Fungal Infections After Lung Transplantation

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KEYWORDS

• Solid organ transplantation • Lung transplantation • Fungal infection • Fungal prophylaxis

KEY POINTS

- Incidence of invasive fungal infections after lung transplantation is variable, with a mean of 8.6%.
- Prevention is a key management strategy for lung transplant recipients with most lung transplant centers providing antifungal prophylaxis for at least 3 months to 6 months postoperatively.
- Although prophylaxis drug regimens vary, common themes include the use of an azole therapy with or without inhaled amphotericin B product (to prevent invasive molds and yeast infections) and trimethoprim-sulfamethoxazole (to prevent *Pneumocystis jirovecii*).
- Manifestations of invasive fungal disease include pneumonia, pleural/mediastinal space infections, anastomotic infections, and disseminated disease.

INTRODUCTION

The first lung transplant was performed in 1963.[1] Since then, lung transplantation has emerged as a potential lifesaving treatment modality for end-stage chronic obstructive pulmonary disease, interstitial lung disease, pulmonary hypertension, and cystic fibrosis. Since 1988, more than 32,224 lung transplantations have been performed in the United States.[2] The median survival after adult lung transplantation is approximately 50% at 5 years.[2]

Survival after lung transplantation is influenced by the occurrence of 2 major complications — allograft rejection and infection (and their complications). In an effort to improve allograft survival, lung transplant recipients are maintained on an often-intense immunosuppressive drug regimen to prevent rejection and maintain allograft function. The downside of this practice, however, is a heightened risk of opportunistic infections, including invasive fungal disease.[3] Up to 8.6% of patients develop invasive fungal infections during the first year after lung transplantation, although the incidence rates reported in clinical studies have varied widely depending on multiple factors, such as patient exposures, patient populations, immunosuppressive drug use, center-dependent practices (including the use of antifungal and other antibiotic prophylaxis), duration of study follow-up, and definitions of invasive fungal infection, among other factors.[3–5]

MICROBIOLOGY AND CLINICAL MANIFESTATIONS

The most common pathogens that cause invasive fungal infections after lung transplantation are *Aspergillus* spp (44%, most commonly *Aspergillus fumigatus*), *Candida* spp (23%, most commonly *C albicans*), and other molds, such as *Scedosporium* spp (20%). Members of the *Mucorales* group (3%,

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including *Mucor* and *Rhizopus*), *Cryptococcus neoformans* (2%), and the endemic mycoses (1%, including *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*) account for only a small proportion of cases.[3–6] The incidence of *P jirovecii* was up to 15% (in the absence of prophylaxis) but this has declined remarkably with the widespread use of prophylaxis.[7]

A majority of invasive fungal infections occur during the first 3 months to 12 months after lung transplantation. Depending on the specific pathogen and associated risk factors, mold infections manifest clinically as ulcerative tracheobronchitis, invasive pulmonary parenchymal disease, disseminated multiorgan disease, and/or fungemia. *Candida* spp infections, on the other hand, often cause fungemia, mediastinitis, and pleural space infection. *Cryptococcus neoformans, H capsulatum*, and *Coccidioides immitis* cause pneumonia, with tendency to disseminate to other organ systems, including the brain. *P jirovecii* also typically causes pneumonia that manifests with nonproductive cough, hypoxemia, and bilateral interstitial infiltrates. A diagnosis of invasive fungal infections after lung transplantation can be established by demonstration of the fungi in affected tissues. This can be accomplished with culture of blood, respiratory fluid, and other clinical samples; antigen detection in blood, respiratory fluid, and other clinical samples (eg, galactomannan, 1,3-β-D-glucan, and cryptococcal antigen); nucleic acid testing of clinical samples; and demonstration of the fungal pathogen in affected tissues.[6]

Collectively, invasive fungal infections directly and indirectly contribute to the poor outcome after lung transplantation.[3–6] They have been associated with a higher risk of bronchiolitis obliterans.[8] The mortality rate is also generally higher, especially in those with invasive and disseminated disease. Historically, the mortality rate is up to 25% among those with fungal tracheobronchitis compared with up to 80% among those with invasive pulmonary aspergillosis.[3,4,6,7] These rates have declined with the use of more effective antifungal drugs. Currently, the overall 3-month mortality rate is up to 22% of all lung transplant recipients with invasive fungal infection,[9] whereas 1-year mortality is up to 44%.[10]

RISK FACTORS

There are several host and environmental factors that increase the risk for invasive fungal infection after lung transplantation. The constant exposure of the transplanted lung to the environment and the abnormal anatomic and physiologic function of the transplanted lung (ie, impaired ciliary function, blunted cough reflex, and denervation injury) predispose to a higher risk of invasive fungal infections. Invasive aspergillosis and other mold infections are more common in older patients, those who have airway ischemia, those who developed cytomegalovirus disease, and those with colonization with *Aspergillus* spp.[11–13] Those who received single lung transplants are also at higher risk of invasive fungal infection compared with double lung transplant recipients, because the retained lung (in single lung transplants) can serve as reservoir for potentially pathogenic fungi. Patients with structural lung diseases, such as cystic fibrosis, are often colonized with fungi, most commonly *Aspergillus* spp, prior to lung transplantation and they have a 4-fold higher risk of invasive aspergillosis.[14] Colonization of the paranasal sinuses can also serve as reservoir for fungal colonization in patients with cystic fibrosis. The need for bronchial stents also predisposes to higher risk of invasive fungal infections, including *Candida* spp and *Aspergillus* spp. An overimmunosuppressed state increases the risk, including those with neutropenia, hypogammaglobulinemia, and T-cell depletion. Lung transplant recipients are especially vulnerable to infection with fungi due to the constant direct exposure of the lung allograft to the outside environment. Environmental exposure is a well-described risk factor for invasive mold infections, especially in areas of farming and construction.[15,16]

PREVENTION

Because of the increased risk of invasive fungal infection, and its association with adverse outcomes,[3] its prevention is a standard of care after lung transplantation. Minimizing environmental exposures, such as avoidance of areas with high concentration of fungal spores (eg, areas of construction) and the use of personal protective equipment (such as masks) during anticipated periods of exposure, are recommendations to reduce the risk. In addition, minimization of indwelling urinary catheters and indwelling central vascular lines help with prevention of *Candida* spp fungemia and funguria in the perioperative period. Preventing invasive fungal infection can further be accomplished with antifungal drugs for either prophylaxis or preemptive therapy. The drugs that are used for prevention are listed in **Table 1**.

There is no widely accepted optimal method for prevention, partly due to lack of comparative clinical trials among various strategies. In worldwide surveys conducted among lung transplant centers, only 31% to 36% of centers perform preemptive

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