Review Article on Lung Transplantation: Past, Present, and Future

Fungal infections in lung transplantation

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Abstract: Lung transplant is a potential life-saving procedure for chronic lung diseases. Lung transplant recipients (LTRs) are at the greatest risk for invasive fungal infections (IFIs) among solid organ transplant (SOT) recipients because the allograft is directly exposed to fungi in the environment, airway and lung host defenses are impaired, and immunosuppressive regimens are particularly intense. IFIs occur within a year of transplant in 3–19% of LTRs, and they are associated with high mortality, prolonged hospital stays, and excess healthcare costs. The most common causes of post-LT IFIs are Aspergillus and Candida spp.; less common pathogens are Mucorales, other non-Aspergillus moulds, *Cryptococcus neoformans*, *Pneumocystis jirovecii*, and endemic mycoses. The majority of IFIs occur in the first year following transplant, although later onset is observed with prolonged antifungal prophylaxis. The most common manifestations of invasive mould infections (IMIs) include tracheobronchial (particularly at anastomotic sites), pulmonary and disseminated infections. The mortality rate of tracheobronchitis is typically low, but local complications such as bronchomalacia, stenosis and dehiscence may occur. Mortality rates associated with lung and disseminated infections can exceed 40% and 80%, respectively. IMI risk factors include mould colonization, single lung transplant and augmented immunosuppression. Candidiasis is less common than mould infections, and manifests as bloodstream or other non-pulmonary invasive candidiasis; tracheobronchial infections are encountered uncommonly. Risk factors for and outcomes of candidiasis are similar to those of non lung transplant recipients. There is evidence that IFIs and fungal colonization are risk factors for allograft failure due to chronic rejection. Mould-active azoles are frontline agents for treatment of IMIs, with local debridement as needed for tracheobronchial disease. Echinocandins and azoles are treatments for invasive candidiasis, in keeping with guidelines in other patient populations. Antifungal prophylaxis is commonly administered, but benefits and optimal regimens are not defined. Universal mould-active azole prophylaxis is used most often. Other approaches include targeted prophylaxis of high-risk LTRs or pre-emptive therapy based on culture or galactomannan (GM) (or other biomarker) results. Prophylaxis trials are needed, but difficult to perform due to heterogeneity in local epidemiology of IFIs and standard LT practices. The key to devising rational strategies for preventing IFIs is to understand local epidemiology in context of institutional clinical practices.

Keywords: Invasive fungal infection (IFI); lung transplant; antifungal prophylaxis

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Introduction

Lung transplantation (LT) has become a potential life-saving procedure for a wide range of end-stage lung diseases. The number of LTs worldwide is increasing every year. In the USA alone, there were 2,714 LTs performed in 2019, a 7.3% increase from previous year and the highest yearly number to date (https://unos.org/data/transplant-trends/, https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/). Although LT increases the life span and quality of life of patients with advanced lung diseases, outcomes after LT remain inferior to those of other solid organ transplants (SOT). The median survival after LT is 78% and 51% at 1-year and 5-years, respectively (https://www.nhlbi.nih.gov/node/3963). High incidence of rejection and infectious complications, especially within the first year of transplantation, contribute to high morbidity and mortality in lung transplant recipients (LTR). While advances in immunosuppressive regimens in the last decade reduced the rates of rejection and increased graft survival, these improvements came at the expense of increased rates of opportunistic infections. Invasive fungal infections (IFI) are frequent complications after LT, causing significant morbidity and up to 3-fold increases in all-cause mortality (1,2). In addition, IFIs lead to excess lengths of stay ranging from 13.6 to 23.5 days, and excess costs ranging from $44,243 to $70,260 depending on the transplant type (3,4). Although antifungal prophylaxis is routinely administered in most LT centers in the USA, there is no consensus on the best agent, or optimal duration, and cost-effectiveness of different antifungal prophylaxis strategies (5). In this review, we will discuss the epidemiology, clinical spectrum, risk factors, short- and long-term outcomes of IFI, and antifungal prophylaxis strategies in LTRs.

Epidemiology and microbiology

IFIs are among the most common opportunistic infections in LTR, with cumulative incidence of 3% to 19% within the first year of LT (1,6-10). These rates are second only to small bowel transplant recipients among all SOT (8). However, the epidemiology of IFIs in LTRs varies greatly between centers, as do LT practices (e.g., types of patient populations transplanted, transplant selection criteria at individual centers, and types of immunosuppression, antifungal prophylaxis and other post-transplant care) and regional environmental factors. Therefore, the first step in devising rational strategies to manage or prevent IFIs is to understand local epidemiology in the context of current practices.

The most common etiologic agents of IFI among LTRs are Aspergillus (44%) and Candida (23%) spp. Members of the Mucorales family (3%), *Cryptococcus neoformans* (2%), *Pneumocystis jirovecii* (2%) and endemic dimorphic fungi (1%) are less common (6,8,11-14) (*Table 1*). Among *Aspergillus* spp, *A. fumigatus* is the most common, with rates of IFIs ranging from 2% to 30% (15-17). Recent studies show emergence of non-*Aspergillus* moulds (e.g., *Scedosporium apiospermum* (most common), *Fusarium* spp, *Mucorales spp*., *Paecilomyces* spp. and *Penicillium* spp), which accounted for 28% of all IMIs (8,10,18-21). IMIs due to non-Aspergillus moulds are more common among LTR than recipients of other SOTs, and they are associated with higher rates of dissemination and mortality than infections due to Aspergillus (8). In part, the higher mortality may be due to a propensity to antifungal resistance, which limits therapeutic options (6). A retrospective review of voriconazole and posaconazole breakthrough IFIs among SOT recipients and other immunosuppressed patients revealed a significant shift toward non-*Aspergillus fumigatus* moulds, including members of *A. ustus* complex, which exhibit relatively high azole MICs, multi-drug resistant moulds such as *Lomentospora prolificans* and *Rasamsonia argillaceae*, and intrinsically azole-resistant *Scopulariopsis* (22). Unlike data from Europe, azole-resistant *A. fumigatus* is uncommon in the US.

Timeline of IFIs

The majority of IFIs occur within the first year of LT (12). Invasive candidiasis generally occurs within the first 3 months following LT, but the rate is highest within the first month (12). Invasive mould infections (IMIs) can be divided into tracheobronchial tree (tracheobronchitis or anastomotic infection), lung parenchyma (pneumonia), and disseminated infections. The common etiologic agents causing IFI among LTR are summarized in *Table 1* (1,6,7,9-13,15-17,19,20,23). Aspergillosis, the most common IMI, usually occurs within 1 year of LT, with the majority of infections occurring within the first 6 months (12). Tracheobronchial aspergillosis, which is more common in LTR than among other SOT recipients, is encountered most often within 3 to 6 months of LT (24-26); however, cases have been reported as late as 3 years post-transplant (27). Invasive pulmonary aspergillosis (IPA) generally occurs later than tracheobronchitis, at median 6 months after LT. Besides Candida and Aspergillus infections,

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Table 1 Pathogens causing IFIs in LTR

Organisms	Incidence range
Yeasts	
Candida spp	3–11.4%
Cryptococcus spp	0.66%
Molds	
Aspergillus spp	3–15%
Mucorales group	0.28–4.8%
Endemic mycosis	
Histoplasma spp[#]	0.13%
Coccidiodomyces spp[#]	0.04%
Blastomyces spp[#]	0.02%
Others	
Fusarium spp[#]	0.24%
Scedosporium spp[#]	0.18%
Pneumocystis jirovecci	NA*

[#], incidence for all SOT recipients; *, the true incidence is unknown due to widespread use of anti-Pneumocystis prophylaxis. In the pre-prophylaxis era, incidence was as high as 15%. IFI, invasive fungal infection; LTR, lung transplant recipient; SOT, solid organ transplant.

LTR are also at risk for cryptococcosis, which is caused by the opportunistic yeast *Cryptococcus neoformans*. Cryptococcosis is more common in LTR than other SOT recipients. The median time from transplant to onset of cryptococcosis is earlier (191 days; range, 7.5–1,816 days) in LTR than in other SOT recipients (464 days; range, 4–2,393 days) (23).

Less commonly, IMIs occur later than 1 year after LT. Although Aspergillus remains the most common etiologic agent, non-*Aspergillus* IMIs have emerged in this later period, especially among LT receiving prolonged antifungal prophylaxis (18). For example, the median times to *Scedosporium* infection and mucormycosis are 12 and 26 months post-LT respectively. Other IMIs, including those caused by *Fusarium*, *Paecilomyces*, *Acremonium*, *Chrysosporium*, *Cladosporium*, *Exophiala* etc., occur at median of 16 months (20).

Spectrum of IFIs

Invasive candidiasis

Candida spp. cause significant nosocomial infections (surgical site infections, sternal wound infection, empyema, catheter-related bloodstream infections). More rarely, endobronchial candidiasis such as necrotizing bronchial anastomotic infections are encountered, especially in the presence of anastomotic dehiscence and bronchial stents (10,28,29). Although *Candida* spp are common colonizers of the airways in LTR, pulmonary candidiasis is exceeding rare.

IMIs

LTRs are disproportionately susceptible to fungal tracheobronchitis, with disease incidence ranging from 5% to 25% (12,30,31). *Aspergillus* spp are the most common pathogens (tracheobronchial aspergillosis); other etiologic agents are non-*Aspergillus* moulds and *Candida* spp (24). Rare and severe cases of Mucorales tracheobronchitis have also been reported (32).

Tracheobronchial infections are diagnosed by bronchoscopy with presence of obstructing, ulcerative or necrotic bronchial lesions or pseudomembranes, and evidence of invasive fungal organisms on biopsy (12,30,31). Ulcerative or necrotic lesions often occur around the suture line of anastomotic sites. Central airway obstruction is a form of fungal tracheobronchitis in which patients present with rapid drops in FEV1, and evidence of large, fibrinous Aspergillus-laden mucous plugs that respond to increased doses of corticosteroids and antifungal therapy (33). A necrotizing pseudomembranous form of invasive fungal tracheobronchitis is most severe, characterized by sloughed off necrotic epithelium and endobronchial mucous overlying the mucosal surface. This disease can lead to more invasive infections and dissemination (34). Invasive tracheobronchial aspergillosis (ITBA) may be asymptomatic and detected incidentally by surveillance bronchoscopy (35). ITBA is associated with a more favorable outcome in LTR than in other severely immunocompromised patients, since early diagnosis by routine bronchoscopy often prompts antifungal treatment before clinical symptoms occur. Complications of tracheobronchial aspergillosis can occur, including bronchomalacia, bronchial stenosis, dehiscence, hemorrhage and progression to parenchymal and disseminated disease.

The lungs are the most common site of IMIs. Fungal pneumonia is defined as radiographic evidence of nodules, cavities or pulmonary infiltrates with tissue invasion observed on histopathology, and isolation of the fungi from respiratory culture. IMIs are considered disseminated when disease is documented histopathologically in ≥2

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Table 2 Risk factors for IMI in LTR

Pre-transplant risk factors
Airway colonization with pathogenic moulds
History of IMI prior to LT
Peri-transplant risk factors
Induction therapy with thymoglobulin or alemtuzumab
Donor lung with pathogenic fungi
Anastomotic dehiscence
Renal replacement therapy
Environmental exposure
Post-transplant risk factors
Early/persistent airway ischemia
Airway colonization with pathogenic moulds
Ongoing allograft rejection and need for immune augmentation
Native lung as a source of infection in single LT
Viral infection: respiratory viruses, CMV infection
CLAD/BOS
Hypogammaglobulinemia

IMI, invasive mold infection; LTR, lung transplant recipient; LT, lung transplantation; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus.

non-contagious organ sites (13). Disseminated infections involving extrapulmonary sites such as central nervous system (CNS), bones and joints, large blood vessels can occur, but they are relatively uncommon.

Risk factors for IFIs

LTRs are at higher risk of developing IFI compared to other SOT recipients for several reasons. First, allograft lungs are directly exposed to moulds that are ubiquitous in the environment. Second, pulmonary host defenses are impaired after LT due to decreased cough reflex from lung denervation, abnormal mucociliary clearance, and disruption of lymphatic drainage. Third, since the bronchial artery is transected during donor lung harvest, the allograft airway and anastomotic site depend on collateral blood supply until revascularization is established (36). Thus, respiratory pathogens have particularly propensity for the bronchial anastomotic site, especially within the first 4–6 weeks after transplant, before vascular collaterals develop (37). Impaired blood flow also impedes the penetration of antifungal drug in the airway. Lastly, LT immunosuppression regimens are more intense than those of other SOTs, and typically involve lifelong three-drug therapy.

Airway colonization is a pre-requisite of subsequent IMIs, both early and late after LT. At any time after LT, the cumulative incidence of mould airway colonization ranges between 20% and 50% (38,39). *Aspergillus* spp. are the most common colonizers; up to 23% of LTRs have Aspergillus airway colonization (38,39). Mould colonization at the time of LT is a well-established risk factor for IMI within 3 months (early onset) (40-43). Overall, approximately 8% and 4% of LT candidates are colonized pre-LT with pathogenic fungi (mould and dimorphic fungi) and *Aspergillus* spp., respectively (3,44). The rate of Aspergillus colonization is much higher among patients with cystic fibrosis. In one study, 70% of patients with cystic fibrosis had pre-transplant Aspergillus colonization, and 39% had Aspergillus recovered from intra-operative bronchoalveolar fluid (43). IMI was found in explanted lung histopathology in 5% of LTRs; in 57% of these cases, IMIs were not diagnosed or suspected pre-transplant (45). IMI of explanted lungs at the time of transplant was associated with a significantly higher risk of IMI and mortality post-LT (45). Colonization with pathogenic moulds is also a risk factor for late-onset IMI. Other factors leading to late-onset IA include age, augmentation of immunosuppression and bronchiolitis obliterans syndrome (BOS) (46-49). Single lung transplant has also been linked to IMI. Risk factors that are found in some studies but not in others are summarized in *Table 2*.

Although LTR are frequently colonized with Candida, invasive candidiasis is much less common after LT than after other SOTs. The factors predisposing to invasive candidiasis among LTR are not different from those in other SOT recipients (13). These include complicated post-operative hospital stay leading to repeated bacterial infections and increased broad-spectrum antibacterial use, prolonged ICU stays and presence of central venous catheters. Furthermore, LTR requiring extracorporeal membrane oxygenation or those with delayed sternal closure might also be at risk for invasive candidiasis (10).

Outcomes of IFIs

IFIs, although less common than bacterial infections, significantly influence the all-cause mortality of LTR (2). Mortality rates among LTR with IFI range from 40–82%

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(17,50-53). The prognosis of disseminated IMI is dismal, with mortality approaching 80%. IFI is an independent risk factor for death after LT in multiple studies (2).

IFIs, particularly invasive aspergillosis, are linked to chronic allograft rejection [bronchiolitis obliterans syndrome (BOS)] (54). BOS is a phenotype of chronic lung allograft dysfunction (CLAD) that manifests as progressive airflow obstruction. Aspergillus colonization, even in the absence of IFI, has also been linked to BOS and BOS-related mortality, independent of rejection (55,56). Colonization with small conidia (≤3.5 μm) of *A. fumigatus*, *A. nidulans*, *A. terreus* and *A. flavipes*, in particular, has been associated with BOS and death. In one study, Aspergillus colonization preceded BOS by a median of 261 days. Transcriptional profiling of cell pellets from BAL fluid obtained from surveillance bronchoscopies of Aspergillus-colonized LTRs at 3 or 6-months post-transplant revealed enrichment of expression of genes involved in responses to host defense, inflammation and wounds compared with non-colonized LTR; moreover, expression of genes involved in these processes were significantly associated with progression to CLAD (56). These findings suggest that Aspergillus colonization might cause subclinical injury and subsequent repair that may ultimately lead to CLAD in some LTR. In other studies, however, an association between Aspergillus colonization and BOS was not confirmed (18,57). In one of these studies, LTRs received lifelong inhaled amphotericin B prophylaxis, a practice that might have modified the risk of BOS. In a multi-center international study of over 900 patients, transplant practices differed between centers and there was no unified therapeutic approach to Aspergillus airway colonization. This heterogeneity of approaches and the use of pre-emptive antifungal therapy at certain centers might have impacted CLAD outcomes (57).

Prevention of IFIs

Given the high morbidity and mortality of IFIs, LT centers have employed a number of preventive strategies, including universal antifungal prophylaxis (administered to all patients after LT), targeted prophylaxis to a subset of LTRs based on risk factors, and pre-emptive therapy (triggered by surveillance bronchoscopy culture and/or fungal markers). The approaches, advantages and disadvantages of each strategy are summarized in *Table 3* (37,58-60).

Universal prophylaxis with a systemic mould-active azole is the most comprehensive strategy (37,61), but it is costly, and associated with drug interactions (e.g., calcineurin inhibitors) and adverse events (e.g., liver toxicity, prolonged QTc with certain triazoles, squamous cell cancer of the skin with prolonged use of voriconazole). Universal prophylaxis with various inhaled amphotericin B formulations is appealing because this mode of administration can deliver a high concentration of antifungal directly to the airway, and at the same time abrogate concerns of systemic adverse events in other organs (58). This approach, however, does not prevent candidiasis, and a recent study revealed high rates of breakthrough pulmonary mould infections with aerosolized ABLC, thus drawing its effectiveness into question (10). Lastly, drug tolerability and outpatient coverage of expensive therapies by third-party payers are potentially problematic with universal prophylaxis. As with any prolonged use of antimicrobial agents, emergence of resistance to systemic and inhaled agents is a concern.

Targeted antifungal prophylaxis is a common approach in liver transplant recipients, because risk factors for IFI are well-defined and relatively easy to monitor in this population. For LTRs, the strongest risk factors in the early post-transplant period are mould culture positivity and airway ischemia, detection of which are dependent upon systematic testing. Risk factors other than colonization and ischemia in LTRs (besides single lung transplant) are less well defined, and they have been identified in some studies and not others. For these reasons, it is difficult to devise comprehensive targeted prophylaxis models. Such models have not been validated in LTRs.

Pre-emptive antifungal therapy based on BAL mould culture and/or fungal biomarkers such as galactomannan (GM) has been attempted in LTR (59). This approach is difficult to adopt in LTR for several reasons. First, the use of screening serum GM and β-D-glucan (BDG) are flawed by lack of sensitivity and specificity, respectively (62). Therefore, pre-emptive approaches are dependent upon invasive bronchoscopic procedures. Scheduled bronchoscopy is usually performed only 4 to 5 times during the first year of LT, thus early recognition of IMI might be missed if infections develop between bronchoscopies. Furthermore, GM detects Aspergillus but not other moulds. BAL culture sensitivity is less than 60% even in cases of IFI. Culture positivity of sputum and other respiratory samples is intermittent post-LT, suggesting that failure to detect colonization at a given time point does not preclude that colonization or disease is present.

There are no published studies demonstrating that fungal prophylaxis improves mortality or other outcomes following LT. In a recent abstract, investigators used administrative

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Table 3 Approach in preventing IFI

Variable	Definition	Patients	Advantages and disadvantages
Universal prophylaxis	Antifungal administered to all LTR	All newly transplanted patients	Advantages: most comprehensive prophylaxis. Disadvantages: Inhaled or systemic: potential selection of antifungal resistance and cost. Inhaled amphotericin B: tolerability (bronchospasm, cough, nausea, after taste); delivery of drug to native lungs is less than to the allograft lung; potential bacterial contamination of the nebulization system (58). Systemic azoles: toxicities, drug-drug interaction. IFI might develop after antifungal prophylaxis is stopped
Targeted prophylaxis	Antifungal administered only to subgroups of patients at risk for IFI. Note: some centers also use targeted prophylaxis plus pre-emptive therapy	Risk group for yeast infection: ECMO, delayed chest closure, etc. Risk group for mold infection: Aspergillus colonization at the time of LT; perhaps pre-LT Aspergillus colonization; single LT, a redo-transplant	Advantages: limiting antifungal use. Disadvantages: knowledge of IFI risk group in LT is still evolving; no prophylaxis for some patients at the period of highest risk of IFI
Pre-emptive therapy (biomarker-driven)	Antifungal administered only to patients at risks that are identified by screening with fungal markers (e.g., *Aspergillus* galactomannan)	Risk groups: positive galactomannan or fungal culture in BAL	Advantages: limiting antifungal use. Disadvantage: requires invasive procedure (bronchoscopy and BAL) for fungal culture and galactomannan testing; IFI might develop between scheduled procedure\s; sensitivity of both markers might not be optimal leading to delay in initiation of antifungal treatment

IFI, invasive fungal infection; LTR, lung transplant recipient; LT, lung transplantation; ECMO, extracorporeal membrane oxygenation.

claims data to determine outcomes of LTRs who received or did not receive prophylaxis (385 and 282 patients, respectively) (61). All-cause mortality was significantly lower in those receiving antifungal prophylaxis versus those who did not (event rate per 100 person-years: 8.77 versus 18.50; hazard ratio, 0.48; 95 percent confidence interval, 0.26 to 0.71; P=0.003), and there were lower rates of IFI (event rate per 100 person-years: 15.09 versus 22.48; hazard ratio, 0.68; 95 percent confidence interval, 0.45 to 1.05; P=0.08) (61). To date, there have not been any studies comparing patient outcome associated with universal prophylaxis versus pre-emptive therapy.

Given the dearth of clinical evidence, the approach to antifungal prophylaxis varies by LT centers. Over the years, antifungal prophylaxis has evolved as more antifungal agents were introduced to the market and their effectiveness and side effects have become better recognized. In a most recent survey of 44 US LT centers performed between November 2018 and February 2019, antifungal prophylaxis practices shifted more strongly toward universal prophylaxis (5). Most centers used a combined regimen of a systemic triazole and nebulized amphotericin B. The choice of triazole also evolved over time, from fluconazole and itraconazole (popular agents during a survey between 1999 and 2002), to voriconazole and itraconazole (during a survey in 2009), to any mould-active azole (itraconazole, voriconazole and posaconazole) in the most recent survey. At present, virtually no centers use fluconazole (5). Isavuconazole was not mentioned in the latest survey, likely because it was only introduced to the market in the spring of 2015.

The two most recent epidemiological studies of IFI among LTR demonstrated large variations in rates at centers using different universal prophylaxis strategies (10,37). The studies were single center and enrolled a large number of LTRs (815 and 300) (10,37). Standard prophylaxis at the first center consisted of universal inhaled amphotericin B lipid complex (ABLC), with a subset of patients deemed at risk for IFI (i.e., those with delayed chest closure or requiring extracorporeal membrane oxygenation (ECMO) post-transplant, or those with mould colonization pre-transplant) also receiving micafungin or a mould-active azole. Standard prophylaxis at the second center was a mould-active azole (voriconazole or isavuconazole) for all patients. IFI rates at 6 months at these centers were 19% and 6%, respectively

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(10,37). Moulds accounted for 43% of IFIs at the first center, and 70% at the second center. Breakthrough IFI rates while on antifungal prophylaxis were 26% and 3%, respectively. At the first center, the breakthrough invasive candidiasis rate was 12% (most cases occurring during micafungin prophylaxis) and the non-Candida IFI rate was 15% (most breakthrough occurred during inhaled ABLC prophylaxis). At the second center, the invasive candidiasis and non-Candida IFI rates were 1% and 2%, respectively, with infections evenly distributed among isavuconazole and voriconazole groups. It is difficult to compare data across centers. However, findings of these studies raise the possibilities that inhaled ABLC might be suboptimal in preventing IMIs (10), micafungin may be suboptimal in preventing invasive candidiasis (10), and universal systemic mould active azoles might be more effective as post-LT prophylaxis. Interestingly, 69% of micafungin breakthrough infections in the first study occurred at extra-blood deep-seated sites, suggesting that micafungin pharmacokinetics at these sites might be problematic.

Results of antifungal prophylaxis studies and surveys should be interpreted with caution. First, none of the antifungal drugs have Food and Drug Administration approval for prophylaxis in LTR. Second, surveys merely describe individual center's practice preferences, which may not represent evidence-based approaches. Indeed, several systematic reviews and meta-analyses of antifungal prophylaxis in LT published between 2001 and 2019 failed to offer any insight into the best approach to preventing IFI due to heterogeneity of published studies/trials, high risk of bias and lack of precision (63). The lack of standardized post-LT care poses particular challenges. For example, the use of induction immunosuppression differs between LT centers, and thymoglobulin induction has been linked to higher rate of IFI (64).

In summary, the optimal approach to preventing IFI among LTR is not known. A randomized study comparing the impact of universal with pre-emptive prophylaxis during the early transplant period on LTR outcome would be valuable. However, such trials have not been performed for reasons listed above, and due to justifiable concerns over high fatality rates associated with IFIs. It is also important to note that even in hematologic malignancy populations where several randomized controlled trials have shown that primary antifungal prophylaxis was associated with significant reductions in fungal-related mortality and documented IFIs (65), there are still ongoing controversies about antifungal prophylaxis. Until trials are performed in LTRs, the need for antifungal prophylaxis depends at least in part upon the local rates of IFI, distributions of patients' characteristics, and/or type of induction and maintenance immunosuppression therapy.

Treatment of IFIs

Optimal management involves early diagnosis and timely initiation of antifungal therapy (66). In selected cases where infected lesions can be resected, surgery should be considered. Furthermore, immunosuppression should be reduced whenever possible. Regarding antifungal management, several guidelines have been published by various organizations, including the International Society for Heart and Lung Transplantation Guidelines for the management of fungal infections (50). The Infectious Diseases Society of America (IDSA) has published specific guidelines for the treatment of aspergillosis (66), candidiasis (67), and other fungal infections including dimorphic fungi. Please refer to appropriate guidelines for antifungal therapy for specific fungi. Our specific recommendations for antifungal therapy for the common IFIs in LTR are summarized in *Table 4*. Mould-active azoles are frontline agents for treatment of IMIs, with local debridement and inhaled amphotericin B as needed for tracheobronchial disease. Echinocandins and azoles are treatments for invasive candidiasis, in keeping with guidelines in other populations. The major problem with triazoles are inhibitory effects on cytochrome p450 system, leading to increased levels of many drugs including calcineurin inhibitors and inhibitors of mammalian target of rapamycin (mTOR). Therefore, it is of utmost importance to monitor the levels of these inhibitors when co-administered with azoles. The dosages of various mould-active triazoles, the need for therapeutic drug monitoring (68) and agent-specific side effects are summarized in *Table 5*.

Conclusions

In conclusion, IFIs contribute significantly to lung transplant morbidity and mortality. Antifungal prophylaxis is commonly administered, but benefits and optimal regimens are not defined. Universal mould-active azole prophylaxis is used most often. Other approaches include targeted prophylaxis of high-risk LTRs or pre-emptive therapy based on culture or GM (or other biomarker) results.

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Table 4 Therapeutic recommendations for commonly encountered IFIs in lung transplant recipients

IFIs	Recommended dose	Alternative therapy	Comments
Commonly encountered IFIs			
Invasive aspergillosis (IA)	Voriconazole 6 mg/kg IV. q12h ×2 doses, then 4 mg/kg IV q12h × at least 7 days; convert to PO when stable and trough level is adequate: 200 mg PO q12h (>40 kg) and 100 mg PO q12h (<40 kg)	Isavuconazole 372 mg IV every 8 h for 6 doses, then 372 mg IV/PO once daily. Lipid formulations of Amphotericin B (AmB): liposomal AmB 3–5 mg IV daily, or; AmB lipid complex 5 mg/kg IV daily. Other agents: itraconazole 200 mg PO q8h ×9 doses, then 200 mg BID (need TDM). Posaconazole 300 mg (IV or PO delayed-release tablet) q12h ×2 doses, then 300 mg IV/PO daily	Avoid using voriconazole in severe cirrhosis. Therapeutic drug monitoring of voriconazole with ideal targeted therapeutic voriconazole level between 1–5 μg/mL. For severe or disseminated IA, combination with an echinocandin can be considered (caspofungin 70 mg IV load then 50 mg IV daily; micafungin 100–150 mg IV daily; or anidulafungin 200 mg IV load then 100 mg IV daily). Echinocandin alone is not recommended for initial treatment of IA
Invasive candidiasis (empyema, candidemia, surgical site and intra-abdominal infections) are the most common manifestations of IC among LTR. Invasive pulmonary candida infection is very rare	Echinocandin: caspofungin 70 mg IV load then 50 mg IV daily, or micafungin 100–150 mg IV daily, or anidulafungin 200 mg IV load then 100 mg IV daily. Transition to fluconazole after 5–7 days after clinically stable	Fluconazole. Voriconazole or posaconazole for Candida isolates susceptible to these agents, but resistant to fluconazole	Therapeutic drug monitoring is recommended if voriconazole is used
Less common IFIs in LTR: yeast infections			
Cryptococcus (pulmonary and extra-CNS disease)	Severe: Liposomal AmB 5 mg/kg IV q24h until improved, then fluconazole 400 mg PO daily. Mild to moderate: fluconazole 400 mg PO daily	Mild to moderate: itraconazole 200–400 mg daily	Low threshold to perform lumbar puncture for CSF cryptococcal antigen to rule out CNS involvement
Cryptococcus (CNS infection)	Ambisome 6 mg/kg IV q24h and flucytosine 25 mg/kg PO qid for ≥2 weeks, then fluconazole. 400–800 mg/d ×8 weeks, then fluconazole 200–400 mg PO daily for 6–12 months as maintenance		Serum flucytosine levels should be measured after 3 to 5 days of therapy, with a target 2-hour post dose level of 30–80 μg/mL; flucytosine levels >100 mcg/mL should be avoided. Fluconazole dose should be adjusted for renal function
Dimorphic fungi			
Blastomycosis (pulmonary and extra-CNS disease)	Severe: ambisome 5 mg/kg IV q24h, until stable/improved then itraconazole 200 mg PO q8h ×3 days, then 200–400 mg PO daily. Mild-moderate: itraconazale 200 mg PO q8h ×3 days, then 200–400 mg PO daily	Mild-moderate: fluconazole 400–800 mg PO daily	
Blastomycosis (CNS disease)	Ambisome 5 mg/kg IV q24h		

Table 4 (*continued*)

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Table 4 (*continued*)

IFIs	Recommended dose	Alternative therapy	Comments
Coccidioidomycosis (pulmonary and extra-CNS disease)	Severe: ambisome 5 mg/kg IV q24h until stable/improved, then fluconazole, 800 mg or itraconazole 200 mg PO q8h ×3 days then 200 mg PO BID. Moderate to severe: itraconazole 200 mg PO q8h ×3 days, then 200 mg PO BID or fluconazole 400 mg PO daily	Moderate to severe: ambisome 5 mg/kg, IV q24h	
Coccidioidomycosis (CNS disease)	Fluconazole 400–1,200 mg IV/PO daily until improved then fluconazole 400 mg daily PO lifelong	Intrathecal AmB deoxycholate 0.1–1.5 mg, itraconazole 200 mg, PO q8h ×3 days, then 400–600 mg q24h	
Histoplasmosis (pulmonary and disseminated)	Severe: ambisome 5 mg/kg IV q24h then itraconazole 200 mg PO q8h ×3 days, then 200 PO mg BID. Mild to moderate: itraconazole 200 mg PO q8h ×3 days, then 200 mg PO BID		
Less common molds in LTR			
Mucormycosis	Ambisome 5 mg/kg IV q24h	Ambisome IV q24h up to 10 mg/kg for severe, CNS involvement, or worsening infection. Or posaconazole IV or PO delayed release tablets 300 mg q12h on day 1, then 300 mg daily thereafter	Check posaconazole trough level ~1 week after initiation. Treatment efficacy is associated with level >1 μg/mL

IFI, invasive fungal infection; LTR, lung transplant recipient.

Table 5 Characteristics of mould-active azole agents

Mold-active azoles	Dose	Advantage	Disadvantage/toxicities	Note
Azole agents: drug-drug interaction due to inhibitory effect on cytochrome p450 system, leading to increased levels of calcineurin inhibitors and inhibitors of mammalian target of rapamycin (mTOR). Major side effect is hepatotoxicity				
Itraconazole	Available only in PO formulation. Solution formulation is preferred over capsule. Itraconazole 200 mg PO q8h ×3 days, then 200 mg PO BID	Potent antifungal against yeast, dimorphic fungi and *Aspergillus*. Solution formulation can be given via tube feed. SUBA-itraconazole has improved oral bioavailability. It has been approved by the FDA for treatment of aspergillosis, blastomycosis and histoplasmosis. Experience in SOT patients is non-existent at the time of this writing	No activity against moulds outside of Aspergillus. IV formulation is no longer available. Erratic absorption of itraconazole capsule which might be affected by H_2 blocker or proton pump inhibitors	Therapeutic drug monitoring is recommended. Target trough level for treatment: >0.5–1 μg/mL measured using HPLC or mass spectrometry

Table 5 (*continued*)

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Table 5 (*continued*)

Mold-active azoles	Dose	Advantage	Disadvantage/ toxicities	Note
Voriconazole	Available in PO and IV formulations. Voriconazole loading dose: 6 mg/kg IV q12h ×2 doses or 400 mg PO BID ×2 doses (weight of at least 40 kg) or 200 mg PO BID ×2 doses (<40 kg). Maintenance dose: 4 mg/kg IV q12h or 200 mg PO BID (at least 40 kg) or 100 mg PO BID (<40 kg)	Expanding spectrum against moulds	No mucorales coverage. Erratic absorption and metabolism. Squamous cell CA of skin and periostitis with prolonged utilization	Therapeutic drug monitoring is recommended. Target trough level for treatment: >1 μg/mL or a trough:MIC ratio of 2–5. Higher trough (>2 μg/mL) is recommended for severe infection. Trough concentration to minimize drug-related toxicity: <4–6 μg/mL
Posaconazole	Available in PO and IV formulations. Posaconazole 300 mg (IV or PO delayed-release tablet) q12h ×2 doses, then 300 mg IV/PO daily	Has *in vitro* activity against mucorales	In consistent bioavailability and pharmacokinetics with old formulations (solution or tablets)	Therapeutic drug monitoring is recommended. Recommended treatment target of >1 μg/mL
Isavuconazole	Available in PO and IV formulations. Isavuconazole 372 mg IV every 8 h for 6 doses, then 372 mg IV/PO once daily	Has *in vitro* activity against mucorales. Better tolerated than voriconazole. Less hepatotoxic than other mould-active azoles. No QTc elongation as observed with other triazoles	Isavuconazole has a more predictable dose response and less interpatient variability than other mould-active azoles. Recent study has shown that adequate level of isavuconazole can be achieved with isavuconazonium capsules administered given via enteric feeding tube	At the time of this writing, there are not clearly defined drug concentration thresholds for efficacy and efficacy

SOT, solid organ transplant.

Prophylaxis trials are needed, but difficult to perform due to heterogeneity in local epidemiology of IFIs and standard LT practices. The key to devising rational strategies for preventing IFIs is to understand local epidemiology in context of institutional clinical practices.

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