Opportunistic Infections Post-Lung Transplantation: Viral, Fungal, and Mycobacterial

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KEYWORDS

• Lung transplant • Opportunistic infection • Immunocompromised hosts

KEY POINTS

- Comprehensive donor and recipient screening for infection risk pre-transplant can reduce infection incidence post-transplant and guide prophylaxis.
- Certain infections (eg, cytomegalovirus, *Aspergillus*, community-acquired respiratory viruses affecting the lower respiratory tract) are more strongly associated with the development of chronic lung allograft dysfunction; prevention, early diagnosis, and aggressive treatment are critical to preserving long-term allograft function.
- Antifungal prophylaxis strategies are variable across transplant centers; there are supportive data for universal prophylaxis, but available evidence has not proven it to be a clearly superior strategy to preemptive approaches.

INTRODUCTION

Lung transplant recipient (LTR) outcomes have improved significantly but remain inferior to other solid organ transplant (SOT) outcomes despite advances in surgical techniques and immunosuppressive strategies, partly because of infection-related complications.[1] Between the first 30 days and 1-year post-transplant, infections are the leading cause of LTR mortality. Certain infections are associated with the development of acute rejection and chronic lung allograft dysfunction (CLAD).[2] Gram-negative bacterial infections are most common, but viruses, fungi, and mycobacteria are also important contributors to LTR outcomes. Risk factors for infection include continuous exposure of the lung allograft to the external environment, high immunosuppression levels, disruptions to allograft bronchial blood supply, lymphatic drainage, and vagal nerve paths causing impaired mucociliary clearance from airway epithelium changes and decreased cough reflex, and impact of the native lung microbiome in single

This article was previously published in *Clinics in Chest Medicine* 44:1 March 2023.
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Infect Dis Clin N Am 38 (2024) 121–147
https://doi.org/10.1016/j.idc.2023.12.001 **id.theclinics.com**

LTRs.[3,4] Infection risk is mitigated through careful pre-transplant screening of recipients and donors, implementation of antimicrobial prophylaxis strategies, and routine post-transplant surveillance.[5] This review describes common viral, fungal, and mycobacterial infectious after lung transplant and provides prevention and treatment recommendations.

INFECTION SCREENING AND PREVENTION

LTR infections can be derived from the donor, reactivated latent infections in the recipient, or newly acquired (**Fig. 1**). Donors and recipients should undergo thorough pre-

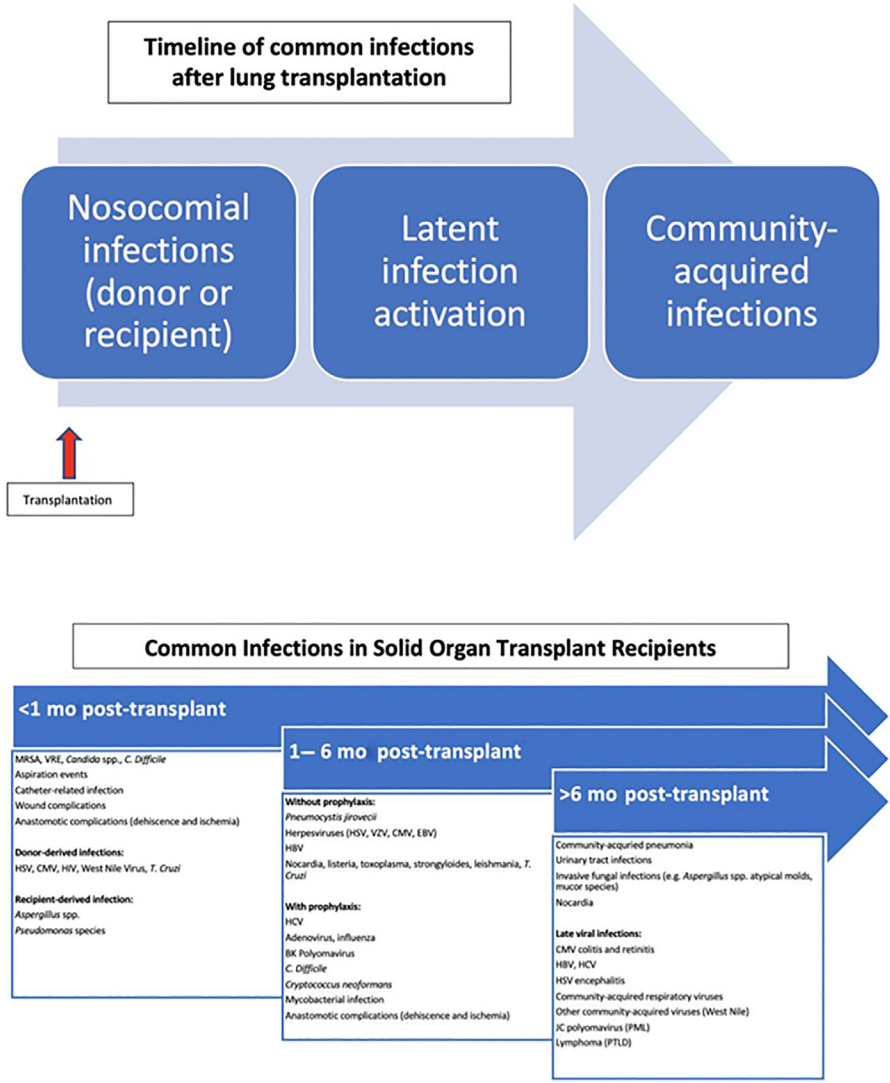

Fig. 1. Types and timing of infections after lung transplantation. (*Modified from* Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357(25):2606.)

transplant evaluation of infection risk. Prior infectious exposures can be ascertained through taking comprehensive medical, social, travel, and immunization histories. Serostatus, sputum, and nucleic acid tests should be confirmed pre-transplant to risk stratify donor to recipient transmission and guide post-transplant infectious prophylaxis (**Table 1**). LTRs with suppurative underlying lung diseases, who have been frequently hospitalized, or who have received broad-spectrum antimicrobials may be colonized with fungi or bacteria. Antimicrobial susceptibilities of colonizing organisms should be known pre-transplant for appropriate perioperative and postoperative antimicrobial selection.[6,7]

Effort should be made to vaccinate potential LTRs when absence of immunity to specific pathogens is identified (**Table 2**). Vaccination timing may be impacted by degree of immunosuppression pre-transplant and post-transplant and transplant urgency. Vaccination may be deferred until immunosuppression levels are significantly reduced post-transplant to better ensure protective immune response. Live attenuated vaccines are contraindicated after SOT.[8–10] Household members and close contacts of LTRs also should adhere to routine immunization schedules.

Infection risk depends on time since transplant surgery. In the first month post-transplant, infections are generally due to donor allograft transmission, reactivation of recipient infections, or acquired from the hospitalization or surgical procedures. Infection risk may be increased in LTRs with comorbid immunodeficiencies or who received immunosuppression pre-transplant. Bacterial infections are most common. Pleural effusions within the first 3 months posttransplant should not be presumed to benign without infection evaluation.[11] Up to 6 months post-transplant, opportunistic infections predominate, though donor-derived infections may still occur. After the first 6 months, infections from broader range bacteria become more common.[12,13]

VIRUSES

Viral infections in LTRs can be grouped into pathogens primarily affecting extrapulmonary tissues (eg, the herpesviruses) and pathogens primarily affecting the respiratory tract (eg, the community-acquired respiratory viruses [CARVs]).

Cytomegalovirus

Cytomegalovirus (CMV) is a ubiquitous herpesvirus that can reactivate from latent infection in SOT recipients; transmission also occurs through allografts or blood product transfusions from CMV-infected donors or close contact with CMV-infected people. Over half of United States adults have serologic evidence of prior CMV infection.[14,15] Owing to relatively increased immunosuppression levels in LTRs and higher viral load transmission from seropositive lung allografts, CMV infection occurs more frequently in LTRs than other SOTs.[16,17] Immunomodulatory effects of CMV increase risks of infection from other opportunistic pathogens, Epstein–Barr virus (EBV)-related post-transplant lymphoproliferative disease, and allograft dysfunction.[18–20] CMV infection is variably associated with acute rejection and CLAD.[21–23] Without antiviral prophylaxis, 54% to 92% of LTRs develop CMV infection or disease.[24,25] Negative serostatus recipients with positive serostatus donors (CMV D+/R-) are at highest risk. CMV D+/R+ recipients have higher rate of infection than CMV D-/R+ recipients (69% and 58%, respectively) due to potential for CMV reactivation or infection with new strains.[26–29] CMV prophylaxis significantly decreases rates of CLAD.[30,31]

CMV disease requires evidence of viral replication in the presence of attributable symptoms or tissue invasion, whereas CMV infection is defined by viral replication regardless of symptom presence.[32] CMV disease most frequently occurs in the early

Table 1
Infection risk screening of lung transplant donors and recipients

Pathogen	Donor and Recipient Screening Test	Special Considerations
Cytomegalovirus (CMV)	CMV Immunoglobulin G (IgG)	
Epstein–Barr virus (EBV)	EBV nuclear antigen, viral capsid IgG	
Varicella-Zoster virus (VZV)	VZV IgG	
Herpes simplex 1 and 2 (HSV-1/HSV-2)	HSV-1 IgG HSV-2 IgG	
Hepatitis B virus (HBV)	HBV nucleic acid test (NAT), anti-HBc antibody, HBsAG	
Hepatitis C virus (HCV)	HCV NAT anti-HCV antibody	Perform testing in LTR immediately before transplant and 4–6 wk post-transplant
HIV	NAT and anti-HIV antibody	Repeat testing in LTR 4–6 wk post-transplant
SARS-CoV-2	Nasopharyngeal PCR	BAL can be considered in donor lung
Measles, mumps, rubella	Measles IgG, mumps IgG, rubella IgG	
Tuberculosis	Tuberculin skin testing (TST) or interferon gamma release assay (IGRA)	TST and IGRA are not validated in donors BAL and sputum can be obtained from donor for AFB smear, culture, and molecular testing Repeat testing in LTR 4–6 wk post-transplant
Treponema pallidum (syphilis)	Venereal Disease Research Laboratory or Rapid Plasma Reagin	
Toxoplasma gondii	Toxoplasma IgG	Toxoplasma IgG
Strongyloides stercoralis	Strongyloides IgG	Can limit screening to endemic areas
	Region Specific Screening	
Pathogen	**Endemic Regions**	**Special Considerations**
Schistosoma spp	Africa, South America, Caribbean, Middle East, southern China, southeast Asia	Cystoscopy may be indicated in renal transplant patients
Trypanosoma cruzi (Chagas disease)	Mexico, Central America, South America	
Leishmania spp	Africa, Asia, Middle East, southern Europe, Mexico, Central America, South America	May cross-react with *T Cruzi*

Coccidioides spp	Southeastern United States, California Central Valley, Mexico, part of Central and South America	
Histoplasma spp	Central and Eastern North America, Central America, South America, Africa, Asia, Australia	
Blastomyces spp.	Midwestern/South-Central/Southeastern United States, Eastern Canada, Africa, South Asia	
HTLV1 and HTLV2	Southern Japan, South America, Caribbean, Middle East, Sub-Saharan Africa, Central Australia, Papua New Guinea	Screening tests may be suboptimal in low prevalence areas
Hepatitis A	Areas with contaminated food and water supply, inadequate sanitation	Consider consultation with infectious diseases experts to determine if testing is indicated

Table 2
Vaccination recommendations for lung transplant recipients

Pathogen Target	Vaccine Type	Current Recommendation	Special Considerations
Influenza	Nonlive	Before and after transplant	Only inactivated, nonlive vaccine should be administered Annual administration to account for changing seasonal strains
Hepatitis B	Nonlive	Before and after transplant if not previously immunized of inadequate immunity	Monitor serostatus to confirm immunity
Hepatitis A	Nonlive	Before and after transplant	
Streptococcus pneumoniae	Nonlive	Before and after transplant if not previously immunized	
Neisseria meningitidis	Nonlive	Before and after transplant for high-risk patients not previously immunized	Risk factors include impaired splenic function and treatment with eculizumab
Haemophilus influenzae	Nonlive	Before and after transplant for high-risk patients not previously immunized	Risk factors include impaired splenic function
Human papillomavirus	Nonlive	Before and after transplant	
Tetanus, diphtheria, pertussis (Tdap)	Nonlive	Before and after transplant	
SARS-CoV-2	Nonlive	Before and after transplant	Boosters should be administrated at recommended intervals
Zoster	Nonlive (recombinant zoster vaccine)	Before and after transplant in LTRs > 19 year old	
Zoster	Live, attenuated zoster vaccine	Before transplant in candidates > 50 year old; *contraindicated posttransplant and in immunosuppressed patients*	
Varicella	Live, attenuated	Before transplant; *contraindicated posttransplant and in immunosuppressed patients*	
Measles, mumps, rubella	Live, attenuated	Before transplant; *contraindicated posttransplant and in immunosuppressed patients*	
Rotavirus	Live, attenuated	Before transplant; *contraindicated posttransplant and in immunosuppressed patients*	

post-transplant period and times of augmented immunosuppression. CMV pneumonitis is the most common presentation in LTRs; characteristics include fever, dyspnea, dry cough, lung function decline on spirometry, and radiographic findings such as ground-glass opacities and patchy consolidations.[33] Some tissue-invasive disease (CMV enteritis) presents with negative serum viral loads. Tissue biopsy with histopathologic findings of CMV inclusion bodies and/or viral antigens confirms diagnosis. Viral shedding in bronchoalveolar lavage (BAL) or bronchial washings cannot be distinguished from tissue-invasive disease and must be interpreted in clinical context.[34–39]

Although no trials have compared the approaches, universal antiviral prophylaxis in the first 6 to 12 months post-transplant with either oral valganciclovir or intravenous ganciclovir is recommended over preemptive serial monitoring of CMV viral loads with initiation of antivirals on viral replication detection.[31,40–42] A recently developed CMV T-Cell immunity panel, measuring CMV-specific CD4+ and CD8+ T-cell immunity by flow cytometry and intracellular cytokine staining has potential to personalize prophylaxis choice and duration and to predict clinically significant CMV events or inability to clear viremia. A measure of 0.2% of CMV reactive CD4+ and CD8+ T cells indicates existing immunity to CMV in a healthy population. The utilization of this test in combination with CMV polymerase chain reaction (PCR) testing is currently being studied in LTRs and could guide treating physicians in deciding continuation of CMV prophylaxis beyond 3 months post-transplant.[43–46]

Ongoing prophylaxis may be considered in CMV D+/R+ or CMV D-/R+ recipients receiving augmented immunosuppression with high-dose glucocorticoids or antilymphocyte antibodies. Myelosuppression is a common treatment toxicity. Oral letermovir lacks the myelosuppressive effects of valganciclovir and has been approved for CMV prophylaxis in hematopoietic stem cell transplant recipients.[47] Successful letermovir use in LTRs has been described in small studies, but there reports of breakthrough viremia and letermovir resistance exist.[48–50]

CMV treatment consists of valganciclovir or ganciclovir and concomitant immunosuppression reduction (particularly in moderate to severe disease). Treatment of asymptomatic viremia to prevent the development of invasive disease is advised. Valganciclovir is equivalent to ganciclovir for mild to moderate disease.[51,52] Ganciclovir is recommended for CMV pneumonitis, with transition to oral medication on clinical and virologic resolution. Treatment duration depends on clinical response and virologic clearance. Antiviral drug dosing should not be reduced if leukopenia emerges because of risk of drug resistance. Treatment with CMV immune globulin (CytoGam) might be considered in severe disease, though data are limited. If no virologic or clinical improvement is observed after 2 weeks of therapy, genotypic resistance testing should be performed.[53–56] The most common mutation conferring resistance is UL97 phosphotransferase. Resistant CMV treatment includes immunosuppression reduction and changing antivirals to foscarnet or cidofovir.[26] Oral maribavir is an alternative salvage treatment of resistant CMV disease approved for use in SOTs, with limited data in LTRs.[56–58] Letermovir can also be considered.

Non-Cytomegalovirus Herpesviruses

Herpes simplex 1 (HSV-1) and HSV-2 disease in LTRs is usually due to reactivation of latent virus in the dorsal root ganglia when herpesvirus prophylaxis is not used.[59] Acyclovir, valacyclovir, or famciclovir should be used in patients not receiving CMV prophylaxis.[60] Patients with limited mucocutaneous infection should be treated with oral medications until lesions are fully healed.[61] LTRs with severe or disseminated infection should be treated with intravenous acyclovir.

Varicella-zoster virus (VZV) infection occurs by airborne acquisition or reactivation from primary infection and presents as herpes zoster in up to 20% of LTRs in the first 5 years post-transplant.[62,63] Prophylaxis is similar in HSV; treatment is with valacyclovir or famciclovir. If lesions progress or new lesions develop despite therapy, treatment should be changed to intravenous acyclovir. Intravenous acyclovir is recommended for primary VZV infection, disseminated disease, or VZV affecting the trigeminal nerve.

Community-Acquired Respiratory Viruses

CARVs are associated with significant morbidity and mortality in LTRs.[64–66] Infection incidence in LTRs may be underestimated because historically studies have been retrospective and only of inpatient populations, whereas severity may be overestimated because studies used culture-based diagnostics in patients with severe respiratory symptoms.[66–68] Seasonal and geographic patterns of CARV infection in LTRs and immunocompetent individuals are similar.[69] Infection prevention strategies generally focus on contact avoidance and isolation and vaccination when available.

Immunosuppression can mute systemic inflammatory responses to CARV infection, and lung function declines from baseline on spirometry might be the sole infection indicators. Radiographic parenchymal abnormalities include ground-glass opacities, tree-in-bud opacities, nodules, and/or airspace consolidations.[70] Progression to lower respiratory tract disease or severe illness increases in LTRs who have had early post-transplant infections and who are receiving augmented immunosuppression or rejection treatment.[64,71]

Definitive diagnosis is achieved through testing respiratory tract samples. Initial testing should be through nasopharyngeal swab or washing and include a wide range of viruses to account for high likelihood of coinfection. Available tests and techniques vary by institution. Washings are more sensitive than swabs.[72] Molecular diagnostic tests are more sensitive than viral culture, direct fluorescent antibody, or rapid antigen detection in symptomatic and asymptomatic immunocompromised patients in outpatient and inpatient settings.[73–78] If initial testing is negative but clinical suspicion remains high, repeat confirmatory testing is advised, particularly if effective antiviral therapeutics are available. BAL may be indicated. When prolonged viral shedding is detected, serial quantitative molecular testing can guide treatment responsiveness.[79]

CARV infection stimulates cytokine and chemokine production that attracts damaging inflammatory cells, thereby changing mucosal epithelium integrity and composition.[80–83] Risk of secondary infection with locally invading bacterial or fungal airway colonizers is increased. Local alloantigen production can incite immune-mediated injury leading to episodes of acute rejection and CLAD development.[84,85] High BAL chemokine concentration prognosticates significant forced expiratory volume in the first second (FEV1) decline 6 months after initial infection.[86] CARV infections (particularly in the lower respiratory tract) are independent risk factors for CLAD, but contemporary studies have failed to demonstrate a strong relationship to acute rejection, possibly because most studies are retrospective single center analyses with variable definitions of acute rejection.[87–96] As expected host response to viral infection is perivascular lymphocytic infiltrate, the presence of lymphocytes on allograft biopsy can signify appropriate response to infection or rejection.

Influenza

LTRs have the highest incidence of influenza among SOTs. Unlike in immunocompetent patients, antiviral therapies are advised for all LTRs with suspected or confirmed influenza infection, regardless of illness severity or interval between symptom onset and diagnosis, due to secondary infections and rejection risks.[79,97] Confirmatory

testing to guide antiviral therapy should be obtained when drug resistance is a concern. Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) are typical first-line treatments; M2 inhibitors (amantadine, rimantadine) are no longer recommended because of resistance and inactivity.[74,98] Therapy should continue until viral shedding is undetectable. Resistance testing should be performed in patients with prolonged symptom duration or clinical deterioration with ongoing viral shedding; empiric treatment with alternative antivirals should be considered while awaiting testing results. Antiviral prophylaxis is generally avoided to minimize development of resistance, except in LTRs likely to have inadequate immunity due to augmented immunosuppression or recent transplantation.[79]

Adenovirus

Adenovirus infection can be acquired throughout the year or reactivate from latent childhood infection to cause pneumonia or disseminated disease.[99] Mild disease is generally managed through immunosuppression reduction. Disseminated disease carries 50% mortality. Cidofovir is recommended for severe pneumonia or disseminated disease. Treatment can cause nephrotoxicity, neutropenia, and Fanconi-type anemia. Weekly quantitative serum viral load is recommended in addition to serial monitoring of renal function, serum electrolytes, and urine protein content.[100]

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a common cause of childhood bronchiolitis that carries 10% to 20% mortality in LTRs. Infection ranges from mild upper respiratory to severe lower respiratory tract disease associated with allograft dysfunction.[101,102] Prophylaxis with palivizumab can be considered. Ribavirin has in vitro activity against RSV; limited data in LTRs suggest ribavirin, with or without concomitant glucocorticoids or intravenous immunoglobulin (IVIG), successfully prevents progression to lower respiratory infection.[103,104]

Human metapneumovirus

Human metapneumovirus has similar presentation to RSV infection in LTRs and has been associated with allograft dysfunction. The main therapy is supportive care; ribavirin with or without IVIG has been used in few severe cases with successful outcome.[102,105]

Parainfluenza

Parainfluenza infects up to 10% of LTRs, with peak seasonal distribution in spring and summer. Infection is usually mild but can progress to severe lower respiratory tract illness and be associated with CLAD.[106,107] Ribavirin has been used in few reported cases with successful outcome.[108] Antivirals, adjunctive steroids, and IVIG generally have not proven beneficial.[71]

FUNGAL INFECTIONS

Invasive fungal infections (IFIs) have an 8% to 10% yearly cumulative incidence in LTRs. *Aspergillus* and *Candida* spp are the most common causative organisms; other culprits include the geographically endemic mycoses (*Histoplasma, Blastomyces,* and *Coccidioides* spp), *Pneumocystis*, *Cryptococcus* spp, mucormycosis agents, and non-*Aspergillus* molds (*Scedosporium* and *Fusarium* spp).[109] Incidence and type of IFI are influenced by immunosuppression intensity, pre-transplant airway colonization and ischemia, microbiome alterations from antimicrobial usage, timing since transplant, and antifungal prophylaxis. Invasive *Candida* spp (IC) infections typically occur in the early post-transplant period as complications associated with surgery,

hospitalization, and ICU length of stay. Most non-*Candida* IFIs are acquired through inhalation or develop from recipient airway colonization. *Aspergillus* infections occur most frequently within the first 6 to 12 months posttransplant.[109] Non-*Aspergillus* mold infections occur later post-transplant and are associated with significantly higher mortality than *Aspergillus* (60.5% vs 39.5%, respectively).[110] IFIs are notably associated with allograft dysfunction. *Aspergillus* colonization is an independent risk factor for CLAD.[111] IFI testing and treatment is summarized in **Table 3**.

For all suspected IFIs, early bronchoscopy is recommended to evaluate anastomotic integrity, inspect airways for tracheobronchial abnormalities (pseudomembranes, erythema, ulcerations, or necrosis), and obtain BAL. Anastomotic dehiscence can be confirmed by chest imaging. Cavitary and nodular lesions are characteristic radiographic features. Cultures and fungal stains are positive in 50% to 70% of cases.[112] *Aspergillus* BAL PCR sensitivity is over 90% but testing cannot distinguish between infection and colonization.[113] Definitive IFI diagnosis necessitates tissue biopsy for visualization of fungal presence or tissue invasion at the suspected infection site.

Galactomannan antigen and 1,3-beta-D-glucan serum assays have variable utility in diagnosing IFIs in LTRs. Galactomannan is a cell wall component of *Aspergillus* sp released during fungal replication that can be detected in serum using enzyme immunoassay (EIA).[114] Serum galactomannan sensitivity is greatest in severely neutropenic patients because preserved immune systems consume circulating galactomannan; sensitivity in LTRs is 30%, versus over 70% in hematopoietic stem cell transplants.[115,116] In BALs of nonneutropenic SOT recipients, sensitivity increases to 88%.[114] Serum and BAL specificity are over 90% in all patients.[115,117,118] Galactomannan EIA cross-reactivity can occur with non-*Aspergillus* molds (*Fusarium* and *Penicillium*) and penicillin antibiotics (less so recently due to improved antibiotic purification).[109] The 1,3-beta-D-glucan is present in most fungal cell walls and particularly abundant in *Candida* spp; 1,3-beta-D-glucan sensitivity and specificity for IC is 80% and 60%, respectively. Patients with *Pneumocystis* pneumonia also have characteristically high levels; 1,3-beta-D-glucan is notably absent in cell walls of *Blastomyces*, *Cryptococcus*, and *Mucorales*. Falsely elevated levels of 1,3-beta-D-glucan can occur in patients on hemodialysis or who have received blood transfusions and intravenous immunoglobulin.[119,120] There is paucity of evidence on 1,3-beta-D-glucan testing in LTRs, and it is best used as a diagnostic adjunct in clinical context.

Prophylaxis strategies targeting both *Candida* spp and molds vary among transplant centers.[116] Questions remain regarding universal versus preemptive prophylaxis, choice of drug, need for monotherapy versus combination therapy, and prophylaxis duration. Studies of IFI prophylaxis have been limited by retrospective, single-center, and nonrandomized designs.[121] Some transplant centers begin universal antifungal prophylaxis immediately post-transplant, whereas others limit prophylaxis to recipients with high risk for IFIs (underlying cystic fibrosis or bronchiectatic lung diseases, evidence of airway colonization, primary graft dysfunction, and history of CMV infection).[122–126] Data on superiority of either strategy are mixed.[127–129] Most centers use monotherapy with aerosolized amphotericin B, or systemic voriconazole or itraconazole; the remainder use combination therapy with inhaled and systemic antifungals. Isavuconazole has been demonstrated to be a safe and effective alternative agent.[130] Duration of prophylaxis varies from 3 to over 12 months post-transplant. In one large retrospective study, incidences of IC and mold IFI were greater than previously reported despite micafungin and amphotericin B prophylaxis, suggesting breakthrough infection because of inadequate tissue penetration of echinocandins, reduced systemic drug concentration in the presence of ECMO circuits, and resistance to

Table 3
Diagnosis and treatment of invasive fungal infections in lung transplant recipients

Pathogen	Diagnostic Tests	Treatment	Special Considerations
Aspergillus sp	• Cultures • Histopathology • Serum galactomannan • BAL galactomannan • Serum PCR: single negative test rules out IA; two positive tests help rule in IA • BAL PCR: Identifies the presence of mold but cannot distinguish infection from colonization without appropriate clinical context • 1,3-beta-D-glucan variably helpful	First-line for IA: voriconazole Alternative agents: • Azoles: posaconazole, isavuconazole • Echinocandins: caspofungin, anidulafungin • Combination therapy can be considered Tracheobronchitis: inhaled amphotericin B in combination with systemic therapy	Treatment considerations: • Azoles: monitoring of hepatic function and calcineurin/mTOR inhibitor levels is advised • Liposomal amphotericin: monitoring of electrolytes, renal and hepatic function is advised • Caspofungin and micafungin: monitoring of hepatic function is advised • Anidulafungin and caspofungin: role as single agent therapy is controversial
Candida spp.	• Cultures • Histopathology • 1,3-beta-D-glucan can be helpful in clinical context T2 Candida assay (detects whole blood Candida cells of the 5 most common species with high sensitivity and specificity) • PCR testing not clinically available	IC and candidemia: • Echinocandins (micafungin, anidulafungin) are initial empiric therapy • Fluconazole as empiric therapy when azole resistance is not a concern • Liposomal amphotericin B Mild oropharyngeal disease: • Clotrimazole, fluconazole • Nystatin Endovascular infection/implantable Device infection: • Liposomal amphotericin B as initial therapy	• Trimethoprim-sulfamethoxazole (TMP-SMX): correct for renal function and maintain adequate hydration • Pentamidine side effects include pancreatitis, hypo- and hyperglycemia, myelosuppression, renal failure, electrolyte disturbances • Avoid primaquine and dapsone in G6PD deficiency

(*continued on next page*)

Table 3
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Pathogen	Diagnostic Tests	Treatment	Special Considerations
		• High-dose echinocandin as alternative therapy	
Mucormycosis	• Mucorales PCR is not clinically available • Cultures grow within 24–48 h • Cultures might be negative despite positive tissue staining • Galactomannan notably not useful	Invasive mucormycosis: • Induction therapy with high dose liposomal amphotericin B • Combination of liposomal amphotericin B with echinocandin or posaconazole can be considered for refractory cases but data are weak • Posaconazole or isavuconazole can be used in patients not tolerating amphotericin but data are weak • Surgical excision and debridement for all extrapulmonary manifestations	
Cryptococcus	• Cryptococcus antigen testing of CSF and serum • CSF culture and stain • BAL culture and stain • Biopsy whenever possible	CNS disease: • Induction with liposomal amphotericin B and flucytosine for 2–4 wk • Consolidation with high-dose fluconazole for 8 wk • Maintenance with lower dose fluconazole for a year • Lumbar puncture as needed to relieve elevated intracranial pressure Pulmonary disease: • Asymptomatic or mild to moderate disease: Fluconazole for 6–12 mo • Severe pulmonary disease: same as CNS treatment	

Fusarium	• Cultures • Histopathology	Invasive fusariosis: • No treatment is clearly superior; voriconazole is typically first line • Amphotericin B in combination with voriconazole for resistant cases • Posaconazole as alternative • Surgical excision and debridement where indicated
Scedosporium	• Cultures • Histopathology	Invasive scedosporiosis • Voriconazole is first line • Amphotericin B, voriconazole, posaconazole, isavuconazole are all options and can be considered in combination • Surgical excision and debridement
Pneumocystis jirovecii	• BAL or tissue biopsy • Immunofluroscent assays are the most sensitive diagnostics • Nucleic acid testing in BAL cannot distinguish colonization from disease without clinical context • Silver stain on BAL excludes *Pneumocystis* pneumonia (PCP) if negative • LDH is nonspecific • 1,3-beta-D-glucan can be a helpful adjunct but is not specific for PCP	*Pneumocystis* Pneumonia: • Trimethoprim–sulfamethoxazole is first-line treatment • Alternatives: inhaled pentamidine: dapsone and trimethoprim • For mild to moderate disease only: atovaquone; combination primaquine and clindamycin • Combination echinocandins and TMP-SMX have shown benefit in animal models but clinical benefit is unknown • Adjunctive steroids are not clearly beneficial in non-HIV populations

inhaled amphotericin B. A recent meta-analysis of 12 antifungal prophylactic strategies among 13 studies did not establish a strong recommendation for a particular regimen.[131,132]

Aspergillus

Aspergillus spp is the most common cause of IFIs after lung transplantation. Owing to higher immunosuppression levels, invasive aspergillosis (IA) occurs more frequently in LTRs than other SOTs. Other risk factors include airway ischemia and prior airway colonization. *Aspergillus fumigatus* most commonly causes IA; other causative species include *Aspergillus terreus* (notable for in vitro resistance to amphotericin B), *Aspergillus flavus*, and *Aspergillus niger*. *Aspergillus* infection can present as tracheobronchitis, anastomotic dehiscence, pneumonia, aspergilloma, and disseminated disease to the sinuses, central nervous system (CNS), spine, pleural or pericardial spaces, or skin. Tracheobronchial aspergillosis typically occurs within 3 months posttransplant with fever, cough, wheezing, hemoptysis, or can be asymptomatic. Pulmonary aspergillosis generally presents 6 months post-transplant.[133,134] Single LTRs are at an increased risk of developing IA posttransplant and consequently experience higher mortality than bilateral or combined heart-LTRs. Among bilateral LTRs cystic fibrosis patients are at higher risk of aspergillosis.[133,135,136]

Voriconazole is the preferred initial treatment for IA; alternative agents include caspofungin and isavuconazole.[137] Azoles increase levels of tacrolimus, cyclosporine, and sirolimus; therefore, immunosuppression reduction and close serum drug concentration monitoring is required during treatment. Nebulized amphotericin B can be an adjunct therapy at the devascularized anastomotic site in tracheobronchial aspergillosis. Anastomotic debridement of necrotic tissue or debris is necessary when there is a threat of airway obstruction. Severe pulmonary and disseminated aspergillosis is typically treated in combination with echinocandins. Treatment duration is not well established but at least 3 months is advised with therapy extension if there is no clinical improvement.

Candida

Candida spp is the second most common cause of IFIs in LTRs. Infections typically occur within the first 3 months post-transplant and are associated with prolonged hospital exposure or critical illness, indwelling catheters, prolonged antibacterial therapy, and neutropenia.[138] Presentation ranges from candidemia to deep tissue infection in the pleural space and at the incision or anastomoses. Although *Candida* is frequently isolated from sputum and BAL specimens, invasive pulmonary disease is rare. Species identification is crucial for guiding treatment because of variable antifungal therapy resistance (fluconazole resistance in *C krusei*; dose-dependent susceptibility to fluconazole and amphotericin, respectively *C glabrata* and *C lusitaniae*). Echinocandins (micafungin, caspofungin) are suggested initial empiric therapy; high-dose fluconazole can alternatively be used in mild to moderate IC with low risk for *glabrata*, pending organism identification. Prompt source control including removal of infected catheters improves outcomes.

Mucormycosis

Mucormycosis is the third most common IFI in LTRs in the first-year post-transplant (2% incidence) and carries high morbidity and mortality (76% in pneumonia, 95% in disseminated disease). *Rhizopus*, *Mucor*, and *Rhizomucor* are the most implicated organisms.[139] Disease can be pulmonary, rhinocerebral, gastrointestinal, cutaneous, anastomotic, or disseminated. Fungal cell wall biomarkers are classically negative,

making diagnosis challenging. Successful treatment depends on early diagnosis and resection of involved tissue when there is evidence of vascular invasion and tissue necrosis.

Cryptococcus

Yearly cumulative incidence of *Cryptococcus* in LTRs is under 1%, but infection risk is higher than other SOTs. Disease onsets within the first 6 to 12 months posttransplant; presentation can be pulmonary or disseminated. Concomitant immunosuppression reduction at the initiation of antifungal therapy is associated with the development of immune reconstitution inflammatory syndrome (IRIS).[140,141]

Non-Aspergillus Molds

Fusarium spp are environmentally ubiquitous but uncommonly pathogenic in LTRs; when they cause IFIs, mortality is high (65% in disseminated disease). Infection occurs through inhalation or mucosal or cutaneous invasion with potential for hematogenous spread.[142] LTRs, especially those with underlying cystic fibrosis (CF), are at increased risk for focal or disseminated IFI with *Scedosporium*. Treatment involves voriconazole, immunosuppression reduction, and surgical debridement.

Pneumocystis Jirovecii

Immunocompromised hosts with depleted T-cell immunity are at increased risk for *Pneumocystis* infection. LTRs are at higher risk than other SOTs. Before universal prophylaxis with trimethoprim–sulfamethoxazole, incidence of *Pneumocystis* pneumonia in LTRs ranged from 10% to 40%; lifelong prophylaxis reduces incidence to 5%.[143,144] Diagnostic testing sensitivity is decreased in LTRs because of reduced organismal burden in non-HIV patients with severe infection.[145]

Endemic Fungi

Infection with *Histoplasma*, *Coccidioides*, and *Blastomyces* may be reactivation of latent recipient infection, transmitted from donors from endemic areas, or acquired de novo from the environment. LTRs are more likely to present with severe pneumonia and disseminated disease.[146]

MYCOBACTERIAL INFECTIONS

Over 200 species of genus *Mycobacterium* exist with wide heterogeneity in prevalence, pathogenicity, and management. Mycobacteria are further divided into species complexes, the most notable being *Mycobacterium tuberculosis* complex which causes tuberculosis (TB). Active pulmonary TB affects more than 10 million people worldwide, and number of latent infections exceeds that. Nontuberculous mycobacteria (NTM) are ubiquitously found in soil and water and more frequently encountered in areas with low TB prevalence. Most NTM infections arise from environmental exposure, though nosocomial infections have also been described.[147,148]

Tuberculosis

Incidence of active TB in LTRs is less than 2% but mortality is highest among SOTs; mortality in all SOT is between 10% and 20%.[149,150] All donors and LTRs should be screened with tuberculin skin test (TST) or interferon gamma release assay (IGRA) and preferably treated for latent TB infection (LTBI) pre-transplant. Transplant urgency may preclude full treatment pre-transplant; if active TB is excluded, LTBI is not a contraindication for transplant and treatment should continue post-transplant.[151,152]

Negative recipients should undergo repeat IGRA testing at an interval post-transplant to verify donor transmission (noting that IGRA sensitivity is decreased with immunosuppression). LTBI treatment options are isoniazid for 9 months, rifampin for 4 months, or combination therapy with isoniazid and rifapentine for 3 months; rifampin and rifapentine are generally avoided post-transplant because of immunosuppressant drug interactions.

Active TB is an absolute contraindication for transplant because of dissemination risk and poor outcomes post-transplant.[153,154] It is not clear when a patient who has been successfully treated for active TB can safely undergo transplant. Diagnosing active TB after SOT can be difficult because of muted immune response, atypical radiographic presentation, and difficulty isolating organisms in culture; late diagnosis increases disseminated disease risk. First-line treatment of susceptible active TB is combination therapy with isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by at least an additional 4 months of rifampin and isoniazid.[155] Prolonged treatment is challenging because of drug toxicities and immunosuppressant interactions.

Nontuberculous Mycobacteria

NTM infection incidence in LTRs may be underestimated due to asymptomatic colonization and lack of reporting to public health agencies. Difficulty in diagnosis and treatment leads to significant morbidity and mortality. There is no clear association between NTM infection and CLAD. LTRs colonized or infected with NTM pretransplant should receive multidrug treatment to reduce disease burden; delay of transplant to complete at least 6 months of therapy can be considered.[156] Infection generally occurs 12 months posttransplant.[157,158] *Mycobacterium avium* complex species are the most common causative organisms. *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium kansasii* are most frequently associated with disseminated infection.[159] *M abscessus* is a virulent, fast growing NTM notable for human-to-human transmission among CF patients and high mortality without significant allograft dysfunction.[160,161] CF patients are at higher risk for NTM infection; risk increases with chronic macrolide therapy or airway colonization with *Pseudomonas aeruginosa* or *Burkholderia cepacia*.[162–164] CF patients with pretransplant *M abscessus* colonization have higher rates of disseminated infection.[165]

Symptoms depend on organism and infection site. In all SOTs, pleuropulmonary disease is the most common presentation with features including chronic productive cough, occasional hemoptysis, and nodular, bronchiectatic, or cavitary parenchymal abnormalities on imaging.[166] Cutaneous, musculoskeletal, and disseminated infection can occur. Immunosuppression might mute expected constitutional symptoms. Treatment is based on distinguishing NTM colonization from disease. Positive BAL acid-fast bacilli (AFB) culture can represent infection or contaminant from the laboratory or environment.[164] Molecular testing is available for some NTM species. Suspicious dermatologic lesions should be evaluated by skin biopsy with AFB staining and culture. The presence of virulent NTM such as *M abscessus* is highly suspicious for infection.

There are limited data and no randomized trials on NTM treatment in LTRs. Initial management involves combination therapy with multiple antimycobacterial drugs and surgical resection for complicated skin or soft tissue involvement. Typical combination therapies can include macrolides, rifamycins, ethambutol, isoniazid, fluoroquinolones, linezolid, tetracyclines, or aminoglycosides for duration of months to years depending on infection site and severity. Treatment is generally longer in LTRs than immunocompetent patients to prevent relapse.[156,167] Bacteriophages are being

investigated as potential therapeutic options for management of drug resistant NTM.[168] Immunosuppression reduction should be considered with caution because of risk of IRIS. A minimum 12 months of treatment following negative sputum cultures is recommended for pulmonary disease. At least 4 to 6 months of therapy is recommended for focal soft tissue or bone infections. The rifamycins, particularly rifampin, reduce serum concentration of tacrolimus, cyclosporine, sirolimus, and everolimus through cytochrome p450 induction. Careful immunosuppressive drug monitoring and adjustment must be made to prevent rejection. Macrolides such as clarithromycin can increase serum concentrations of calcineurin inhibitors and sirolimus through cytochrome p450 inhibition; azithromycin is less likely to cause this effect. Outcomes of treatment are not well established due to relatively low incidence of infection.

SUMMARY

LTR outcomes are compromised by the wide range of infections to which the allograft is exposed. Comprehensive pre-transplant screening and careful post-transplant prophylaxis can mitigate infection risk and prevent infectious complications including development of allograft dysfunction. Future research in infection prevention, diagnostics, and therapeutics can further reduce LTR morbidity and mortality from infection.

CLINICS CARE POINTS

- Risk factors for infection in lung transplant recipients (LTRs) include continuous exposure of the lung allograft to the external environment, high levels of immunosuppression, impaired mucociliary clearance from airway epithelium changes due to disruptions in allograft blood supply and lymphatic drainage, and impact of the native lung microbiome in single LTRs.
- In the first month post-transplant, infections are generally due to donor allograft transmission, reactivation of recipient infections, or acquired from the hospitalization or surgical procedures; bacterial infections are the most common.
- Up to 6 months post-transplant, opportunistic infections predominate, though donor-derived infections may still occur; after the first 6 months, infections from broader range bacteria become more common.
- Comprehensive donor and recipient screening for infection risk pre-transplant, and vaccination of potential LTRs when absence of immunity to specific pathogens is identified, can reduce infection incidence post-transplant and guide prophylaxis choice and duration.
- Cytomegalovirus, *Aspergillus*, and community-acquired respiratory viruses affecting the lower respiratory tract are among the infections more strongly associated with the development of chronic lung allograft dysfunction; prevention, early diagnosis, and aggressive treatment are critical to preserving long-term allograft function.
- There are supportive data for the use of universal antifungal prophylaxis in lung transplant recipients, but available evidence has not proven it to be a clearly superior strategy to preemptive approaches in preventing invasive fungal infections, and antifungal prophylaxis strategies are variable across transplant centers

DISCLOSURE

The author has nothing to disclose.

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