Pulmonary Infections in Lung Transplant Recipients

Contributors:
Bradford C. Bemiss, MD
Fellow, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO

Chad A. Witt, MD
Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO

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INTRODUCTION

A total of 3640 lung transplant procedures were performed in 2011, as reported to the International Society for Heart and Lung Transplantation (ISHLT), an all-time high.¹ The most common indications for lung transplantation include non-alpha-1-antitrypsin deficiency chronic obstructive pulmonary disease (COPD) (34%), interstitial lung disease (24%), cystic fibrosis (17%), and COPD associated with alpha-1-antitrypsin deficiency (6%). The average survival for patients who have undergone lung transplantation is 5.6 years. During the first year after transplant, the most common cause of death is non-cytomegalovirus infection. After 1 year, chronic rejection (in the form of bronchiolitis obliterans syndrome [BOS] or the more recently termed and broader concept of chronic lung allograft dysfunction [CLAD]) and non-CMV infection contribute to the majority of lung recipient mortality.¹ The ISHLT notes that the probable risk factors for BOS include acute cellular rejection, lymphocytic bronchitis/bronchiolitis, medication noncompliance, and cytomegalovirus (CMV) pneumonitis. Potential risk factors include bacterial, fungal and non-CMV infection, organizing pneumonia, older donor age, more prolonged ischemic time, and donor antigen-specific reactivity.² Specific associations have been made with Pseudomonas, Aspergillus, and community-acquired respiratory viruses (eg, respiratory syncytial virus, parainfluenza viruses), among many other infectious organisms.³–⁶

Lung transplant recipients are particularly susceptible to infection due to their immunosuppressed state. In fact, lung recipients are generally more immunosuppressed than recipients of other solid organ transplants. Typically, lung recipients remain on lifelong 3-drug immunosuppression. The most frequently utilized immunosuppression regimens include a calcineurin inhibitor (tacrolimus or cyclosporine), a cell-cycle inhibitor (mycophenolate mofetil or azathioprine), and corticosteroids. In addition to immunosuppression, lung transplant recipients have other unique risk factors making them more susceptible to infection, including preoperative colonization by microorganisms, transmission of infection from donor lungs, blunted cough due to denervation of the transplant lungs, impaired mucociliary clearance, poor lymphatic drainage, ischemic large airways postoperatively, and constant exposure to the external environment.⁶–¹⁰

With knowledge of the risk posed by infection on the lung transplant population and through use of
prophylaxis, early recognition, and treatment, it is possible to reduce the risk for the major causes of death among these patients. This article reviews the major infectious threats facing lung transplant recipients and discusses their major symptoms and treatment as well as occasions where prophylaxis may be employed.

**PREOPERATIVE PERIOD**

Prior to surgery, both the donor and recipient are susceptible to colonization and infection. Donor lungs frequently come from patients who have been declared brain dead after head injury. This population is susceptible to aspiration and ventilator-associated pneumonia. Cultures are routinely taken from donor lungs by either bronchoscopy or tracheal aspirate. Ruiz et al reported that of 197 donors, 65 (32%) had graft colonization. Bacteria were isolated in 90.5% of donors ventilated for more than 48 hours. Gram-positive cocci were the most commonly isolated type of bacteria. Transmission of the donor organism to the recipient occurred in 15 of 210 (7.1%) transplants. Two of the recipients died secondary to the transmitted organism (Aspergillus fumigatus and methicillin-resistant *Staphylococcus aureus* [MRSA]). However, positive donor Gram stain was not predictive of worsened outcome.

Pre-transplant infections of the recipient also can affect graft function and survival. Patients with suppurative lung diseases, such as cystic fibrosis (CF)—related bronchiectasis, are often colonized with multidrug-resistant bacteria prior to transplantation. In a single-center retrospective study, CF patients were compared with non-CF patients after transplant. The CF patients had a higher rate of respiratory infection when data was normalized to events per 100 patient-days. These events mostly comprised increased numbers of *Pseudomonas aeruginosa* infections. This difference was present both early (<100 days after transplant) and at all other time intervals examined (101–365 days, >365 days).

Of specific interest and relevance to patients with CF are the *Burkholderia* organisms. There are more than 60 species of *Burkholderia*, but many of these do not cause disease in humans. Most relevant to this discussion is *Burkholderia cepacia* complex and *Burkholderia gladioli*. These bacteria were formerly considered part of the *Pseudomonas* genus, but with further taxonomic studies are now considered separate. Similar to *Pseudomonas*, *Burkholderia* can produce severe resistant respiratory infection in patients with CF. There are 17 different species within the *B. cepacia* complex, formerly classified as genomovars. Two members of the *B. cepacia* complex, *B. cenocepacia* (former genomovar III) and *B. multivorans* (former genomovar II), make up approximately 70% of *Burkholderia* species isolated from CF patients. Furthermore, approximately 15% of the remaining species are *B. gladioli*. Early reports from Toronto revealed a high rate of mortality (47%) among CF patients colonized with *B. cepacia* prior to transplant. A large retrospective study by Murray et al evaluated 88 CF patients registered with the Scientific Registry of Transplant Recipients with *Burkholderia* infection who underwent transplant. Patients with *B. cenocepacia* (hazard ratio [HR], 2.52) and *B. gladioli* (HR, 2.23) had higher mortality than noninfected post-transplant patients. Patients with *B. multivorans* had a similar survival rate as lung transplant recipients with CF not colonized with *Burkholderia* species. In another study, having *B. cenocepacia* susceptible to antibiotics was not predictive of better outcome. Therefore, *Burkholderia* colonization, especially *B. cenocepacia* and *B. gladioli*, is generally considered a relative contraindication to lung transplantation.
At the time of lung transplantation, patients are in a very vulnerable, immunosuppressed state. There are no randomized controlled trials in lung transplant patients evaluating the role of perioperative antibiotics. However, within the thoracic surgery literature, data suggest that some perioperative antibiotic prophylaxis to prevent mediastinitis, empyema, and pneumonia is warranted. As described above, patients are often already colonized with known bacteria. As the donor lungs are transplanted sequentially into the recipient, the proximal portions of the mainstem bronchi and the trachea are retained. In addition, resident colonizing bacteria are commonly present in the recipient’s upper airways and sinus cavities. Therefore, knowledge of the native bacteria in the recipient and the most common post-transplant infections should guide perioperative antibiotic prophylaxis. Of 49 consecutive lung transplant patients reported by Campos et al, *P. aeruginosa* (33.3%) and *Staphylococcus aureus* (26.9%) were the most common bacterial infections identified in the perioperative period. Therefore, in patients without known colonization, it is reasonable to use prophylaxis with an antipseudomonal beta lactam and an antibiotic to cover MRSA, such as vancomycin, given the prevalence of MRSA in the general population. Broad-spectrum antibiotics are generally given for 7 to 10 days, or extended longer if indicated clinically (Table). Because preoperative colonization with *Aspergillus* species and non-
tuberculous mycobacteria (NTM) can also cause significant disease post transplant, when present these organisms should also be accounted for in perioperative prophylaxis regimens and treated prior to listing for lung transplant, if necessary.\textsuperscript{14,22}

**POSTOPERATIVE PERIOD**

**BACTERIAL INFECTIONS**

Bacterial infection is common in the immediate postoperative period in lung transplant recipients. In the RESITRA cohort from Spain, after a median follow-up of 180 days, 26\% of patients developed pneumonia, with the majority (40 of 85 episodes) occurring within the first month postoperatively.\textsuperscript{23} Bacteria (82.7\%) were the causative organisms in the majority of the episodes. Gram-negative bacilli made up nearly 60\%, with \textit{P. aeruginosa} accounting for approximately one-quarter of the total episodes. Other bacteria identified in this cohort included \textit{S. aureus}, \textit{Acinetobacter baumannii}, \textit{Escherichia coli}, \textit{Klebsiella pneumoniae}, \textit{Stenotrophomonas maltophilia}, \textit{Pseudomonas putida}, \textit{Serratia marcescens}, and \textit{B. cepacia}.\textsuperscript{23}

Other bacterial causes of pneumonia have also been described, including \textit{Chlamydia pneumoniae} and \textit{Nocardia} species.\textsuperscript{24,25} At the University of Pittsburgh, a retrospective review of \textit{Nocardia} infection, which occurred in 2.1\% of their lung transplant patients, revealed that all cases occurred more than 5 months out from lung transplant. Of those cases, 50\% were preceded by biopsy-proven rejection during which immunosuppression was increased. \textit{N. nova}, \textit{N. farcinica}, \textit{N. asteroids} complex, and \textit{N. brasiliensis} were identified. The most common presentation among those with \textit{Nocardia} infection was lobar pneumonia (in 4 of 10 patients).

Following transplantation, it can be difficult to distinguish infectious from noninfectious causes of dyspnea, declining lung function, and abnormal chest radiography. Therefore, when clinically appropriate, bronchoscopy with bronchoalveolar lavage (BAL) with or without transbronchial biopsies should be performed to evaluate for a specific causative organism or noninfectious causes of symptoms. Possible noninfectious causes include airway complications, acute cellular or humoral rejection, or obliterative bronchiolitis. In patients with clinical concern for pneumonia, treatment with antibiotics should cover the most common organisms encountered after transplant mentioned above, including \textit{P. aeruginosa} and MRSA. Treatment is generally continued for at least 2 weeks and the spectrum of antibiotics narrowed as appropriate based on culture results.

Bacteria are also responsible for post-transplant infections other than pneumonia.\textsuperscript{26–28} For example, in a single center retrospective evaluation of \textit{S. aureus} infection in the first 90 days after transplant, pneumonia and tracheobronchitis were the most common infections. However, \textit{S. aureus} was also responsible for bacteremia as well as intrathoracic and skin and soft tissue infections. Of all the positive cultures, 55\% were methicillin-sensitive \textit{S. aureus} (MSSA) and 45\% were MRSA.\textsuperscript{29} In a retrospective case series from Pittsburgh, Nunley et al observed 14 cases of empyema in 392 transplant patients, or 3.6\% of the total transplants.\textsuperscript{26} The most prominent organisms were coagulase-negative \textit{Staphylococcus} species; however, gram-negative bacilli accounted for 3 of the episodes.

Aside from early infection after transplant, bacteria can also play a role in the development of BOS as a late post-transplant complication. Botha et al reported a series of lung transplant recipients who had \textit{P. aeruginosa} colonization of the airways after transplant.\textsuperscript{30} Of 64 patients in the series, 44 had persistent \textit{Pseudomonas} from pre-transplant cul-
tures and 20 were colonized de novo. Eight of those 20 patients went on to develop BOS, significantly more than those who did not have *Pseudomonas* in their post-transplant cultures. In a separate prospective study, Gottlieb et al reported that absence of *Pseudomonas* from the allograft was predictive of freedom from BOS. The development of BOS after *Pseudomonas* colonization may at least in part result from persistent neutrophilic airway inflammation and subsequent airway remodeling.

**Fungal Infections**

Fungal infection develops in approximately 14% of lung transplant recipients. The majority of cases are caused by *Aspergillus* and *Candida*. Among *Aspergillus* species, *A. fumigatus*, *A. flavus*, *A. niger*, and *A. versicolor* infections have all been described; however, *A. fumigatus* (59%–75%) is the most common. Colonization with *Aspergillus* species occurs in 30% of patients within the first 6 months following lung transplant. *Candida albicans* is the most common *Candida* species isolated, although a shift toward non-albicans species has been observed recently.

*Aspergillus*

The most severe fungal infections in the lung transplant population are invasive pulmonary aspergillosis and disseminated aspergillosis; however, *Aspergillus* is also known to cause tracheobronchitis and anastomotic site infections. Tracheobronchitis is the most common manifestation of *Aspergillus* infection, accounting for 37% of infections, and typically occurs within the first 3 months after transplantation. Clinical manifestations of tracheobronchitis include ulcers around the anastomosis, necrotic tissue around the site of infection, and pseudomembrane formation without involvement of the pulmonary parenchyma. Both detection of asymptomatic *Aspergillus* colonization and tracheobronchitis put patients at risk for progression to invasive pulmonary aspergillosis. In one study, once *A. fumigatus* was colonized in the airway, patients were 11 times more likely to develop invasive disease.

In addition to causing infection, *Aspergillus* colonization has been associated with the development of BOS. In a retrospective cohort study at UCLA, Weigt et al used a univariate regression model to identify 2 risk factors for development of BOS in their patient population, acute cellular rejection and colonization with *Aspergillus* species. Given these findings, a multivariate Cox proportional hazards model was constructed, which again showed *Aspergillus* colonization to be a risk factor for the development of BOS (HR, 1.81).

**Presentation.** Invasive pulmonary aspergillosis, which accounts for 32% of *Aspergillus* infections, classically presents with fever, pleuritic chest pain, and hemoptysis. Invasive pulmonary aspergillosis occurs later after transplant than tracheobronchitis and carries a more significant mortality risk at upwards of 80%. *A. fumigatus* has been reported to cause up to 100% of invasive pulmonary aspergillosis. While neutropenic patients have been described to demonstrate an early “halo sign” on chest radiograph (a nodular infiltrate with surrounding area of ground glass), in lung transplant recipients this finding is unusual. The only known risk factors for development of invasive pulmonary aspergillosis are previous colonization with *Aspergillus* species and airway ischemia.

**Diagnosis.** Diagnosis of invasive pulmonary aspergillosis is more difficult in lung transplant recipients as well. In one case series, no fungus was identified in the BAL fluid of patients who had active invasive disease. Newer tests such as the ELISA for galactomannan, a polysaccharide on the *Aspergillus* cell wall, do not perform as well in lung trans-
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plant patients as they do in an immunocompetent patient population. Husain et al found that the serum galactomannan assay had only approximately 30% sensitivity when using an optic density of 0.5 or greater.\(^{39}\) None of the cases of tracheobronchitis alone had a positive assay. The sensitivity improved to 60% when assessing galactomannan in a BAL sample from lung transplant recipients with invasive aspergillosis.\(^{40}\) However, false-positive tests do occur, especially in the setting of piperacillin/tazobactam usage.

**Treatment.** Treatment of invasive pulmonary aspergillosis has evolved over the past 2 decades as new therapeutic agents have become available. Previously, amphotericin B was the drug of choice for invasive aspergillosis. However, this drug was limited by its adverse effects, most importantly nephrotoxicity and infusion reactions. In a 2002 study by Herbrecht et al,\(^{41}\) voriconazole was compared with amphotericin B in a population that was mostly made up of stem-cell transplant recipients and patients with acute leukemia, although 10% of participants were solid organ transplant recipients. Patients treated with voriconazole had a lower mortality rate (29% vs 42%) and fewer adverse reactions compared to those taking amphotericin B. Notably, voriconazole, like the other azole antifungal agents, is a potent inhibitor of cytochrome P450 and requires close monitoring of calcineurin inhibitor levels when it is used. Typically, doses of tacrolimus or cyclosporine need to be significantly reduced to avoid toxicity. Voriconazole is favored over itraconazole given its more predictable bioavailability.\(^{42}\)

Posaconazole is a newer agent that has fewer adverse effects compared with voriconazole—specifically, it causes less photosensitivity. It has been investigated as salvage therapy in solid organ transplant recipients when disease was refractory to, or the patient could not tolerate, standard antifungal regimens. A complete or partial response was observed in 57% of patients.\(^{43}\) Unfortunately, posaconazole remains unstudied as a first-line treatment of invasive aspergillosis.

Other studies have looked at echinocandins (eg, anidulafungin, caspofungin, and micafungin) as possible first-line agents in the treatment of invasive aspergillosis. A study by Groetzner and colleagues showed promising results, with 10 of 11 patients having a favorable outcome when using caspofungin as a first-line agent, but given the low number of definite invasive pulmonary aspergillosis cases in this study, these results need to be viewed with skepticism.\(^{44}\)

**Prophylaxis.** Given the prevalence of *Aspergillus* colonization of the airways, the possibility of progression to invasive pulmonary aspergillosis, and the high mortality associated with invasive disease, strategies to prevent disease and progression have been evaluated. Universal prophylaxis and targeted prophylaxis (use in patients colonized with *Aspergillus* prior to transplant or who become colonized de novo after transplant) are examples of strategies used at the majority of lung transplant centers evaluated in a large multicenter survey. The majority of centers used universal prophylaxis (69%) versus targeted prophylaxis (31%). The most common agent used in prophylaxis was aerosolized amphotericin B deoxycholate with or without itraconazole for 1 to 3 months.\(^{45}\) However, this study was performed in 2002–2003, prior to widespread use of voriconazole. Since then, Husain et al has compared universal voriconazole prophylaxis for 4 months to targeted prophylaxis in which fluconazole was given until *Aspergillus* was detected and then was switched to itraconazole with or without amphotericin B deoxycholate nebulized for a minimum of 3 months.\(^{46}\) The incidence of invasive aspergillosis at 1 year with uni-
versal voriconazole versus targeted itraconazole ± nebulized amphotericin B was 1.5% and 23%, respectively. However, 73% of the voriconazole group had transaminase levels elevated to more than 3 times normal, which returned to normal after withdrawal of the drug. As such, there has been a switch to voriconazole as the major agent used in prophylaxis for invasive aspergillosis. While these studies have all shown reduced incidence of invasive aspergillosis, they have not demonstrated a reduction in Aspergillus colonization.

**Candida**

*Candida* species are commonly isolated from the respiratory tract on BAL or sputum culture, but rarely cause invasive pulmonary infection. This is likely related to the fact that most lung recipients receive prophylaxis for mucocutaneous candidiasis when they are most immunosuppressed during the first month after transplant. *Candida* species are, however, the third most common cause of bloodstream infections in lung transplant recipients. Both *C. albicans* and *C. glabrata* have been isolated from the bloodstream in post-transplant patients, and have been reported to cause 18% of all bloodstream infections.

While fluconazole and other azoles generally have good coverage against *C. albicans*, they do not provide reliable coverage against nonalbicans species. Therefore, amphotericin B was previously considered the treatment of choice for candidemia and invasive candidiasis. However, multiple studies have shown that echinocandins are as effective as and cause fewer side effects than amphotericin B. Given these findings, echinocandins should be considered a first-line therapy for *Candida* infection until speciation into albicans versus nonalbicans can be performed. Amphotericin B should be reserved for refractory cases.

**Pneumocystis**

*Pneumocystis jiroveci* is a fungus that routinely infects immunosuppressed patients without appropriate prophylaxis. It is most commonly associated with HIV and AIDS. Prior to the use of routine prophylaxis, up to 70% of lung transplant recipients developed *P. jiroveci* pneumonia (PJP). An early study from the Mayo Clinic involving non-HIV patients identified patients on as little as 30 mg of prednisone for 12 weeks to be at increased risk for developing PJP. Approximately 25% of the patients in this study had solid organ transplants.

*P. jiroveci* typically causes pneumonia between 4 to 6 months after transplant. Lung transplant recipients are similar to AIDS patients in that they can have an insidious presentation. In one study by Gryzan et al., only 35% of patients identified as having PJP were asymptomatic. A typical presentation for PJP includes fever, dyspnea, and diffuse pulmonary infiltrates (Figure 1 and Figure 2).

In a meta-analysis, a 91% reduction in the number of patients with PJP was seen when prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) was started; this study identified a number needed to treat of 15. This corresponded to a significant reduction in mortality as well (relative risk [RR], 0.17). In the case of sulfa allergy or intolerance, atovaquone, nebulized pentamidine, and dapsone have also been shown to be effective. Desensitization to TMP/SMX can also be considered. The drug of choice for treatment of PJP is high-dose TMP/SMX in addition to corticosteroids if an elevated alveolar-arterial gradient is present.

**Cryptococcus**

*Cryptococcus* species are the third most common invasive fungal infections seen in solid organ transplant recipients, accounting for between 0.3% and 5% of all infections. The most common spe-
cies encountered are *Cryptococcus neoformans* and *Cryptococcus grubii*. It is unclear whether infection after transplant is reactivation of previous cryptococcal infection or de novo infection. However, in one study, treatment with 2 doses of antithymocyte globulin or alemtuzumab predisposed liver and kidney transplant recipients to a higher rate of cryptococcal infection, suggesting reactivation does occur. Infection can be either limited to the lung or disseminated. Limited disease typically causes a lobar pneumonia, while disseminated infection can involve the central nervous system (CNS), skin, soft tissue, joints, or bones. The overall mortality rate for invasive cryptococcal infection has been reported to be 42%. Diagnosis of *Cryptococcus* infection can be made with a serum cryptococcal antigen assay. A lumbar puncture should be obtained to rule out CNS disease because treatment of disseminated disease and localized pulmonary disease is vastly different. For disseminated disease, an initial phase of amphotericin B plus flucytosine should be followed by consolidation treatment with fluconazole and maintenance fluconazole. Mild to moderate pulmonary disease need only be treated with fluconazole.

Other Fungi

In recent years, non-*Aspergillus* mycelial fungi (NAMF) have been more frequently recognized as pathogens in lung transplant recipients. One theory is that with increased prophylaxis against *Aspergillus* species these fungi are being selected for in the airways of transplant patients. Molds such as *Scedosporium apiospermum*, *Scedosporium prolificans*, and the zygomycetes (*Rhizopus* and *Mucor*) are particularly concerning given their resistance to common antifungal agents. Also complicating early diagnosis is the fact that it is difficult to differentiate between *Aspergillus* and *Scedosporium* on routine staining; for this reason, fungal culture is necessary. NAMF have been associated with a higher mortality and higher incidence of disseminated disease compared with *As-
pergillus species. Based on smaller case reports, risk factors for development of Scedosporium infection include previous CMV disease and augmented immunosuppression. In one series of lung transplant recipients, Tamm et al reported 7 patients with Scedosporium-positive BAL cultures, 4 of whom subsequently cultured S. prolificans. The mean time to positive cultures was 21 months after transplant, although Scedosporium infection has been described to occur around 4 months after transplant in other cases. All 7 of these patients had airway complications, including 1 with an implantable stent for bronchial stenosis. Four of these 7 patients died from complications related to their fungal infection. Successful treatment has been described with the use of combined therapy, voriconazole plus terbinafine, until sensitivities are determined.

VIRAL INFECTIONS

Viruses are the second most common cause of infections in lung transplant recipients, making up 31% of all infections in one cohort. CMV infection is the most important and frequently encountered. However, others such as herpes simplex virus, Epstein-Barr virus, and community-acquired respiratory viruses are increasingly recognized as causing morbidity within the lung transplant population.

Cytomegalovirus

CMV is a beta herpes virus that causes a mononucleosis-like infection in immunocompetent patients. After infection the virus remains dormant in the patient’s leukocytes. More than half of the population has circulating antibodies to CMV. The same is true for lung transplant recipients and donors. Prior to transplant, CMV serologies are drawn from the donors and recipients. The interaction of donor and recipient CMV exposure is a significant factor in determining whether that patient is at risk for developing a CMV infection. In a landmark study from 1989, 244 recipients of heart or heart-lung transplants were reviewed to determine severity and prevalence of CMV disease. Forty-three patients were diagnosed with primary CMV disease and 76 had evidence of reactivation. The incidence of CMV disease among the population was as follows: donor positive/recipient negative (D+/R–) patients developed CMV disease 81.1% of the time, donor positive/recipient positive (D+/R+) developed CMV disease 67% of the time, donor negative/recipient positive (D–/R+) developed CMV disease 42.2% of the time, and donor negative/recipient negative (D–/R–) developed CMV disease 20% of the time. All 7 deaths from CMV disease occurred in the D+/R– population. As is readily apparent from these data, recipients who are CMV mismatched (D+/R– have the highest risk for subsequent development of CMV disease.

Apart from direct infection, CMV has been associated with other complications in lung transplant recipients. Previous reports indicate that CMV infection is associated with more opportunistic infections, increased risk of acute cellular rejection and BOS, increased risk of malignancy, and increased patient mortality. An early study by Duncan et al evaluated the sequelae of CMV infection among lung transplant patients. Fifty-six patients developed CMV and 62 remained free of infection. Having started with similar pulmonary function tests, the lung recipients with a history of CMV exhibited consistently lower expiratory flows. Differences were initially seen within 3 months and persisted throughout the 2-year period of evaluation. In addition, CMV-positive patients had significantly more episodes of bacterial and fungal pneumonia (1.02 episodes) compared to their CMV-negative
counterparts (0.5 episodes). Since this study was performed prior to widespread use of anti-CMV prophylaxis and availability of ganciclovir for treatment of CMV disease, Snyder et al sought to evaluate whether CMV pneumonitis is still a risk factor for BOS. In their cohort, 21% of patients developed CMV pneumonitis approximately 15 weeks after transplant despite prophylaxis. In a multivariate analysis, patients with CMV infection at any time after transplant had an increased risk of developing BOS (HR, 1.88). Also, if CMV infection developed within the first 6 months post transplant, patients had an increased mortality (HR, 1.82).

Presentation. CMV infection can present in a spectrum ranging from asymptomatic CMV viremia to tissue-invasive disease causing pneumonitis, enteritis, or hepatitis. Primary disease, as in immunocompetent patients, can present as fevers, chills, myalgias, and arthralgias. Incidence of CMV infection has been reported to be approximately 40%. The mean time to development of CMV viremia and pneumonitis in one study was 40 and 55 days, respectively. However, time to disease can vary depending on institution-specific prophylaxis protocols. The most common finding on computed tomography (CT) imaging of a patient with CMV pneumonitis is ground glass changes in 66% of patients; however, findings can include consolidation, nodular infiltrates, or a range of other abnormalities.

Diagnosis. Diagnosis of CMV infection can be made by testing for either CMV pp65 antigen (a CMV structural protein) within circulating leukocytes or by polymerase chain reaction (PCR) assay for CMV DNA. Weinberg et al compared viral culture, pp65 antigenemia, and CMV DNA PCR in 41 lung transplant recipients who developed 11 episodes of CMV disease over a 12-month period. Viral culture only detected 1 case of symptomatic CMV disease and missed 10 others. Antigen testing detected 4 of 9 acceptable specimens for a sensitivity of 48%. Qualitative CMV PCR detected virus in 9 of the 11 symptomatic patients and the quantitative measurement seemed to correspond to disease severity. In another early study, the detection of circulating viral DNA on CMV DNA PCR was found to be a risk factor for developing CMV disease. Therefore, when available, CMV PCR should be the diagnostic test of choice for CMV infection. However, there is wide variation between institutions due to differences in assay design. International organizations are now working tostandardize the CMV PCR test to make comparison of viral loads between institutions more uniform. For definitive diagnosis of organ-specific disease, biopsy is necessary to confirm tissue invasion and is notable for positive CMV immunostaining and typical cytomegalic cells with intracellular inclusion bodies.

Prophylaxis and treatment. Understanding that CMV is a common pathogen after transplant and can cause both acute infection and downstream sequelae such as acute and chronic rejection, prophylaxis against disease has been investigated. As with Aspergillus, 2 strategies of prophylaxis are commonly used, universal and targeted. In general, with universal prophylaxis, any recipient who is high risk (D+/R–) or moderate risk (D+ or –/R+) is given a period of prophylaxis with valganciclovir or ganciclovir. With targeted prophylaxis, patients get weekly testing with either the CMV PCR or CMV pp65 antigen test. When virus is detected at a prespecified level, treatment of CMV infection is started. In a survey of transplant centers, 94.9% used universal prophylaxis in D+/R– patients. A large majority, 86.4%, of centers used universal prophylaxis in R+ patients. For D–/R– patients, 35.6% of centers used targeted prophylaxis, while
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an equal number reported no prevention strategy. Prophylaxis was continued for 3 or 6 months, and this varied to a degree based on differences in CMV serostatus. Of note, D–/R– patients should be routinely given CMV-negative blood to prevent primary CMV infection. At our institution, we employ both strategies based on CMV status of the donor and recipient. CMV-mismatched recipients (D+/R–) at highest risk receive universal prophylaxis for 6 to 12 months, while with moderate-risk recipients (D+/R+ or D–/R+) we practice targeted prophylaxis.

Oral valganciclovir (900 mg daily) and intravenous ganciclovir (5 mg/kg/day) are the drugs of choice for prevention of CMV disease, dose adjusted as indicated for renal dysfunction. Previously, oral ganciclovir was used, but due to low bioavailability and inefficient suppression of viral replication, valganciclovir was studied and found to be at least equivalent.

In addition to these medications, CMV-specific immune globulin is used at one-third of centers for D+/R– patients and to a lesser degree in lower-risk patients. This strategy has been advocated based on a study in heart and heart-lung transplant recipients that showed that when compared with intravenous (IV) ganciclovir prophylaxis, patients treated with CMV-specific immune globulin had a lower rate of CMV disease, BOS, and mortality compared with historical controls. CMV-specific immune globulin alone has no role in the prophylaxis of lung transplant recipients. Therefore, prophylaxis against CMV disease should include oral valganciclovir 900 mg daily (assuming normal renal function) or IV ganciclovir 5 mg/kg/day with or without CMV-specific immune globulin (Table).

One concern about universal CMV prophylaxis is the development of late-onset CMV disease. Late-onset disease typically occurs 3 to 6 months after transplant. Risk factors for late-onset disease include D+/R– serostatus, higher levels of immunosuppression, and allograft rejection. It has been proposed that a longer period of CMV prophylaxis would reduce the risk of late-onset disease. Therefore, a multicenter, double-blind, placebo-controlled trial of extending CMV prophylaxis to 12 months versus 3 months of prophylaxis followed by placebo was performed. There was more CMV disease in the placebo group (32%) than in the 12-month prophylaxis group (4%). There were similar numbers of CMV resistance mutations in the extended prophylaxis group as compared with short-course prophylaxis.

The same medications used for prophylaxis against CMV are utilized in the treatment, but the dosing strategy is different. IV ganciclovir is the drug of choice for CMV disease at a dose of 5 mg/kg twice daily. However, recently oral valganciclovir 900 mg twice daily has been studied as an alternative. Asberg et al studied the effects of this oral regimen compared with IV ganciclovir in solid organ transplant recipients. CMV eradication at day 21 was achieved in 45.1% of the valganciclovir group and 48.4% of the IV ganciclovir group. The most common adverse event was leukopenia, which occurred with similar frequency in both groups. Therefore, CMV disease can be treated with either IV ganciclovir or oral valganciclovir. Antiviral therapy is typically continued until CMV PCR is negative for at least 1 week and at least 2 total weeks of therapy. If CMV viremia is
not eradicated with therapy after 2 weeks, the addi-
tion of CMV-specific immune globulin can be con-
considered. In addition, in cases of CMV that are
refractory to ganciclovir or valganciclovir treatment
at appropriate doses, an assessment of CMV re-
sistance should be considered. Treatment options
for resistant CMV include foscamet or cidofovir, but
renal toxicity is a limiting factor with both of these
medications.

CMV resistance is more common in D+/R−
patients, in patients with prolonged ganciclovir
use, and with ongoing CMV replication. CMV
resistance is caused by mutations in UL97 phos-
phototransferase (conferring resistance to ganci-
clovir) or UL54 pol. The UL97 mutation causes a
5- to 10-fold increase in the IC50 to ganciclovir, and
switching to foscamet is recommended. However,
UL54 pol mutations, which typically occur as a
second mutation after UL97, cause high-level re-
sistance to ganciclovir and possibly other anti-CMV
therapies such as foscamet. In a retrospective
review, 5.2% of transplanted patients were found to
have partial or full resistance. These patients had
a longer exposure to ganciclovir compared with the
nonresistant patients prior to resistance diagnosis
and more episodes of CMV pneumonitis. They had
a higher mortality and earlier onset of BOS com-
pared to nonresistant controls.

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a gamma herpes
virus that causes infectious mononucleosis in ado-
lescents and young adults. Approximately 90% of
the population has been exposed to EBV, leav-
ing the virus to lay dormant in memory B-cells.
Of those patients who have not been exposed to
EBV prior to transplant, mononucleosis has been
shown to develop after transplantation from an
EBV-positive donor, presenting with fever, malaise,
headache, and sore throat. However, for the large
majority of lung transplant recipients, the most clin-
ically relevant concern associated with EBV is the
development of post-transplant lymphoproliferative
disorder (PTLD).

PTLD encompasses a wide spectrum of lym-
phoid proliferative disorders ranging from reactive,
polycylic hyperplasia to aggressive non-
Hodgkin’s lymphoma. It typically occurs in the
first year after transplantation when T-cell immu-
nity is at its weakest. PTLD can be polyclonal
(as in early follicular hyperplasia) or monoclonal.
Monoclonal disease can occur as polymorphic or
monomorphic PTLD. Whereas polymorphic PTLD
can include monoclonal and polyclonal popula-
tions that infiltrate underlying tissue, monomorphic
PTLD contains monoclonal transformed B-cells,
often with cytogenetic abnormalities that invade
tissue and fulfills pathologic diagnostic criteria for
lymphoma. Between 70% and 90% of PTLD is
EBV-positive. Higher levels of immunosuppres-
sion, specifically anti-T-cell therapy, have been
implicated in the development of PTLD.

In a large cohort at the University of Pennsylva-
nia, the incidence of PTLD was approximately 6%
at 5 years after lung transplant. While occurring
at a median of 11 months after transplant, PTLD
was diagnosed anywhere between 11 days and 5
years post transplantation. Patients presented with
nonspecific complaints of fatigue, pain, or weight
loss. The most common non–lymph node site of
disease was the lung, seen in 49% of patients.
The occurrence of PTLD in the transplanted organ
has been demonstrated in other solid organ trans-
plant recipients as well. However, the later after
transplant PTLD presents, the more likely it is to
involve distant organs, as shown by Paranjothi et
al. Within this cohort, once again approximately
6% of lung transplant recipients developed PTLD.
Fourteen cases occurred during the first year and 16 cases occurred later (on average 4.3 years after transplant). In the early group, 12 of 14 cases occurred within the thorax, while in the late group only 2 of 16 cases were intrathoracic. The majority (9 of 16) in the late group involved the gastrointestinal tract. However, if a lung transplant recipient is newly infected with EBV, extrathoracic disease can present early after transplant (median 175 days after transplant; Figure 3).90

The diagnosis of PTLD is similar to lymphoma; an excisional lymph node biopsy is preferred. There is no standardized staging system for PTLD; generally, it is staged similar to non-Hodgkin’s lymphoma. Initial staging should include imaging of the chest, abdomen, and pelvis in addition to a bone marrow biopsy.86 EBV PCR is a potentially useful tool in the diagnosis of PTLD. In one center, however, in EBV-positive tumors, only 39% had EBV detected on serum PCR; serum EBV PCR was negative in all patients without PTLD and on EBV-negative tumors.91

Unsurprisingly, given the nature of the disease, first-line treatment for PTLD is reduction of immunosuppression. While this does increase the risk of rejection, reduction in immunosuppression has historically been the most commonly studied and utilized therapy. Tsai et al reviewed a cohort of patients treated with reduction of immunosuppression.92 Of the 42 patients included in that study, 73.8% achieved a complete remission in a median of 3.6 weeks. Elevated lactate dehydrogenase, organ dysfunction, and multi-organ involvement were risk factors for progression of disease despite reduction of immunosuppression. However, of those treated with reduction of immunosuppression, 31% developed acute rejection of the allograft. Localized disease is sometimes treated with surgery and radiation.87

Given the pathophysiology of EBV proliferation in B-cells, it is logical that the anti-CD20 monoclonal antibody rituximab would be part of the treatment of PTLD refractory to reduction of immunosuppression. In a multicenter evaluation of treatment practices within Chicago, Evens et al report that 3-year progression-free survival and overall survival were improved with rituximab-based therapy (70% and 73%, respectively) when compared to those without rituximab (21% and 33%, respectively).93 However, rituximab treatment alone leads to short time to progression of disease after initial response.94 Treatment with CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone/prednisolone) alone demonstrated a durable response but had a 31% treatment-related mortality.95 A recent phase II trial has investigated whether sequential treatment with 4 cycles of rituximab once weekly followed by four 21-day cycles of CHOP might be less toxic than CHOP alone but have a longer time to progression than rituximab.
alone. In this trial, 90% of patients had complete or partial response to treatment, which was durable out to more than 79 months, with only 11% treatment-related mortality.96

**Community-Acquired Respiratory Viruses**

Community-acquired respiratory viruses (CARVs) are common in lung transplant recipients. This umbrella term encompasses many different groups of viruses including Picornaviridae (eg, rhinovirus and enterovirus), Coronaviridae (eg, coronavirus), Paramyxoviridae (eg, respiratory syncytial virus [RSV]), parainfluenza, and human metapneumovirus), Orthomyxoviridae (eg, influenza A and B), and Adenoviridae (eg, adenovirus). Diagnosis of CARV infections, while difficult to make in the past, is becoming technically much easier with newer multiplex PCR assays. In lung transplant recipients, the danger of these viruses occurs when upper respiratory tract disease migrates to become lower respiratory tract disease. These viruses account for 28% to 43% of all lower respiratory tract infections (LRTI) in lung transplant recipients.97 Presentation can include anything from being asymptomatic to mild upper airway symptoms to pneumonia.

Aside from causing LRTI, CARVs are known to be a risk factor for development of BOS. In one retrospective cohort, 259 consecutive lung transplant patients were found to have 21 episodes of CARV infection. CARV infection was found to have a HR of 2.05 for development of BOS stage 1, and LRTI with a CARV increased the HR to 3.03.98 This finding was echoed in a prospective trial, where CARV-infected patients had a 1-year incidence of BOS of 25% versus 9% for non–CARV-infected patients.99

*Paramyxoviridae* cause the viral infections most frequently implicated in later development of BOS. In one study by Khalifah et al, BOS risk was increased particularly in patients with LRTI.98 Therefore, many centers have begun treating RSV and other *Paramyxoviridae* upper respiratory tract disease with ribavirin to prevent progression to LRTI. Typical treatment involves the nebulization of 6 g of ribavirin daily (either continuously or in 3 separate sessions) for 3 to 5 days. McCurdy et al100 describe a 72% resolution of airway obstruction in patients treated with nebulized ribavirin in a small cohort, which was superior to historical controls.101 Ribavirin has also been studied in intravenous and oral forms, although both of these routes of administration can be complicated by hemolytic anemia, which is reversible after the drug is withdrawn.102–104 Other proposed treatments for paramyxovirus LRTI include palivizumab (an RSV-specific monoclonal antibody), IV immunoglobulin, RSV-IVIG (no longer available), and RNA interference.105–108

Influenza causes up to 4% of all LRTIs in lung transplant recipients and likely more during winter months due to its seasonality.97 In recent years, with the emergence of the 2009 H1N1 strain, it has become more apparent than ever that influenza is a potentially deadly virus. An emphasis should be placed on having patients vaccinated prior to influenza season. However, if disease occurs, treatments do exist that may decrease the severity and duration of influenza. Oseltamivir, a neuraminidase inhibitor, was evaluated against placebo in immunocompetent patients. Both the 75 mg twice daily and 150 mg twice daily dosing were evaluated and found to decrease duration of symptoms, lower symptom scores, and decrease viral shedding compared with placebo.109 The duration of therapy should be at least 5 days, extending to 7 to 14 days if clinically indicated in severe disease.

**Herpes Simplex Virus**

Herpes simplex virus (HSV) is an alpha herpes virus that is characterized as either type 1 or type 2.
Both viruses remain dormant either in the trigeminal or sacral ganglia after primary infection. Prior to antiviral prophylaxis with acyclovir, a retrospective study evaluated the prevalence of HSV infection in 51 heart-lung transplant recipients. Mucocutaneous HSV occurred in 7.8% and HSV pneumonia occurred in 9.8% of transplant recipients. HSV pneumonia presented with dyspnea, a decrement in spirometry, diffuse pulmonary infiltrates on chest radiography, and fever. One of the five patients with HSV pneumonia died of disseminated disease.110 There are few trials in solid organ transplant recipients; however, in each acyclovir was shown to reduce HSV disease compared with historical controls.111,112

**Varicella Zoster Virus**

Varicella Zoster virus (VZV) is an alpha herpes virus which is best known for causing chicken pox as a primary infection and herpes zoster when reactivated from its dormancy in the dorsal root ganglia. Up to 90% of recipients have already been exposed to VZV at the time of transplant. Fuks et al reviewed a cohort of lung transplant patients and examined the amount of VZV infection encountered.113 Patients were receiving universal prophylaxis for CMV for 6 or 12 months depending on their risk for developing disease. Reactivation within a single dermatome, or shingles, was common, occurring in 11.6% of lung transplant recipients. Only one case (0.5%) presented as disseminated VZV. In another retrospective study in a population of heart and heart-lung transplant recipients, over a 10-year period disseminated VZV was diagnosed in 1.7% of patients. Among those infected, the mortality rate was 64%.114 Due to the risk of developing disseminated VZV and its high mortality, prophylaxis with acyclovir is generally used for prevention.111

**Human Herpes Virus 6 and 7**

Human herpes virus (HHV) 6 and 7 are common beta herpes viruses, infecting most individuals at some point during childhood. Like the other herpes viruses, after the primary infection HHV6 and HHV7 become dormant, residing mostly within T-cells. Reactivation after solid organ transplant has been identified in 31% to 55% of recipients within the first month. HHV6 and HHV7 are associated with allograft rejection, bone marrow suppression, and increased risk for development of CMV disease.112 In a study by Lehto et al,115 HHV6 and HHV7 antigens were detected in the serum of 91% and 50% of lung and heart-lung transplant cases at 16 and 31 days, respectively. Even when patients were on anti-CMV prophylaxis, HHV6 and HHV7 antigens were detected in 79% and 37%, respectively. On review of the cases, it was difficult to determine what, if any, clinical illness these viruses caused. Two diagnoses were temporally related to onset of antigenemia, one episode of pneumonitis and another of encephalitis. In another single center study, HHV6 in the BAL fluid correlated with BOS stage 1 or greater and death. Patients with HHV6 positivity developed BOS 45% of the time versus 18% for those without HHV6 in BAL fluid.116

**MYCOBACTERIAL INFECTIONS**

**Nontuberculous Mycobacteria**

NTM are present in the environment and cause clinical infection in patients who are immunocompromised and/or who have chronic lung disease.117 NTM disease is diagnosed based on a constellation of clinical, radiological, and microbiological criteria. Patients must have pulmonary symptoms (typically chronic cough in addition to other nonspecific symptoms), nodular or cavitary opacities on chest radiograph, or high-resolution CT with multifocal bronchiectasis and multiple
small nodules (Figure 4). In addition, microbiologically they must have 2 separate sputum samples growing NTM (or one bronchial wash or BAL/biopsy). Disseminated disease is exceedingly rare in HIV-negative patients receiving immunosuppression.\textsuperscript{118}

In a population of pre-transplant patients with CF, 19.7% had cultures positive for NTM. The most common organisms isolated were \textit{Mycobacterium avium} complex (45%), \textit{M. abscessus} (41%), \textit{M. gordonae} (7%), and \textit{M. fortuitum} (3%). Of these patients, 39% cultured positive for NTM after transplantation despite completion of treatment prior to transplant. Only 11% of patients without pre-transplant NTM developed mycobacterial disease after transplant. \textit{M. abscessus} was most likely to cause disease after transplant, which occurred in all 3 patients where NTM was re-isolated. However, the survival of patients infected with NTM was not worsened in this series. NTM infection is not an absolute contraindication to lung transplantation.\textsuperscript{22,119}

Treatment of NTM varies depending on the organism encountered. For \textit{M. avium} complex, the regimen typically includes a macrolide (eg clarithromycin or azithromycin), ethambutol, and a rifamycin (eg, rifabutin or rifampin). A parenteral aminoglycoside can be added based on severity of disease. Treatment should be continued until 12 months of negative sputum cultures for NTM is achieved. Other recommendations regarding treatment can be found in the treatment guidelines by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) statement regarding NTM.\textsuperscript{118}

**Tuberculosis**

Pre-transplant patients are often screened for \textit{Mycobacterium tuberculosis} (TB) and treated for latent tuberculosis if positive.\textsuperscript{120} The decision to screen for latent tuberculosis varies by center and the regional prevalence of tuberculosis. There are very few cases in the literature of lung transplant recipients developing tuberculosis.\textsuperscript{121} In one review, Singh and Paterson describe 511 cases of patients who developed tuberculosis after solid organ transplant, with only 13 cases in lung or heart-lung transplant.\textsuperscript{122} Average time to development of tuberculosis was 9 months after transplant. Predictors for development of tuberculosis were non-renal transplant, allograft rejection less than 6 months prior to tuberculosis, and type of immunosuppression, with tacrolimus imparting the greatest risk (more than azathioprine or cyclosporine).

Treatment should be initiated with a typical regimen of isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA), and rifampin (RIF) per the ATS/Centers for Disease Control and Prevention/IDSA guidelines.\textsuperscript{123} However, regimens containing
both INH plus RIF and INH alone have been tried, primarily in Europe, with no reported increase in mortality (21% vs 24%, respectively).\textsuperscript{122}

**SUMMARY**

When providing care for lung transplant recipients, an extremely high-risk population, infections must be high on the differential diagnosis with every complaint. Aside from the infections discussed in this article, one must be mindful about how immune dysregulation can lead to chronic rejection of lung recipients’ allografts. Antibacterial agents, antifungal agents and antiviral agents are available to aid in treating a broad range of infectious complications. This vulnerable population is at increased risk for a number of major infections, and in many instances it is appropriate to provide prophylaxis against the most dangerous culprits. Understanding the above infections, timing of presentation, and different treatment strategies, the goals of management are to prevent infections when possible, identify and treat infections early, limit adverse effects of the treatments, and prevent the downstream consequences of infectious episodes.

**BOARD REVIEW QUESTIONS**

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**REFERENCES**


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