STATE OF THE ART REVIEW

Infectious Complications in Lung Transplant Recipients

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Abstract

Lung transplantation is a lifesaving intervention for patients with advanced lung disease. Due to a combination of immuno-suppression, continuous exposure of the lungs to the environment, and complications at the anastomotic sites, lung transplant recipients are at high risk for infectious complications. The aim of this review is to summarize recent developments in the field of infectious diseases as it pertains to lung transplant recipients.

Keywords Lung transplant · Infection · Aspergillosis · Cytomegalovirus · Coronavirus · Bronchiolitis obliterans syndrome

Introduction

Over the past 20 years, lung transplantation has emerged as a lifesaving surgery for those with chronic lung disease, leading to significantly improved outcomes. According to the International Society for Heart and Lung Transplantation registry, there have been 69,200 adult lung transplants performed worldwide as of June 30th, 2018, with a median survival of 7.8 years and 4.8 years for double lung transplant and single lung transplant, respectively [1]. While life expectancy has increased over time, infections remain a common cause of morbidity and mortality in transplant recipients, and are the leading cause of death between one month and one year post-transplant [1].

The high rate of infection seen post-transplant is multifactorial. Continuous exposure of the lungs to the environment, the potency of immunosuppression required to prevent rejection, complications at the anastomotic sites, and impaired mucociliary clearance all play an important role [2]. While direct microbial damage contributes to overall morbidity and mortality in lung transplant patients, the complex relationship between infection and chronic graft rejection is also a key factor. Bronchiolitis obliterans syndrome (BOS), a subtype of chronic rejection, is the leading cause of mortality >1-year post-transplant [3]. Infections, particularly due to cytomegalovirus (CMV) and other respiratory viruses, are known to contribute to the development of BOS. Furthermore, concomitant increases in immunosuppression needed to control rejection result in an increased risk of subsequent infection, which can make lung transplant recipients challenging to manage. The success of lung transplantation depends on the careful balance of immunosuppression to prevent rejection while at the same time minimizing infectious risks. In order to maximize contribution to the extensive literature on this subject, this review focuses primarily on recent developments in the field.

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Pre-transplant Screening

Infections in lung transplant recipients can be acquired *de novo* post-transplant but can also be donor-derived or caused by reactivation of latent infection in the recipient. Therefore, a comprehensive pre-transplant screening of both recipients and donors is required. Special note should be made of all previously diagnosed infections. This is particularly important for patients with cystic fibrosis or other suppurative lung diseases since these patients often have complicated infectious histories, including both active infections and colonization with multi-drug resistant organisms (MDROs). Such patients should receive double lung transplantation to prevent infection of the allograft, and the presence of MDROs may change perioperative antimicrobial management.

In addition to infectious history, a detailed social history including (but not limited to) country of origin, travel, occupational history, recreational activities and contact with pets and domesticated animals should be obtained from the recipient to assess for potential latent infections. If a latent infection is identified, treatment is often recommended pre-transplant. Other screening, such as CMV serologies, are key for assessing post-transplant infectious risk and determination of post-transplant prophylaxis (Tables 1 and 2) [4].

The donor should be tested for bacterial, viral, fungal, mycobacterial and parasitic infections and both sputum and serologic tests should be confirmed to evaluate for these organisms. Though donor screening strategies can identify many transmissible infections, some infections, such as rabies and West Nile virus, may still go undetected and be transmitted to the recipient [5, 6]. Geographic considerations should be taken into account when identifying infectious risks.

Knowledge about specific immunity to certain infections is crucial as it guides the need for post-transplant

Table 1 Screening recommendations

Organism	Recommended donor screening test	Recommended recipient screening test
CMV	CMV IgG	CMV IgG
SARS-CoV-2	Nasopharyngeal PCR, consider donor lung BAL	Nasopharyngeal PCR
EBV	EBV nuclear antigen, viral capsid IgG	EBV nuclear antigen, viral capsid IgG
HSV/VZV	HSV 1/2 IgG, VZV IgG (at some centers)	HSV 1/2 IgG, VZV IgG
HBV/HCV	HBV NAT, anti-HBc, and HBsAg, HCV NAT and anti-HCV ab	HBV NAT, anti-HBc, and HBsAg, HCV NAT and anti-HCV ab (Immediately prior to transplantation and 4-6 weeks post- transplant)
HIV	NAT and anti-HIV ab	NAT and anti-HIV ab (Immediately prior to transplantation and 4-6 weeks post- transplant)
Measles, Mumps, Rubella	Measles IgG, Mumps IgG, Rubella IgG (at some centers)	Measles IgG, Mumps IgG, Rubella IgG
Strongyloides stercolis	Testing not routinely performed	Strongyloides IgG (for recipients from endemic areas)
Toxoplasma gondi	Toxoplasma IgG	Toxoplasma IgG
Syphilis	Screening treponemal testing followed by confirmatory non-treponemal testing	Screening treponemal testing followed by confirmatory non-treponemal testing
Tuberculosis	Obtain sputum or BAL specimens for acid-fast bacilli smears, cultures and molecular diagnostics depending on risk factors	Tuberculin skin testing (TST) or interferon-gamma release assay (IGRA)

Bacterial and fungal screening may vary among transplant centers

Table 2 Region-specific screening

Disease	Region of Risk
Schistosomiasis	Africa, South America, Caribbean, the Middle East, Southern China, parts of Southeast Asia
American Trypanosomiasis	Mexico, Central America and South America
Leishmania	Africa, Asia, the Middle East, southern Europe, Mexico, Central America and South America
Histoplasmosis	Central and Eastern North America, Central and South America, Africa, Asia and Australia
Coccidiodes	Southwestern United States, the Central Valley of California, Mexico and parts of Central and South America
HTLV 1/2	Southern Japan, the Caribbean, sub-Saharan Africa, the Middle East, South America, Papua New Guinea and central Australia

prophylaxis. Donors and recipients are routinely screened for antibodies to CMV, Epstein-Barr virus (EBV) and toxoplasmosis. Those with the highest risk include recipients who are seronegative and receive organs from seropositive donors. All donors and recipients should also be screened for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by nasopharyngeal polymerase chain reaction (PCR) regardless of symptoms immediately prior to donation and transplant, respectively. While data and guidelines regarding transplantation in the setting of the coronavirus disease 2019 (COVID-19) pandemic are emerging, all attempts should be made to ensure there is no evidence of active disease at the time of transplant, and if there is any concern or ambiguity sending PCR from bronchioalveolar lavage (BAL) of the donor lung should be considered.

In 2020, new guidelines by the Centers for Disease Control and Prevention (CDC) regarding screening for human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) were released. Recommended testing includes antibodies to HIV- 1/2 (anti-HIV-1/2) and HIV nucleic acid testing (NAT), total antibody to HBV core antigen (anti-HBc), HBV surface antigen (HBsAg), and HBV NAT, as well as antibodies to HCV (anti-HCV) and HCV NAT [7]. The recommendations further state that all deceased donor should be tested within 96 hours of organ procurement, and transplant candidates should be tested immediately prior to transplantation, as well as 4–6 weeks post-transplant, regardless of donor risk profile [7]. Transplant recipients are also at an increased risk for cervical cancer due to human papilloma virus (HPV), and should be screened with an increased frequency, concurrent with guidelines for HIV-infected individuals [8].

Perioperative Antimicrobial Management and Prophylaxis

Perioperative antimicrobials are imperative in lung transplant recipients, however, there are no established guidelines or treatment standards for these patients [9]. At most institutions, recipients are empirically covered for Gram-positive and Gram-negative organisms, most often with an anti-pseudomonal beta lactam as well as an agent with activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotics should begin immediately prior to surgery and continue for at least 2–5 days, though the optimal duration of therapy is not well established. In patients with suppurative lung diseases and known history of infections and/or colonization, perioperative therapy should be targeted based on previous culture results and longer duration of therapy is often needed. In those patients undergoing single lung transplantation, cultures from the native lung should be obtained to guide perioperative therapy. Results from donor blood, sputum, and bronchial washing cultures should be followed and antimicrobial coverage adjusted as needed. Though donor-derived pneumonia is always a concern, a retrospective review of 149 lung transplant recipients showed that use of donor lungs with Gram-stain positive respiratory cultures did not impact the development of pneumonia within the first thirty days or overall mortality, but was associated with an increase in time on the ventilator post-transplantation, as well as an increased length of hospital stay [10].

Due to the high rate of fungal infections among lung transplant recipients, particularly invasive aspergillosis infection (IAI), anti-fungal prophylaxis is often given in the months immediately post-transplant, though prophylaxis strategies vary among transplant centers due to the lack of well established guidelines [9]. While oral voriconazole therapy has been found to be effective at preventing IAI, this therapy may be limited by side effects and as such, use of an inhaled antifungals, typically amphotericin, is an appropriate alternative [11].

All patients should start prophylaxis for opportunistic infections (OI) in the perioperative period. The American Society of Transplantation (AST) recommends CMV prophylaxis based on risk determined by serostatus of the donor and recipient, with seronegative recipients receiving seropositive organs being the highest risk. Therapy with antivirals is recommended for recipients at high and intermediate risk for CMV, with the duration of therapy to be determined by risk stratification, with a minimum of 6–12 months for lung transplant recipients [12]. Cytomegalovirus hyperimmune globulin can also be considered for prophylaxis of the highest risk patients, though the benefit of such treatment remains unclear [13]. Secondary prophylaxis for CMV is controversial and practices vary between transplant centers. Patients receiving CMV prophylaxis do not need additional herpes simplex virus (HSV) or varicella zoster virus (VZV) prophylaxis, but HSV/VZV prophylaxis should be considered after transplantation for seropositive organ recipients who are not on antiviral therapy for CMV [14]. Duration of therapy for HSV/VZV prophylaxis is not well established but certain centers continue lifelong therapy. In patients with chronic HBV (HbsAg positive), societal guidelines recommend initiation of prophylaxis with nucleos(t)ide analogs at the time of transplant, to be continued indefinitely [15]. In those recipients with markers of previous HBV infection (HBsAg negative, anti-HBc positive ± anti-HBs positive), risk of reactivation is considered to be low and universal antiviral prophylaxis is not recommended [15]. Lifelong prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) is recommended for all lung transplant recipients, for which trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice [16].

Bacterial Infections

During the first year post-transplant, the risk of infection among lung recipients is highest during the first month (17.3 episodes per 1000 transplant-days), as well as between 6 and 12 months (2.6 infections per 1000 transplant-days) [17]. Of those with documented infections, respiratory tract infections with *Pseudomonas aeruginosa* and Enterobacteriaceae predominate [17]. One of the main contributors to morbidity and mortality among lung transplant recipients is BOS and one study analyzing 155 lung transplant recipients showed a strong association between the development of BOS and allograft colonization with *Pseudomonas aeruginosa* [18]. *Pseudomonas aeruginosa* has also been associated with humoral rejection and the development of donors-specific antibodies [19]. *S. aureus* is also another frequent cause of nosocomial pneumonia, as well as Gram-negative bacteria such as *Acinetobacter* spp. and *Stenotrophomonas maltophilia* [20]. Though Gram-negative infections are the most frequently isolated, atypical infections should also be considered. Infections with *Ureaplasma* species have been reported to cause fatal hyperammonemia syndromes and outpatients are at risk of infections with organisms such as *Mycoplasma pneumoniae*, *Haemophilus influenzae* and *Streptococcus pneumoniae* [21, 22].

Prevalence of tuberculosis varies based on geographic location and individual risk varies depending on certain exposures, such as homelessness and incarceration. In one large prospective cohort study, a total of 4388 solid organ transplant recipients were monitored, of whom 303 were lung transplant recipients. Though the prevalence was low, lung transplant recipients were at increased the risk of developing tuberculosis when compared to other solid organs [23]. Therapeutic regimens for TB in these patients are particularly challenging, since drug-related toxicities and drug-drug interactions are common.

Nontuberculous mycobacteria (NTM) are also significant pathogens in this patient population, with pleuropulmonary disease being the most frequent site of infection [24]. In a single center review of 1303 lung transplant recipients, 26 were found to have *Mycobacterium abscessus*. Six of these patients tested positive for the isolate during their pre-transplant period, and twenty of them did not [25]. This study found a statistically significant trend toward mortality in the group that met the criteria for NTM disease. Although treatment of *M. abscessus* in this population is challenging, the use of clofazimine was associated with a favorable outcome [25].

Viral

CMV is a leading cause of infection among lung transplant recipients and is associated with significant morbidity and mortality. CMV infection is defined as the presence of CMV replication in tissue, blood or other bodily fluid, even in the absence of signs or symptoms, while CMV disease requires clinical signs or symptoms to be present [26]. CMV disease can manifest in a variety of ways including an acute viral syndrome, pneumonitis, colitis and hepatitis [27]. CMV also plays a role in the pathogenesis of graft rejection, with one retrospective study showing an association between CMV infection and the development of BOS, irrespective of the degree of viral replication, invasive disease or symptoms [28]. Prophylaxis against CMV has significantly decreased the incidence of infection and disease [27]. The approach to prophylaxis varies by institution, and can be either universal or preemptive with close monitoring for asymptomatic viral replication. Due to the association between CMV and BOS, most transplant centers prefer universal prophylaxis in lung transplant recipients considered to be high or intermediate risk such as CMV-seronegative or CMV-seropositive recipients who receive organs from CMV-seropositive donors [29].

EBV is associated with post-transplant lymphoproliferative disorders (PTLD), a spectrum of lymphoproliferative malignancies to which transplant patients are particularly vulnerable. PTLD is associated with significant morbidity and mortality, as well as an increased risk of graft loss [30]. EBV donor and recipient mismatch, specifically a seropositive donor and a seronegative host, increases the likelihood of development of PTLD [31]. One retrospective review found that although EBV seronegative recipients of organs from EBV seropositive donors were at a higher risk for development of PTLD, they did not have a worse survival than EBV seropositive recipients [32].

Other herpes viruses are also common. Reactivation of herpes simplex 1/2 and varicella zoster is well documented in transplant recipients. Human herpes 6 infection (HHV-6) has also been reported to cause encephalitis in immunocompromised hosts and should be considered in the differential of viral encephalitis in transplant patients [33]. Though rare, disseminated forms of Kaposi's Sarcoma have been described in organ recipients from human herpes virus 8 (HHV-8) positive donors [34].

Lung transplant recipients are also vulnerable to severe infection from common community acquired respiratory viruses. While typically causing self-limited upper respiratory symptoms in healthy hosts, infections with these viruses can be protracted and severe in lung transplant populations and progress to lower respiratory tract involvement. Some of the most problematic community acquired viruses include respiratory syncytial virus (RSV), parainfluenza virus (PIV), rhinovirus, coronavirus, human metapneumovirus, influenza and enterovirus. RSV and PIV can be especially aggressive in lung transplant recipients, with mortality as high as 20% and associated with the development of BOS [35, 36]. Though therapy for RSV is mostly supportive, multi-drug regimens have been used

in various centers. Ribavirin with or without steroids has been used in immunocompromised hosts to reduce mortality and morbidity. Intravenous immunoglobulin (IVIG), as well as palivizumab, a RSV-specific monoclonal antibody, have also been used, though with less convincing evidence as to its efficacy [37–40]. However, not all infections with respiratory viruses lead to severe disease. One study found that while 22% (18/80 patients) of lung transplant recipients developed adenovirus viremia during the first year post-transplant, the majority of infections were asymptomatic [41].

Chronic viral hepatitis, such as HBV and HCV, can also complicate post-transplant care given the level of immunosuppression [42]. Recent breakthroughs in the treatment of HCV prompted a study involving the transplantation of organs from HCV infected donors to uninfected recipients who were subsequently treated with 4 weeks of sofosbuvir-velpatasvir. A total of 44 patients were enrolled, 36 of whom were lung transplant recipients. Of the 35 enrolled who had completed at least 6 months of follow up, all had sustained undetectable viral loads [43]. The use of HCV NAT positive organs has the potential to greatly expand the donor organ pool.

Patients with chronic hepatitis B, defined as recipients who are HBsAg positive, should be virally suppressed prior to transplant. These patients are at high risk for reactivation in the post-transplant setting and should be maintained on lifelong therapy with nucleos(t)ide analogs such as entecavir or tenofovir disoproxil fumarate with the goal of keeping HBV DNA levels undetectable. Patients with evidence of previous infection, including those that are HBsAg negative but anti-HBc positive and +/- anti-HBs positive, are at lower risk for reactivation and thus antiviral therapy should be considered on a case by case basis [15]. Non-hepatic donors who are HBsAg negative but anti-HBc positive and +/- anti-HBs positive carry a much lower risk of HBV transmission but antiviral therapy can be considered in high risk patients [44, 45]. The risk is considered negligible to recipients immune to HBV and pre-transplant vaccination is currently the most effective way to prevent transmission to non-immune recipients [15].

While extensively performed in other organs, lung transplantation in HIV-seropositive patients has been rare but successful cases have been reported [46].

The COVID-19 pandemic has been especially concerning for SOT recipients. One study reviewed outcomes in their solid organ transplant recipients during the first 3 weeks of the outbreak in New York City, including 17 lung transplant recipients. Of these 17 patients, 7 were considered to have severe disease and overall, solid organ transplant recipients had more severe outcomes [47]. Another case series described 10 lung transplant recipients with severe acute respiratory distress syndrome due to COVID-19 infection,

one of who required admission to the intensive care unit and subsequently died. The authors noted that cell cycle inhibitors were withheld in all ten patients, while calcineurin inhibitors and corticosteroids were continued at the same dose [48]. Finally, a multi-center cohort study of 482 solid organ transplant recipients, including 30 lung transplant patients, showed an overall 28-day mortality rate of 20.5% [49]. Optimal management of immunosuppression in patients with COVID-19 remains unclear.

Though an emerging topic, lung transplantation has been performed in patients with COVID-19-related pulmonary fibrosis. One review described three patients with end-stage pulmonary fibrosis after COVID-19 infection who underwent lung transplantation. Two of these patients survived, supporting the idea of lung transplantation as a final option in patients with COVID-19-related fibrosis [50].

Fungal

Lung transplant recipients have a high rate of invasive fungal infections, with invasive aspergillosis (IA) being the most frequent culprit. Impaired cough reflex and mucociliary clearance of the host contribute to colonization and potential progression to invasive infection. Patients are also particularly vulnerable to infection at the anastomotic sites due to impaired blood flow to those regions with subsequent epithelial sloughing, which serves as a nidus for growth of fungal hyphae [51]. Infection with *Aspergillus* spp. can manifest in a variety of ways, ranging from airway colonization to tracheobronchitis to life-threatening lower respiratory tract infections. Currently, the optimal strategy for *Aspergillus* prophylaxis has yet to be defined and there is variability among transplant centers regarding choice of therapy and duration [9, 52]. Systemic administration of an azole such as voriconazole is a widely used approach to reduce rates of IA among lung transplant recipients, but its use may be limited by drug interactions and hepatotoxicity [52, 53].

Though invasive candida infection is typically a threat to patients who have undergone combined heart-lung transplantation, one prospective study showed a prevalence rate of invasive candidiasis to be 11.4 infections per 100 lung transplant surgeries [54]. A case of donor-derived *Candida auris* infection has also been reported in a lung transplant recipient [55].

PJP remains an important cause of pneumonia in lung transplant recipients. The organism is ubiquitous in nature and the exact mechanism of transmission, environmental versus person-to-person, is unclear [56]. Prior to established prophylaxis, the incidence of PJP in lung transplant recipients ranged from about 10–40%. Prophylaxis has greatly decreased the incidence of clinical infection in these patients

to below 5.8%, and lifelong prophylaxis is recommended [16, 57].

Parasites

A prominent parasite found worldwide is *Toxoplasma gondii*, which can be transmitted by consumption of undercooked meat/shellfish, accidental ingestion of cat feces, transplacentally or via organ transplantation. In immunocompetent hosts, toxoplasmosis is usually self-limited and may present as fever, malaise and lymphadenitis. In immunocompromised hosts, manifestation of disease depends on the site of infection and can include encephalitis, myocarditis and pneumonia. Typically, prophylaxis with TMP-SMX prevents disease. Transmission of infection from seropositive donors to seronegative recipients has been described in patients placed on pentamidine for prophylaxis [58, 59].

Helminths are a rare but potentially severe cause of infection after organ transplantation. A major human pathogen is *Strongyloides stercoralis*, a threadworm most prevalent in tropical countries. Infection occurs when humans come into contact with soil that is contaminated with filariform larvae, which then penetrate the skin and enter the lymphatic system. Infection with this organism is particularly dangerous for transplant recipients, as they can develop *S. stercoralis* hyperinfection syndrome from proliferative larval production and migration, leading to disseminated disease and the potential for life-threatening bacterial gut translocation [60].

The pork tapeworm *Taenia solium* can cause life-threatening illness in immunosuppressed patients. Humans develop intestinal infection through consumption of undercooked pork containing cysticerci, and subsequently excrete the eggs in their stool. Disseminated infection is acquired via ingestion of these eggs in food or water. Infection can then spread to the central nervous systemic, called neurocysticercosis, which can manifest itself as seizures or increased intracranial pressure due to obstruction [61]. Infection is unlikely to be transmitted via organ transplantation, though primary acquisition after a renal transplant has been reported [62].

Donors and recipients who have lived or had prolonged travel to endemic areas, including Mexico, Central and South America should undergo screening for *Trypanosoma cruzi,* the cause of Chagas disease. *T. cruzi* can cause a chronic inflammatory process of the heart, esophagus and colon, leading to diffuse interstitial fibrosis and organ dysfunction. Although transplantation of hearts from donors with Chagas disease is currently not recommended, the safety of lung transplantation from infected donors remains unclear. Currently, successful lung transplantation from a seropositive donor, as well as a case of donor-derived transmission have both been described [63–65].

Conclusion

The success of lung transplantation continues to improve and enhancements in the approach to infectious disease is instrumental to that improvement. While guideline instituted protocols help guide therapy, each regimen should be individually tailored based on history of infection or colonization and balanced with the degree of immunosuppression. With appropriate screening, prophylaxis and peri-operative treatment, as well as rapid identification of new infections, the treatment of lung transplant recipients can continue to be optimized.

Compliance with Ethical Standards

Conflict of interest None.

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