransplant colonization was not associated with invasive pulmonary disease, and pulmonary fungal infections were not associated with chronic allograft rejection or death (Liu et al. 2009b). A larger retrospective multicenter study with patients transplanted in 1988–2006 found tacrolimus-based immunosuppression, cytomegalovirus sero-mismatch, age over 15 years, and prior episode of rejection greater than A2 were risks for pulmonary fungal infection, but the study did not investigate colonization as a risk factor (Danziger-Isakov et al. 2008). Additionally, pulmonary fungal infection was independently associated with decreased 12-month survival. Mortality for proven and probable infection was 38 and 11%, respectively, similar to what has been reported for adults (Danziger-Isakov et al. 2008). Bronchial airway anastomotic complications occurred in 14% of 214 pediatric lung transplant recipients in a single center cohort, and this complication was associated with prior episodes of posttransplant fungal infection (Choong et al. 2006). These studies indicate that fungal infection in pediatrics significantly impact posttransplant morbidity and potentially mortality.

## Specific Organisms

### *Candida* Species

While *Candida* species isolated from respiratory secretions may represent normal commensal flora, invasive infections due to *Candida* species have been reported in pediatric lung transplant recipients. In addition to bronchial anastomotic infection, pleural infection, pulmonary fungal infections, and bloodstream infections appear in the pediatric literature (Danziger-Isakov et al. 2005; Danziger-Isakov et al. 2008; Liu et al. 2009b). Non-*albicans* species including *C. krusei*, *C. glabrata*, *C. parapsilosis*, and *C. dubliniensis* can all cause disease but may have differing antibiotic susceptibilities. Identification to the species level is important to facilitate optimum treatment especially as non-*albicans* species have been associated with increased mortality (Andes et al. 2016).

### *Aspergillus* Species

*Aspergillus* species cause posttransplant infections including tracheobronchitis with anastomosis infection, invasive pulmonary disease, and disseminated disease (Hosseini-Moghaddam and Husain 2010). Risk factors for invasive disease include ischemia at the anastomosis site, single lung transplant, hypogammaglobulinemia, placement of bronchial stent, CMV infection, and colonization (Robertson et al. 2009; Hosseini-Moghaddam and Husain 2010; Chong et al. 2015). As with *Candida* species, speciation of *Aspergillus* is important. While *A. fumigatus* causes the majority of disease, other species including *A. niger*, *A. terreus*, *A. flavus*, and *A. ustus* appear to be increasing in prevalence especially with the use of inhaled amphotericin as prophylaxis (Hosseini-Moghaddam and Husain 2010; Peghin et al. 2016).

Prompt diagnosis of invasive *Aspergillus* infection is imperative to improve outcome; however, newer diagnostics have not been specifically evaluated in pediatric lung transplantation. In pediatric cancer patients, the sensitivity and

specificity of galactomannan (GM), beta-D-glucan, and PCR-based assays were highly variable (Lehrnbecher et al. 2016). In adult lung transplant recipients, the serum GM assay has excellent specificity but poor sensitivity while bronchoalveolar lavage GM appears more promising for diagnosis with a sensitivity of 88–100% and specificity of 89–90% depending on the cutoff used for diagnosing invasive pulmonary aspergillosis (Husain et al. 2004; Pasqualotto et al. 2010; Luong et al. 2011). Further, a pan-*Aspergillus* real-time PCR assay also performed well with a sensitivity and specificity of 100% and 93%, respectively (Luong et al. 2011). As newer diagnostics emerge, their utility in pediatric lung transplantation will need assessment.

### Endemic Fungi

Histoplasmosis, blastomycosis, and coccidioidomycosis are endemic fungi with restricted geographical distribution. They are found in the environment as molds and the route of infection is inhalation of spores. Posttransplant disease with these organisms is rare in adults and has not been reported in the pediatric lung transplant literature to date (Neofytos et al. 2010; Assi et al. 2013).

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### Treatment

Treatment of invasive fungal infection in pediatric lung transplant recipients should include input from an infectious diseases specialist particularly regarding drug choice and dosage. Several national and international guidelines present treatment recommendations for invasive fungal infections (Pappas et al. 2016; Patterson et al. 2016). New antifungal agents have emerged in the past decade including second-generation azole medications and echinocandins (Lewis 2011). While these agents are improving outcomes related to fungal infections, clinicians must pay careful attention to therapeutic drug monitoring, interactions with immunosuppressive agents



(both calcineurin inhibitors and mTORs), and medication side effects to reduce potential complications.

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## Prophylaxis

Despite the significant morbidity and mortality associated with fungal infections following lung transplantation, there are not established guidelines for prophylaxis. In pediatrics, the impact of prophylaxis to prevent colonization and progression to infection is uncertain. Several small, non-randomized clinical trials in adult recipients have demonstrated efficacy ranging from 80 to 100% (Hosseini-Moghaddam and Husain 2010; Brizendine et al. 2011). Three main approaches have been used in lung transplant recipients: universal prophylaxis, targeted prophylaxis, and pre-emptive therapy. Universal prophylaxis is given to all recipients immediately post transplantation while targeted prophylaxis is given to patients with known risk factors (Neoh et al. 2011). Further, response to positive cultures on routine posttransplant bronchoscopy may prompt initiation of pre-emptive therapy, but the optimal response to positive BAL cultures is unclear (Avery 2011). While inhaled amphotericin has recently been linked to a decrease in post-transplant *Aspergillus*, amphotericin-resistant strains have emerged indicating that intervention is not benign (Peghin et al. 2016).

A recent world-wide survey of antifungal prophylaxis (Neoh et al. 2011) showed a highly variable approach with the majority (58%) using universal prophylaxis that primarily focused on preventing *Aspergillus* infections. A survey of centers performing pediatric lung transplantation (50% exclusively pediatric) revealed an equally variable approach. Universal prophylaxis is provided in 28% of centers, while 48% use targeted prophylaxis primarily to patients with cystic fibrosis or pretransplant fungal colonization (Mead et al. 2014). The focus of prophylaxis includes both *Aspergillus* and *Candida* species with most centers reporting the use of either voriconazole or inhaled amphotericin. Additionally, the duration of prophylaxis is widely distributed from 3 to

6 months to more than 12 months. The optimal approach for fungal prophylaxis in pediatric lung transplant recipients is undefined and there are sparse data for this population to guide recommendations.

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## Viral Infections

### Cytomegalovirus

The introduction of preventative antiviral regimens has improved the natural history of cytomegalovirus (CMV) after adult lung transplantation (Patel and Paya 1997; Zamora et al. 2004; Chmiel et al. 2008); however, CMV remains associated with increased morbidity and mortality after transplantation (Husni et al. 1998; Monforte et al. 2001; Ruttman et al. 2006; Chmiel et al. 2008). To improve the clarity of CMV reporting in the literature, specific definitions have been suggested and updated with diagnostic evolution (Humar and Michaels 2006; Husain et al. 2011; Ljungman et al. 2017). CMV *infection* refers to the presence of active replicating virus by any method without associated symptoms. CMV *syndrome* includes the presence of virus plus one or more associated symptoms including fever, fatigue/malaise, leukopenia, atypical lymphocytes, thrombocytopenia, or transaminitis. Those with evidence of tissue invasion are defined as end-organ CMV *disease*. Newer definitions take into account the availability of quantitative CMV PCR testing, but a specific viral load in BAL to determine CMV pneumonitis has not yet been established (Ljungman et al. 2017).

### Pediatric-Specific Studies

Cytomegalovirus (CMV) occurs in approximately 30% of pediatric lung transplant recipients (Danziger-Isakov et al. 2003b; Danziger-Isakov et al. 2009) and is associated with decreased survival in this population (Metras et al. 1999; Danziger-Isakov et al. 2003b; Danziger-Isakov et al. 2009). The largest multicenter study from the International Pediatric Lung Transplant Collaborative identified CMV donor seropositivity,

A2 rejection, and transplant in the earliest era of transplantation (1985–1993) as increased risks for CMV. Progression from CMV infection to disease occurred in 22% (Danziger-Isakov et al. 2009). Interestingly, CMV developed in 7% of CMV D–/R– recipients and induction therapy increased the risk for CMV in this group (Danziger-Isakov et al. 2009).

### Prevention Strategies

The optimal preventative regimen against CMV remains uncertain in pediatric lung transplant recipients. Controversies include choices around the use of universal prophylaxis, risk-based prophylaxis, or pre-emptive therapy and duration of prevention strategy (Danziger-Isakov et al. 2003a). As the merits and potential disadvantages in the limited population of pediatric transplant recipients are difficult to discern, extrapolation from the adult lung transplant population directs current practice (Kotton et al. 2013). Data from adult lung transplantation indicates that prolonged prophylaxis (9–12 months) with valganciclovir has both short- and long-term benefits preventing CMV events and decreasing risk for bronchiolitis obliterans syndrome (Finlen et al. 2011; Mitsani et al. 2010; Palmer et al. 2010). Pre-emptive therapy is NOT currently recommended for high-risk CMV D+/R– lung transplant recipients (Kotton et al. 2013; Razonable et al. 2013). Antiviral complications including nephrotoxicity, bone marrow suppression, gastrointestinal manifestations, and the development of viral resistance mutations must be considered when developing prevention strategies (Mitsani et al. 2010; Danziger-Isakov and Mark Baillie 2009). A study in pediatric transplantation showed safety and efficacy of an oral valganciclovir dosing algorithm, but no pediatric lung transplant recipients were enrolled (Vaudry et al. 2009).

Pediatric studies have assessed long-term intravenous ganciclovir and the adjunctive use of CMV hyperimmune globulin (CMVIG) (Spivey et al. 2007; Ranganathan et al. 2009). In a study of nine pediatric lung transplant recipients, 12 weeks of intravenous ganciclovir was feasible, safe, and effective prevention, although cases of catheter-

related bloodstream infections did occur when the catheters remained in place beyond the 12-week ganciclovir administration period (Spivey et al. 2007). CMVIG administration as part of a prevention regimen was associated with a threefold decrease in CMV infection but did not impact the incidence of CMV disease or other post-transplant morbidities and mortality in a multinational retrospective study (Ranganathan et al. 2009).

Each institution should assure that a consistent prevention strategy and adequate monitoring are in place (Kotton et al. 2013).

### Monitoring Schema

CMV monitoring is an integral part of any prevention strategy and potentially allows identification of CMV infection prior to the development of CMV symptoms or end-organ disease. Viral culture or a pp65 antigenemia assay has been replaced by more sensitive polymerase chain reaction (PCR) (Weinberg et al. 2000). As interassay and intercenter variability has been reported for PCR testing even in controlled research settings; utilization of a consistent assay is crucial so that results can be compared for an individual subject over time (Pang et al. 2009; Rychert et al. 2014). Based on multicenter retrospective evaluation of pediatric lung transplant recipients (Danziger-Isakov et al. 2009), the highest risk period for CMV infection occurs during the first 6 weeks after discontinuation of prophylaxis; thus, appropriate monitoring should occur during this high-risk period. Additionally, evaluation for CMV should occur with new onset symptoms suspicious for CMV infection including fever, fatigue, and lymphadenopathy even in CMV D–/R– patients. Increased frequency of CMV surveillance is suggested during periods of increased immunosuppression, but not limited to cytolytic therapy for refractory rejection, plasmapheresis, or prolonged lymphopenia (Kotton et al. 2013). Additional monitoring for CMV-specific immunity continues to develop (Westall et al. 2008; Kumar et al. 2009; Snyder et al. 2011; Manuel et al. 2013b) and may be employed in the future to personalize CMV prevention strategies.



## Treatment

Treatment of CMV infection and disease relies primarily on antiviral therapy and, if possible, decreasing immunosuppression. A multicenter randomized clinical trial of predominantly adult kidney transplant recipients reported non-inferiority of oral valganciclovir compared to intravenous ganciclovir for nonlife-threatening CMV disease; however, no pediatric patients were enrolled (Asberg et al. 2007). Current recommendations from the Transplant Society Consensus Statement include the use of intravenous ganciclovir for pediatric-aged patients as first-line therapy with acknowledgement that some experts would use oral valganciclovir for CMV infection (Kotton et al. 2013). Oral ganciclovir, acyclovir, famciclovir, or valacyclovir should not be used to treat CMV. Adjunctive therapy with immunoglobulins for severe pneumonitis (either intravenous immunoglobulin or CMVIG) can be considered (Kotton et al. 2013). Resistant CMV is rarely reported in pediatric transplant recipients (Martin et al. 2010; Kim et al. 2012), but concern may prompt consideration for alternative antiviral therapy including high-dose ganciclovir, foscarnet, and cidofovir (Kotton et al. 2013). Newer antiviral agents are under investigation as options for either prevention or treatment including brincidofovir, letermovir, and maribavir. Emerging data on the adoptive transfer of CMV-specific T-cells and the use of small-molecule drugs such as sirolimus, leflunomide, and artesunate may alter the future of treatment, but currently no data related to these interventions exist for pediatric lung transplant recipients.

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## Other Herpesviruses

### Human Herpes Virus 6 and 7

#### Epidemiology and Risk

Human herpes virus (HHV) 6 and 7 are ubiquitous, common viruses that cause mild infections in young children so frequently that by 5 years of age, practically all children have been infected. There are two types of HHV-6, and although the epidemiology of HHV-6A is not clearly defined,

HHV-6B is the most common cause of pediatric infections. Young infants, especially those under 2 years of age, are at risk for community-acquired or nosocomial HHV-6 infection after solid organ transplantation, while infection may also be acquired through the allograft or as a reactivation of a prior infection in older children. Overall, symptomatic or significant infection with HHV-6 after lung transplantation is uncommon, and the overall incidence in solid organ transplant recipients has been reported to be less than 1% (Razonable 2013). HHV-7 infection seems to be common, but its clinical manifestations are less well characterized.

#### Associated Clinical Syndromes

The most typical disease manifestation of HHV-6 infection is roseola infantum (also known as exanthem subitum or sixth disease), a classic febrile illness in young children where the resolution of a high fever of short (3–5 days) duration is followed by the appearance of a characteristic erythematous rash. While young children may present with roseola after lung transplantation, the most likely clinical manifestation in these patients may be a nonspecific febrile illness that may or may not be associated with an erythematous diffuse rash, hepatitis, pneumonia, encephalitis, and leukopenia. HHV-7 coinfection with HHV-6 is reported frequently, and HHV-7 infection alone appears to be asymptomatic or associated with milder clinical manifestations.

#### Diagnosis

HHV-6/7 infection is confirmed by detection of the virus in otherwise sterile samples (blood, CSF, tissue) by nucleic acid identification (PCR) or consistent histopathologic changes. Quantification of viral load might be helpful to assess the progression of viremia. However, there is no known clinically relevant viral load threshold to predict progression or severity of disease. Immunohistochemical staining is available in some laboratories and might be helpful to determine the presence of infection in specific organs. However, HHV-6/7 latency in human cells may result in the identification of these viruses in samples without correlation with infection.

## Treatment

The first step in the treatment of suspected or confirmed HHV-6/7 infection in immunocompromised solid organ transplant patients is decreasing immunosuppression to allow the host's immune system to control the virus. There are no specific antivirals recommended for treatment of HHV-6/7. However, antiviral activity has been described with ganciclovir and its oral form valganciclovir, foscarnet, and cidofovir. Consultation with an infectious diseases expert for the antiviral management of these infections is recommended.

## Prevention

There are no vaccines available for the prevention of HHV-6/7 infections. Suppression may be observed with antivirals used after transplantation for CMV, such as ganciclovir and valganciclovir; however, specific antiviral prophylaxis for HHV-6/7 is not recommended. Hand hygiene is the most effective method to prevent transmission.

## Human Herpes Virus (HHV)-8

HHV-8, known as the cause of Kaposi's sarcoma, is an oncogenic virus associated with a variety of malignancies (primary effusion lymphoma and Castleman disease) and other disease syndromes such as febrile illness, bone marrow suppression, hemophagocytosis, and multiorgan failure in highly immunocompromised patients, including transplant recipients (Razonable 2013). However, the incidence of HHV-8 infection and disease in children is very rare in the United States. Residence in HHV-8 endemic areas is a risk factor, as is receipt of an organ from a donor coming from an endemic area. HHV-8 serology is not routinely obtained in solid organ recipients or donors. As with other human herpesviruses, latency can be established. Decreasing immunosuppression is recommended, while treatment of associated malignant disease may also include surgical debulking, cytotoxic chemotherapies, and

antivirals (for which the efficacy has not been established).

## Adenovirus

### Epidemiology and Risk

Adenoviruses commonly cause self-limited respiratory and gastrointestinal infections in immunocompetent children, but infections can be severe in lung and other solid organ transplant recipients. Adenovirus infections are more common in pediatric than in adult transplant recipients. Primary adenovirus infections may be acquired after transplantation in young children, while reactivation of latent infection or infection from the transplanted organ may occur in older children and adolescents (Florescu et al. 2013). Lung transplant patients are at particularly high risk for complicated respiratory tract infection though inhalation of infected aerosol particles or direct contact transmission from infected individuals. Gastrointestinal infection may occur via fecal–oral transmission. Most infections occur in the first few months after transplantation, or during periods of enhanced immunosuppression. Nosocomial and community exposures may be the source of infection.

### Associated Clinical Syndromes

Clinical manifestations of adenovirus depend on the organ affected. Adenovirus infection can result in severe respiratory disease in lung transplant recipients, including rapidly progressive, necrotizing and potentially fatal pneumonia, as well as development of chronic lung disease with fibrosis and bronchiectasis (Liu et al. 2010). Adenovirus may also cause gastroenteritis, hepatitis, meningoencephalitis, and disseminated disease with multiorgan involvement (Florescu et al. 2013). Asymptomatic infection, defined as the identification of adenovirus in clinical specimens by nucleic acid detection (PCR) or culture, has been reported more commonly in adults. In children, persistent and rising viremia should be considered a concerning sign of end organ infection and risk for disseminated disease. Graft failure

may result from acute adenovirus infection after lung transplantation (Doan et al. 2007).

### Diagnosis

The diagnosis of adenovirus infection requires the presence of consistent clinical symptoms and the identification of adenovirus by viral culture, molecular methods, direct antigen detection, or characteristic histopathology. Most adenovirus serotypes (with the exception of adenovirus 40 and 41 which cause gastroenteritis) can be isolated in cell culture; however, diagnosis by PCR is more commonly used and available. The sensitivity of rapid antigen detection tests is variable and not reliable in immunocompromised hosts. While adenovirus can be identified in respiratory secretions, stool, and urine, these are places where prolonged shedding after infection may occur. Therefore, the diagnosis of acute infection is more reliable when viral identification is associated with consistent clinical symptoms, or when adenovirus is found in otherwise sterile specimens such as blood and cerebrospinal fluid or in tissues. Rising viremia and detection of virus in two or more sites is considered consistent with invasive adenovirus disease. A viral load cutoff or threshold does not exist to predict the progression of disease or its outcome. However, higher and/or persistent viral loads are concerning for progressive or disseminated disease and typically indicate the need to intervene.

### Treatment

Decreasing the level of immunosuppression to allow for the host's immune response to handle the virus is the most important treatment strategy to manage adenovirus infections in young solid organ transplant patients. In certain cases, antiviral treatment may be useful, if instituted with the guidance and follow-up of a pediatric infectious diseases specialist. While there are no approved adenovirus-specific antivirals, some agents such as cidofovir have activity against adenovirus and have been used empirically for treatment. However, use of this agent is limited by its propensity to cause nephrotoxicity and bone marrow suppression. Close follow up

and monitoring for these side effects is recommended. The standard dose of cidofovir in children is 5 mg/Kg once weekly. However, more frequent, lower dosage (1 mg/Kg three times per week) and pre- and post-dose hydration have been used in an attempt to reduce the risk of renal toxicity (Doan et al. 2007). Treatment is usually continued until resolution of viremia and/or symptoms, with close monitoring for side effects. Other antivirals have been evaluated for treatment of adenovirus, including a lipid conjugate of cidofovir (CMX001, Chimerix Inc.), which is administered orally and has a lower risk for nephrotoxicity; however, its use remains experimental at this time. Lung transplant patients with severe infection may have hypogammaglobulinemia, and in these cases, administration of intravenous immunoglobulin (IVIG) for replacement has been used, although its benefit has not been proven (Mawhorter and Yamani 2008). An effective novel treatment strategy has been developed with the use of antigen-specific cytotoxic T lymphocytes (CTL) directed against adenovirus in hematopoietic stem cell transplant recipients; CTLs have not been evaluated in lung or other pediatric solid organ transplant recipients (Leen et al. 2009).

### Prevention

Prolonged shedding after resolution of the acute infection may occur; therefore, strict hand hygiene and disease prevention strategies need to be implemented. There are no licensed vaccines for the prevention of adenoviruses.

## Respiratory Viral Infections

### Epidemiology and Risk

Pediatric solid organ transplant recipients and particularly lung transplant recipients are at increased risk of medical complications and mortality when acquiring common respiratory viral infections (Manuel et al. 2013a). Common respiratory viruses that circulate with well-described

seasonality in the United States include influenza virus, respiratory syncytial virus (RSV), human metapneumovirus, human rhinovirus, parainfluenza viruses, coronaviruses, and other respiratory viruses that are being more frequently described, such as bocaviruses. Lung transplant recipients are at risk for community and nosocomial exposures during the typical time of circulation of these viruses. Infection with respiratory viruses may also increase the risk for secondary bacterial pneumonia and other bacterial or fungal infections, particularly in the first few months after transplant (Liu et al. 2009a). After an acute lower respiratory virus infection, the risk for graft rejection or chronic allograft dysfunction may increase as shown in adult lung transplant recipients; however, this is controversial and has not been shown in pediatric lung transplant recipients to date (Liu et al. 2010; Liu et al. 2009a; Vu et al. 2011).

### Clinical Manifestations

Although upper respiratory infections may present similarly in solid organ transplant recipients as in immunocompetent hosts, progression to lower respiratory tract disease manifestations with tachypnea, cough, abnormal breath sounds, hypoxemia, and respiratory failure is a concern in lung transplant recipients. Clinical deterioration due to respiratory viruses is more frequently reported in the period of highest immune suppression shortly after transplant.

### Diagnosis

Prompt diagnosis with viral detection using nucleic acid amplification methods (PCR) is recommended in immunocompromised hosts. Viral cultures could be obtained but are not as useful given that results are delayed in comparison with PCR. PCR platforms that test for multiple viruses at the same time are most helpful in lung transplant recipients. Rapid antigen detection tests are no longer recommended for influenza due to their variable sensitivity; but they could still be useful for the diagnosis of RSV. Respiratory secretions including nasal wash or swabs, nasopharyngeal aspirates, and tracheal or bronchoalveolar lavage can be used. These viruses do not tend to be associated with viremia.

### Treatment

Supportive measures must be instituted promptly in lung transplant recipients with progression to lower respiratory tract disease. The need for invasive mechanical ventilation or other higher level of supporting measures such as extracorporeal membrane oxygenation (ECMO) is not uncommon in patients with severe disease. Specific antiviral treatment is available for influenza A and B infection. Immediate initiation of neuraminidase inhibitor (oseltamivir and zanamivir) therapy in lung transplant patients with fever and/or other respiratory symptoms during the period of influenza circulation may decrease the risk of complications and death associated with influenza. Although influenza antivirals are usually preferred within 48 h of the onset of clinical symptoms, lung and other solid organ transplant patients have improved outcomes even with later treatment initiation (Kumar et al. 2010). In some cases, a more prolonged duration of antiviral therapy has been used given these patient's immune-suppressed status and prolonged viral shedding. Intravenous peramivir (also a neuraminidase inhibitor) is now licensed for adults, with clinical studies underway in children and adolescents. Intravenous administration might be preferred in patients who have inadequate enteral absorption and who are severely ill with influenza.

Ribavirin, an aerosolized antiviral with *in vitro* activity against RSV, parainfluenza, human metapneumovirus, and other viruses, is FDA approved but not routinely recommended for treatment of these infections due to lack of definitive efficacy. However, ribavirin has been used early in the course of RSV and other respiratory virus infections, as well as in more severe cases of respiratory disease, in lung transplant patients due to its antiviral effects. No randomized controlled trials have been performed although data from adult lung transplantation has indicated a potential response to aerosolized, intravenous, and oral ribavirin (Glanville et al. 2005; Pelaez et al. 2009; Li et al. 2012). An inhaled small-interfering RNA that targets RNA (ALN-RSV-001) has also been investigated as a therapy for RSV in adult

lung transplantation showing potential reduction in bronchiolitis obliterans syndrome after RSV infection (Zamora et al. 2011; Gottlieb et al. 2016). Utilization of an RSV antibody preparation (monoclonal antibody) along with antiviral treatment in severe cases has been reported to reduce RSV-associated mortality in some cases (Chavez-Bueno et al. 2007).

Similar to the management of other viral infections, decreasing immune suppression is advisable when respiratory viral infections are identified.

### Prevention

Influenza immunization prior to and/or after transplantation for the recipient and all close contacts and family members is recommended to prevent infection and severe disease. Inactivated influenza vaccine should be administered ideally prior to the start of the season, to ensure optimal protection. However, after transplant, and in some patients prior to transplant depending on their underlying diagnosis or need for chronic steroid or other medication use, the immune responses to vaccination might be suboptimal in lung and other solid organ transplant recipients. Therefore, vaccination of close contacts and avoidance of contact with sick individuals become important measures for prevention of infection (Avery et al. 2013). Prophylactic antivirals may also help decrease the risk of infection and complications in exposed unvaccinated or unprotected transplant recipients. There are no other vaccines available for the prevention of respiratory infection in most pediatric lung transplant recipients. However, palivizumab, a monoclonal antibody against RSV, can be used during the RSV season in young children less than 2 years of age who are lung transplant recipients, immunosuppressed, or who have underlying chronic lung or hemodynamically unstable heart disease (American Academy of Pediatrics Committee on Infectious Diseases and American Academy of Pediatrics Bronchiolitis Guidelines Committee 2014).

All lung and solid organ transplant patients with suspected or known respiratory viral infections need to be isolated from other patients using standard contact and droplet precautions.

### Conclusion

Posttransplant, infections remain a significant factor causing both morbidity and mortality in pediatric lung transplant recipients. Pathogens are diverse including bacteria, fungi, and viruses with timing of events dependent on time from transplant. All events can have both immediate and long-term consequences in this at-risk population. Prevention, identification, and early intervention for infectious events can improve outcomes after pediatric lung transplantation.

### Cross-References

- ▶ [Best Practice for Long-Term Central Venous Access and Management of Complications](#)
- ▶ [Intensive Care of the Child After Kidney Transplantation](#)
- ▶ [Intensive Care of the Child After Liver Transplantation](#)
- ▶ [Pretransplant Considerations](#)

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