Current Transplantation Reports (2022) 9:63–75
https://doi.org/10.1007/s40472-022-00363-4

THORACIC TRANSPLANTATION (J PATEL AND A MARTIN HOLM, SECTION EDITORS)

Fungal Infections in Lung Transplantation

Claudia Ramirez-Sanchez[1] · Vi N. Nguyen[2] · Nancy Law[1]

Accepted: 31 January 2022 / Published online: 9 May 2022

Abstract

Purpose of Review We aim to understand the most common fungal infections associated with the post-lung transplant period, how to diagnose, treat, and prevent them based on the current guidelines published and our center's experience.

Recent Findings Different fungi inhabit specific locations. Diagnosis of invasive fungal infections (IFIs) depends on symptoms, radiologic changes, and a positive microbiological or pathology data. There are several molecular tests that have been used for diagnosis. Exposure to fungal prophylaxis can predispose lung transplant recipients to these emerging molds. Understanding and managing medication interactions and drug monitoring are essential in successfully treating IFIs.

Summary With the increasing rate of lung transplantations being performed, and the challenges posed by the immunosuppressive regimen, understanding the risk and managing the treatment of fungal infections are imperative to the success of a lung transplant recipient. There are many ongoing clinical trials being conducted in hopes of developing novel antifungals.

Keywords Lung transplant · Fungal infections · Aspergillosis · Candidiasis · Antifungal · Endemic fungi

Introduction

Since the advent of lung transplantation (LT) in 1963, the annual rate has been increasing with 4600 LTs performed worldwide in 2019, of which about 50% were performed in the USA, with a 5-year survival rate between 62 and 75% [1–4]. The benefits of transplantation come with the challenge of balancing immunosuppression (IS) with infection risks. Despite antifungal therapies and prophylactic strategies, lung transplant recipients (LTRs) still have a high risk for developing invasive fungal infections (IFIs) [5•, 6••], which can increase the post-transplant mortality rate by as much as threefold [7•, 8]. According to the transplant associated infection surveillance network (TRANSNET), 8.6% of LTRs will develop IFIs in the first 3 to 12 months post-LT [9]. The successful management of fungal infections is a great clinical challenge. Antifungals require intensive therapeutic drug monitoring (TDM) [10] as adequate levels are crucial for successful treatment and prevention of drug-related toxicities [11]. This review will highlight fundamental issues in managing fungal infections in LTRs including risk factors, diagnosis, treatment, antifungal prophylaxis, and recommendations in drug monitoring.

Epidemiology

The incidence of IFIs is lower than fungal colonization after LT, with the rate of 3–14% compared to 20–50% respectively [12••]. Invasive pulmonary aspergillosis (IPA) is the most common IFI post-LT with mortality rates of 23–82%, whereas invasive candidiasis (IC) follows with a mortality rate as high as 40% [7•]. Risk factors include IS regimen, impairment of mucociliary clearance, such as underlying cystic fibrosis, airway injury, altered alveolar macrophage function, underlying pulmonary architectural distortion, and mucosal defects, and geography and environmental exposure [8, 12••, 13••]. The use of tacrolimus or sirolimus was also demonstrated to be an independent risk factor for developing

This article is part of the Topical Collection on *Thoracic Transplantation*

✉ Nancy Law
nalaw@health.ucsd.edu

[1] Division of Infectious Diseases and Global Public Health, University of California San Diego, 9444 Medical Center Drive, MC 0879, La Jolla, CA 92093-0879, USA

[2] Department of Pharmacy, University of California San Diego, La Jolla, CA, USA

IFIs [14]. Other risk factors recognized are chronic rejection, cytomegalovirus (CMV) infection, and hypogammaglobulinemia [12••]. The lower respiratory tract is the most common site of mold diseases, especially for the multi-drug-resistant (MDR) infections [15].

Diagnosis

The diagnosis of IFI is divided into categories ranging from possible, probable, or proven depending on the presence of symptoms, radiologic changes, and a positive culture (sputum, bronchial washings, or urine). Proven IFIs have histologic findings supporting fungal elements [14]. Several molecular tests have been used for diagnosis which we will briefly discuss in this section.

The role of serum galactomannan (GM), an enzyme-linked immunosorbent assay that detects polysaccharides present in the fungal cell wall, has been controversial since its sensitivity in non-neutropenic cardiothoracic recipients is about 30% [6••, 16, 17]. When a GM is obtained from a bronchoalveolar lavage (BAL) sample, the sensitivity rises to 82–86% and specificity 89–92% with the positivity cutoff of 0.5–1.5 [18–21]. In comparison, the use of BAL *Aspergillus* polymerase chain reaction (PCR) showed a median pooled sensitivity of 79% compared to serum PCR which had a sensitivity ranging 75–88% [22]. Respiratory PCR testing is considered more sensitive than fungal culture and can also help in antifungal resistance testing; unfortunately, it cannot distinguish between colonization versus invasive infection, nor can it discern between *Aspergillus* subspecies [12••, 18].

In contrast, when looking at (1→3) beta-D-glucan (BDG), a component of the fungal cell wall released into circulation during IFI, the sensitivity is 76–80% and specificity is 82–85% (not specific for any particular mold, or yeast) [23]. Notably, iatrogenic contamination with blood fractionation products (IVIg and albumin), invasive use of surgical materials, and cellulosic dialysis membranes are associated with falsely elevated BDG levels [12••, 24]. New diagnostic tools are under development, such as urinary antigen for Aspergillus detection, lateral flow devices using monoclonal antibodies, and other non-specific biomarkers like Pentraxin-related protein and cytokines [6••].

Radiologic criteria include a "halo sign" observed in 56% and 8% of neutropenic and solid organ transplantation (SOT) patients, respectively [6••]. Other diagnostic signs include macronodules, less commonly peribronchial consolidations, and ground glass opacities. Tree-in-bud nodules/bronchial wall thickening were also reported [12••]. Different diagnostic strategies will be discussed under each IFI.

Special Clinical Presentation

Most common fungal infections

Aspergillosis

Aspergillus spp. is an important cause of life-threatening infection and is the most common IFI in LTRs from either colonization or inhalation of spores [25]. Aspergillosis occurs typically within 1 year but can affect patients up to 3 years after transplant [26]. The overall incidence of IPA in LTRs ranges from 4 to 23% [27••]. The mortality of IPA in LTRs varies according to the clinical presentation, ranging 23–29% in patients with tracheobronchitis to 67–82% in patients with invasive pulmonary disease [27••, 28]. The most common infecting species is *Aspergillus fumigatus*, with *A. niger*, *A. terreus*, and *A. flavus* being less common.

IPA in LTRs can originate from latent infection, colonization of trachea or retained lung, or donor-derived [25]. Aspergillus tracheobronchitis is seen only in LTRs, and requires systemic therapy with voriconazole in addition to nebulized amphotericin B for at least 3 months [26]. In LTRs, the risk factors for infection include single-LT, early airway ischemia, colonization of airway, CMV infection, and increased IS [27••, 29]. Cystic fibrosis increases the risk of pre-transplant airway colonization with *Aspergillus* spp.

Voriconazole is the treatment of choice [27••, 30], although some studies have demonstrated non-inferiority of posaconazole and isavuconazole in the treatment of IPA [31•, 32, 33•]. Decreasing IS also plays an important role. Since LTRs are at high risk of IPA, the published guidelines currently recommend prophylaxis for patients with *Aspergillus* colonization pre-transplant and within the first year after transplantation, cystic fibrosis patients with positive intraoperative *Aspergillus* culture, and single LT. Targeted prophylaxis can be considered in those with two or more of the following risk factors: early airway ischemia, induction with alemtuzumab or thymoglobulin, CMV infection, augmented IS due to rejection, and hypogammaglobulinemia [25, 27••]. However, in the systematic review by Bhaskaran et al., no reduction in IPA was found when comparing prophylaxis versus no prophylaxis [34]. There have been studies supporting the use of voriconazole [35] and posaconazole for IPA prophylaxis [36]. However, a multicenter randomized controlled trial to determine the most appropriate prophylactic regimen is still needed [29].

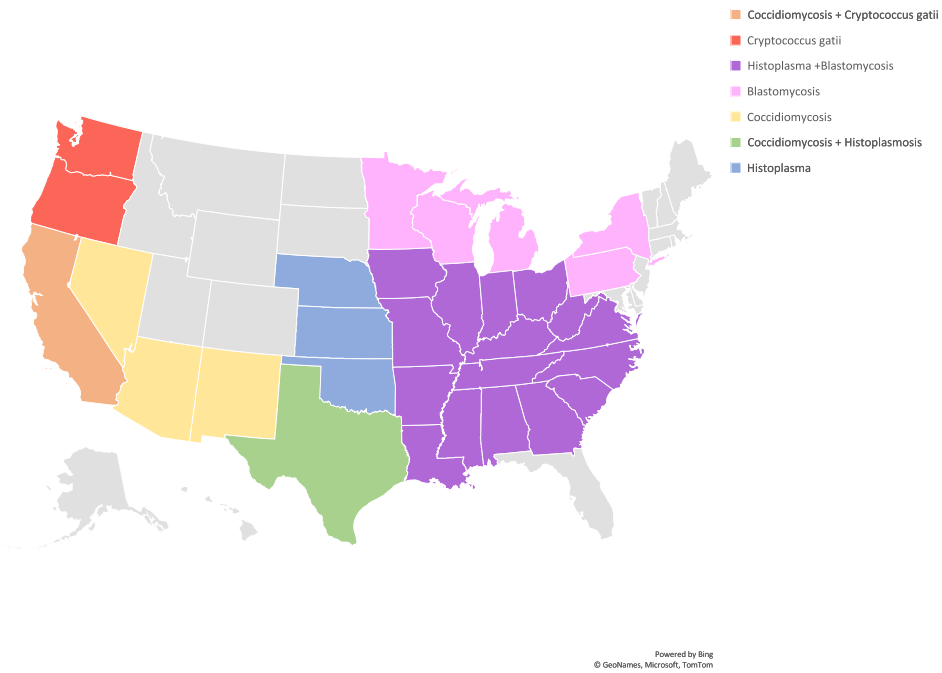

Fig. 1 Endemic mycoses—map of the USA with the distribution of endemic mycoses

Candidiasis

Candida spp. can be found in the pharynx oralis; therefore, it is difficult to distinguish between colonization and IC. When *Candida* is detected in sputum culture, it is important to note it rarely causes pulmonary infections [37]. In the first month following LT, candidiasis usually presents as candidemia, and is associated with high mortality (54.5%) [6••]. Factors associated with candidemia are high-dose steroids, immunomodulators, long-term catheters [38], as well as open chest and ECMO support post-transplant. Other manifestations of infection include pleural space and local anastomotic site infections [29, 39, 40]. The treatment for IC for LTR is an echinocandin as empiric therapy then transitioning to an azole once the organism's susceptibilities are available [6••].

Endemic fungi

These mycoses are a group of organisms with similar characteristics. They are dimorphic in nature and are found in different geographic areas (Fig. 1) [41]. It is important to counsel patients on the risk of exposures in these endemic areas post-transplant.

Cryptococcosis

Largely caused by *Cryptococcus neoformans*, though in the past few years *Cryptococcus gatti* has been prevalent in the Pacific northwest region [25]. Cryptococcosis tends to occur between 2 and 5 years post SOT [25], however could be sooner in the case of donor-derived, especially in LTR [42, 43]. In SOT patients, the rate of cryptococcosis is 6–7% [25] with reactivation of quiescent infection being the most common cause [44]. Serum cryptococcal antigen (CRAG) may be a useful tool, though they are frequently negative when the organism burden is low such as those limited to the lung or with single nodule. According to current literature, there is insufficient data to determine the role of CRAG monitoring during treatment for pulmonary cryptococcosis [45]. Central nervous system (CNS) involvement is observed in nearly 50% of transplant recipients with pulmonary cryptococcosis; therefore, a lumbar puncture should be performed in all LTRs to rule this out [25, 44]. Notably, as per Husain et al., transplant recipients on calcineurin inhibitors have shown lower prevalence of CNS involvement suggesting a potential degree of anticryptococcal activity [46, 47]. Whenever possible, gradual reduction in IS during cryptococcosis treatment is advised. However, this could be difficult to do if the patient is receiving T-cell-depleting agents such as alemtuzumab or thymoglobulin; in which case, the rapid reduction in IS may cause adverse acute organ rejection or immune reconstitution inflammatory syndrome (IRIS) [44]. IRIS may cause ventricular obstruction with increased intracranial pressure and hydrocephalus [29].

The treatment for cryptococcosis in LTRs is the same as in other patients, including a lipid formulation amphotericin B plus 5-flucytosine (5-FC) as induction therapy for CNS disease, disseminated disease, and moderate to severe pulmonary disease. This should be followed by fluconazole consolidation and maintenance regimen. However, in mild or asymptomatic disease, initial treatment with fluconazole

is the preferred therapy. Dexamethasone does not seem to be effective for cryptococcal meningitis treatment [44].

Coccidiomycosis

Endemic mycosis caused by organism *Coccidioides immitis* and *Coccidioides posadasii*, prevalent in the desert soil of the north of Mexico, southwest USA, and California's central valley [48, 49]. The most common exposure is inhalation of spores (or arthroconidia). Transmission of coccidiomycosis via organ transplantation is common in LT with a rate of 1.4–6.9% in endemic regions. Most cases occur within the first year post-transplantation with a mortality rate up to 30% [23, 49]. Clinical infection is uncommon and can be prevented or mitigated in patients receiving preemptive therapy [49, 50]. Manifestations range from asymptomatic infection to severe pneumonia or disseminated disease, with the latter being more common in the immunocompromised host. This can then progress to acute respiratory distress syndrome (ARDS) and respiratory failure.

Radiologic findings include mass-like lesions, lobar consolidations, pulmonary nodules, cavities, or interstitial infiltrates [49]. Peripheral eosinophilia, though not diagnostic, is present in a third to a half of patients with coccidiomycosis [23]. Diagnosis of coccidiomycosis includes histopathologic findings of spherules containing endospores; *Coccidioides* species also grow well in most mycologic and bacteriologic media within 5 to 7 days [23, 49]. Immunologic assays have been largely utilizing immunoglobulin detection with tube precipitin (TP) and complement fixation (CF). TP turns positive within weeks of infection, whereas CF took 2 to 3 months to turn positive, demonstrating that TP corresponded to immunoglobulin M (IgM) and CF to immunoglobulin G (IgG). CF tends to uptrend when the infection is poorly controlled [48]. Similar to TP, latex particle agglutination assay (LPA) also detects IgM. Currently, a serological ELISA method based on detection of IgM and IgG is typically used for initial screen, with a sensitivity of 95.5% and specificity of 98.5% [48, 49]. The enzyme immunoassay (EIA) IgM test is the least compelling diagnostic evidence and can produce false-positive results due to interference from other fungal infections, medications, or technical issues [51]. It is recommended to repeat testing for anticoccidioidal antibodies over subsequent weeks to help resolve these discrepancies and improve the certainty of a diagnosis [49, 52]. Other methods of diagnosis are antigen enzyme immunoassay (available for urine, serum, BAL, and cerebrospinal fluid (CSF)) and molecular assays based on DNA hybridization and PCR/qPCR methods [49].

The treatment for coccidiomycosis depends on the severity of the disease, ranging from 3 to 12 months to lifelong treatment, as in the case of CNS infections. The drug of choice for treatment is fluconazole [48]. However, in severe or disseminated coccidiomycosis, lipid formulation amphotericin B is preferred until patient is stabilized and then can transition to fluconazole. There have been reports of infection relapse of coccidioidal meningitis after discontinuation of azole; therefore, treatment is recommended indefinitely or until withdrawal of IS [23, 49, 50].

Pre-transplant evaluation should include history of exposure or residence in an endemic area, as well as current or past symptoms of infection, radiologic evaluation, and serologic testing [23]. Lifelong fungal prophylaxis with an azole is recommended in endemic areas [49], in the setting of positive serological screening, and active infection of the donor [53]. Currently, there are no concrete guidelines on either universal or targeted screening for donor-derived infection [50].

Histoplasmosis

Histoplasma capsulatum is endemic to the Mississippi and Ohio River Valleys [54, 55]. Exposure to the spores is from soil disruption around construction and agricultural sites with large concentrations of bird droppings [25, 56]. In immunocompromised hosts with impaired cell immunity, such as LTRs, the organism remains viable within macrophages, which poses a risk for disseminated disease [49, 57]. Fortunately, histoplasmosis is rare in SOT recipients with an estimated incidence of less than 1% in endemic areas.

Histoplasmosis can be acquired most commonly via inhalation or reactivation of prior disease while on IS, as well as in rare cases (1:10,000 transplants) through donor-derived allograft transmission [49]. Unexpected histoplasmosis was found in 18 of 1000 LTR in endemic areas in a case series [58•].

Most infections are reported within the first 2 years of transplantation. It can present in an occult manner in the transplant population but most commonly (81% of transplants) presents as disseminated infection with subacute febrile illness, progressing to hepatosplenomegaly, pneumonia, GI involvement, and weight loss [59]. Mucocutaneous histoplasmosis presents in 25% of transplant recipients, and CNS involvement is also described in this population [59]. The use of mycophenolate and fungemia are risk factors for severe disease.

Histopathologic visualization of yeast forms (with or without granulomas) confirms the diagnosis as culture can take up to 4 weeks. In SOT recipients, urine *Histoplasma* antigen EIA demonstrates the highest sensitivity at 92%, with a lower sensitivity in pulmonary disease versus disseminated disease. This is also true about the slightly less sensitive serum *Histoplasma* antigen (86%), which can be followed to evaluate therapeutic response. However, the specificity of the test is compromised as there is a 90%

cross-reactivity with other endemic fungi such as *Blastomyces* and in lower proportion with *Coccidioides* [49, 60]. Serologic testing is not recommended for diagnosis in immunosuppressed host.

The treatment of histoplasmosis depends on the severity of illness. Itraconazole is often used in mild to moderate illness. For moderate to severe infections, amphotericin B is utilized as the initial treatment for 2 weeks followed by itraconazole for 12 months [60]. Second-line therapy is fluconazole, though voriconazole, posaconazole, and isavuconazole have also been reported in case reports as successful treatments and may be the preferred choice for non-HIV infected immunosuppressed patients given that fluconazole has high relapse rates in this subpopulation [49]. The concomitant reduction of IS, especially calcineurin inhibitors, is recommended when feasible to decrease relapse risk.

Pre-transplant screening for histoplasmosis is not recommended even in endemic areas because of the poor serologic predictive value of current tests. Secondary prophylaxis as well as antigen monitoring may be considered with recent infection within the past 2 years. Primary prophylaxis might be considered in LT with evidence of donor-derived allograft infection [49, 58•].

Blastomycosis

Blastomyces dermatitidis is endemic to the Mississippi and Ohio River Valleys, the Great Lakes region, and the St. Lawrence Seaway. Infection with *B. dermatitidis* is through inhalation of spores and less commonly direct cutaneous inoculation. Blastomycosis in immunocompromised individuals is associated with disseminated disease [61] and can increase the risk of allograft loss and overall mortality [62]. However, blastomycosis remains very rare in post-transplant recipients even in endemic areas. There is no significant amount of data reporting the rate of blastomycosis in LTRs, with studies underlying transmission in other SOT but no evidence of transmission in lungs [62]. The clinical presentation includes pneumonia with or without extrapulmonary dissemination. The spectrum of infection ranges from subclinical pulmonary disease to acute or chronic pneumonia, with a subset of patients developing fulminant multilobar pneumonia and ARDS.

The definitive diagnosis of blastomycosis is made from culture isolation of the organism. However, due to the 2 to 4 weeks growth period, histopathologic visualization of yeast forms is the most commonly used method of diagnosis. EIA is also available to detect antigens in body fluids (urine, serum, BAL, or CSF) with a sensitivity of 62–83% but has a low specificity given the cross-reactivity with *H. capulatum* [63].

Treatment of blastomycosis, particularly in severe pulmonary cases, should start with lipid formulation of amphotericin B for 1 to 2 weeks or until clinical improvement. It should be followed by itraconazole for 12 months or longer if symptoms have not resolved. The exact duration of therapy has not been determined [64]. In the setting of CNS infection, amphotericin B should be extended for 4 to 6 weeks, followed by voriconazole instead of itraconazole given the lower CSF penetration from the latter (< 1%) [49, 64]. Itraconazole monotherapy can be considered initial therapy in mild to moderate cases with close monitoring.

Pre-transplant screening can be done in candidates with prior history of exposure. There is no recommendation on primary prophylaxis against blastomycosis given the lack of supporting studies [49].

MDR mold infections

Non-*Aspergillus* spp. mold infections have posed an increased challenge in LTRs [29] given the difficulty to discern them from *Aspergillus* spp. and each other, their intrinsic resistance to antifungals, and their aggressive characteristics of disease [13••, 15]. Exposure to these emerging molds could be from cutaneous contact or spore inhalation from the environment. It has also been noted that exposure to fungal prophylaxis such as voriconazole or inhaled amphotericin can predispose LTRs to these emerging molds [13••].

Scedosporium and Lomentospora prolificans (formerly Scedosporium prolificans)

They are soil saprophytes that are commonly found in temperate climates. LTRs are at higher risk than other organ transplants during the first 12 months post-transplantation [15]. A recent survey found that 48% of a total of 45 LT centers had positive cultures [65]. Pre-transplant colonization plays an important role in Scedosporiosis, which becomes a contraindication for many LT centers [66•]. Infection can occur within a month after transplantation in those previously colonized, but develops 6 months or after in those not previously colonized [13••]. Some of the risk factors for scedosporiosis are underlying cystic fibrosis, prior use of amphotericin, and enhanced IS [13••]. The treatment response depends on the site of infection, the extent of dissemination, and the host's degree of IS. Outcomes are better with localized disease to either the skin or lungs compared to disseminated disease. In vitro, voriconazole has the most potent activity against *Scedosporium*. Surgical debridement is the preferred treatment against *Lomentospora* since it is virtually resistant to all antifungals available, and with reduced susceptibility to echinocandins, especially caspofungin and anidulafungin [67]. Some reports suggested

voriconazole [26] or a combination of voriconazole and terbinafine [68].

Mucormycoses

Invasive mucormycosis is a devastating disease with an overall mortality rate of 40–50% [69], and even reported up to 90% [26]. Mucormycetes are ubiquitous in the air but are associated mostly with natural composts and soils of potted plants [13••]. LTRs have the highest incidence of pulmonary mucormycosis in the first year after transplant [13••, 15], with 78% of infections occurring within the first year and 40% within the first month [70]. Given its angiotropic nature, mucormycetes tend to cause tissue infarction and necrosis [70]. Rhino-orbital-cerebral infection is one of the most common presentations as the fungal spores get inhaled through the sinuses, which is more common in patients with uncontrolled diabetes mellitus but also found in one-third of SOT patients [71].

Surgical excision and debridement is the standard of care for all non-pulmonary infectious processes, with amphotericin being the treatment of choice for induction therapy [13••, 26], in addition to reduction of IS. Isavuconazole is the newest triazole approved for treatment of invasive mucormycosis and IPA [13••, 72]. However, in the absence of prospective studies of mucormycosis in LTRs, the management is mainly based on case reports and retrospective studies [70].

Fusariosis

Pulmonary disease is common with *Fusarium* spp. in LTRs; however, their larger conidia (compared for instance with Aspergillus) can get trapped in the upper airway and sinuses causing upper airway disease. In other severely immunosuppressed individuals, cutaneous manifestations tend to be more common. Voriconazole is the first line of treatment, though surgical excision alone of localized cutaneous disease can effectively treat the infection, in addition to reduction of IS [26].

Prophylaxis

There are several prophylactic strategies described for LTRs. Universal prophylaxis is defined as antifungal agent(s) administered to all patients during the immediate post-transplant period [6••]. Preemptive treatment is the administration of antifungal agents for mold isolated during the surveillance post-transplant bronchoscopy without evidence of invasive disease. A third strategy, "targeted prophylaxis," refers to an antifungal medication started in the post-transplantation period prior to isolating any fungal pathogen in patients who are deemed high risk for infection, such as in cystic fibrosis or prior fungal colonization [6••]. No randomized trials have been performed comparing these prophylactic strategies [12••]. Though a recent meta-analysis concluded that anti-Aspergillus prophylaxis did not result in significant reduction in IPA or *Aspergillus* colonization [34]; another meta-analysis from 2016 concluded that universal prophylaxis reduced the incidence of IA in LTRs compared to no or targeted prophylaxis [26, 73]. Universal prophylaxis has several disadvantages especially adverse events associated with azole use: hepatotoxicity, neurotoxicity, QT interval prolongation, and drug interactions. The exposure to universal prophylaxis has also increased the emergent resistance of other fungal infections [6••]. The difficulty determining the appropriate approach highlights the need for a multicenter randomized trial in LTRs [34, 74].

Therapeutic Drug Monitoring

As discussed previously, TDM of azoles is crucial in ensuring treatment success and minimizing drug toxicity, as detailed in Table 1. All azoles can cause hepatotoxicity at any point during therapy. Liver function test abnormalities were reported in up to 60% of LTRs receiving voriconazole whereas less than 10% of patients developed hepatotoxicity on posaconazole and isavuconazole [33•, 35, 75–78•]. In a meta-analysis, fluconazole was found to have better hepatic safety profiles than other antifungal agents [79, 80]. Liver enzyme abnormality is reversible upon azole discontinuation or by switching to an alternative azole therapy.

Amphotericin B is associated with high incidence of infusion-related reactions and nephrotoxicity. The lipid formulations have less nephrotoxicity compared to conventional amphotericin B deoxycholate [80, 91, 92]. Hypokalemia and hypomagnesemia are common side effects so close monitoring of renal function and electrolytes is recommended [93].

The triazole antifungals are inhibitors of the cytochrome P450 system, which results in significant drug interactions [12••]. The coadministration of mTOR inhibitors and voriconazole or posaconazole is contraindicated per manufacturers' recommendations. However, the use of these combinations seemed to be safe as demonstrated in retrospective studies and case reports, as well as in our center's experience [94–101]. Recommendations for IS dose adjustment when starting triazoles are detailed in Table 2. However, because of the significant interpatient variability, providers should weigh the risk of drug toxicity and rejection risk in deciding dose modification for a given patient.

Clinical Trials and Future Studies

There are several ongoing clinical trials investigating new therapies and novel approaches to IFI. IA-DUET from The Netherlands investigates the combination of

Table 1 Therapeutic drug monitoring (TDM)

Medications	Common dosing	TDM	Toxicity threshold	Comments
Fluconazole Tablet (100 mg, 150 mg, 200 mg) Oral suspension (40 mg/mL) Intravenous (IV)	Doses differ based on indication and renal function	Studies do not support routine TDM, can consider in patients with severe disease, complex drug interactions, or toxicities [10]	Not defined	Dose adjust in renal impairment
Itraconazole Capsule (100 mg) Oral solution (10 mg/mL)	Varied based on indications	• AST/IDSA/ISHLT: 0.5-1 mg/L • Check trough after > 10 – 14 days†	• AST: N/A • IDSA: 3 mg/L • ISHLT: 2 mg/L	Non-linear pharmacokinetics, caution with dose adjustments
Voriconazole* Tablets (50 mg, 200 mg) Oral suspension (40 mg/mL) Intravenous (IV)	• IV**: 6 mg/kg Q12H × 2 doses, followed by 4 mg/kg Q12H • PO (> 40 kg): 400 mg Q12H × 2 doses, followed by 200 mg Q12H	• AST: 1–5.5 mg/L. Higher target 2–6 mg/L for severe infections or elevated MICs (> 2 mg/L) • IDSA: 1–1.5 mg/L • ISHLT: 1–2 mg/L • Check trough at least 5 days after loading dose, consider recheck in 1 week†	• AST: 5.5–6 mcg/mL • IDSA: 5–6 mg/L • ISHLT: 4–5 mg/L	• Interpatient variability in serum levels due to CYP2C19 polymorphisms • Non-linear pharmacokinetics, caution with dose adjustments
Posaconazole DR tablet (100 mg) Oral suspension (40 mg/mL) Intravenous (IV)	• IV**/PO DR tab: 300 mg Q12H × 2 doses then 300 mg daily • PO suspension: 200 mg TID-QID (poor bioavailability)	• AST: > 1 mg/L (preferably > 1.25 mg/L) • IDSA: > 0.7 mg/L • ISHLT: 0.7 mg/L for prophylaxis, 1.25 mg/L for treatment • Check trough at least 5 days after loading dose, consider recheck in 1 week†	Not defined. In one study, pseudohyperaldosteronism was observed in level > 3 mcg/mL [81]	DR tablet and oral suspension are not interchangeable
Isavuconazole Capsule (186 mg) Intravenous (IV)	IV/PO: 372 mg Q8H × 6 doses, then 372 mg daily	• Not defined. Mean concentrations from clinical studies and real-world data were similar, ranging from 2 to 4 mcg/mL[72, 82–84] • AST: Trough level 2–3 mg/L after day 5 suggests adequate drug exposure • Check trough after ≥ 7 days	Not defined. Two studies proposed a toxicity threshold of 4.6–5.13 mcg/mL [72, 84]	Studies suggested a linear increase of plasma isavuconazole trough levels of 0.032 mg/L per day in cases of prolonged therapy [72, 84]
Flucytosine Capsule (250 mg, 500 mg)	25–37.5 mg/kg Q6h based on indications	• Trough ≥ 25 mg/L	Hepatotoxicity and bone marrow suppression are concentration dependent, possibly avoidable with concentrations less than 100 mg/L	• Dose adjust in renal impairment • Mainly used as combination drug because of the frequent development of resistance

†Consider additional levels when: dose or route change, repeat levels after early level checks, initiation or discontinuation of interacting medications, IV to PO switch, diarrhea and receiving enteral formulation, concern for non-adherence or toxicity, fungal disease progression

*Consider using adjusted body weight in obese patients

**IV formula: caution in CrCl < 50 mL/min due to potential risk of sulfobutylether-β-cyclodextrin accumulation

AST, American Society of Transplantation Infectious Diseases Community of Practice; *IDSA*, Infectious Diseases Society of America; *ISHLT*, International Society for Heart and Lung Transplantation [10, 11, 28, 30, 72, 81–90]

Table 2 Immunosuppression drug interactions

	Cyclosporine	Tacrolimus	Sirolimus	Everolimus
Fluconazole[a,b]	Clinical studies: ↓ dose by 50% [102, 103]	Clinical studies: ↓ dose by 40–56% [104, 105]	Case report: fluconazole 200 mg/day increased sirolimus level by 3.5-fold on day 7 despite empiric 25% dose reduction [106]	Case report: withdrawal of fluconazole resulted in 3.5-fold increase in everolimus dosage [107]
Itraconazole[b]	Clinical studies: ↓ dose by 48–56% [108, 109]	Clinical studies: ↓ dose by 50–66% [109–112]	Case report only. Itraconazole 400 mg/day resulted in twofold increase in blood sirolimus concentration [113]	No data
Voriconazole	Package insert and clinical studies: ↓ dose by 50% [114]	• Package insert: ↓ dose by 2/3 • Clinical studies: ↓ dose by 75% [115]	• Package insert: coadministration is contraindicated • Clinical studies: ↓ dose by 50–90% or cap sirolimus dose at 0.5–1 mg/day [97, 99]	• Package insert: coadministration is not recommended • Clinical studies: ↓ dose by 75% [98]
Posaconazole	• Package insert: ↓ dose by 25% • Clinical studies: ↓ dose by 14–29% [116]	• Package insert: ↓ dose by 2/3 • Clinical studies: posaconazole increased the Cmax and the AUC for tacrolimus by 121% and 358% [116]	• Package insert: coadministration is contraindicated • Clinical studies: 33–70% empiric sirolimus dose reduction [94–96]	• Package insert: coadministration is not recommended • Clinical studies: ↓ dose by 75% [101, 117]
Isavuconazole[b]	Clinical studies: one retrospective study of 34 HSCT patients found that isavuconazole's effect on cyclosporine level was similar to that of fluconazole [118]	Clinical studies: a case report in a lung transplant recipient suggested an initial 50% reduction and further dose decreases of 25–50% [119]. In contrast, a study of 55 SOT patients suggested no empiric dose reduction required [120]	Clinical studies: a study of 20 HSCT patients showed that the interaction can be managed with close serum concentration monitoring without empiric sirolimus dose reductions [121]	No data

[a]CYP3A4 inhibition is dose-dependent occurring generally when the dose of fluconazole is at least 200 mg/day in patients with normal renal function, although drug interaction has been reported with fluconazole doses as low as 100 mg/day

[b]No guidance on dosage adjustments according to prescribing information

AUC, area under the concentration–time curve; *Cmax*, maximum blood concentration; *HSCT*, hematopoietic stem cell transplant; *SOT*, solid organ transplant

azole-echinocandin for IPA in neutropenic stem cell transplants patients [122]. There is also a phase IIb clinical trial studying F901318, FORMULA-OLS for the treatment of IPA and MDR fungal infections such as *Scedosporium* and *Lamentospora* [123]. Ibrexafungerp—a glucan synthase inhibitor—is being evaluated for the treatment of several IFIs including refractory endemic mycoses [124]. Lastly, AEGIS is a phase II clinical trial studying the efficacy and safety of fosmanogepix (APX001), a novel antifungal targeting the Gwt1 enzyme required for localization of glycosylphosphatidylinositol-anchored mannoproteins in fungi [125]. These trials highlight the interest and need for novel therapies for the treatment of fungal infections.

Conclusion

This review describes different fungal organisms that have the potential to cause invasive infections in LTRs. We discussed their epidemiology, clinical presentation, diagnosis, treatment, and prevention of disease. We also delved into TDM and drug interactions in the setting of immunosuppressive agents, which are important factors in the treatment of these IFIs.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Kennedy CC, Razonable RR. Fungal infections after lung transplantation. Clin Chest Med. 2017;38(3):511–20.
2. van der Mark SC, Hoek RAS, Hellemons ME. Developments in lung transplantation over the past decade. Eur Respir Rev. 2020;29(157):190132.
3. Chambers DC, Perch M, Zuckermann A, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK, Potena L, Sadavarte A, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-eighth adult lung transplantation report - 2021; Focus on recipient characteristics. J Heart Lung Transplant. 2021;40(10):1060–72.
4. Valapour M, Lehr CJ, Skeans MA, Smith JM, Miller E, Goff R, Foutz J, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2019 annual data report: lung. Am J Transplant. 2021;21(S2):441–520.
5.• Baker AW, Maziarz EK, Arnold CJ, Johnson MD, Workman AD, Reynolds JM, Perfect JR, Alexander BD. Invasive fungal infection after lung transplantation: epidemiology in the setting of antifungal prophylaxis. Clin Infect Dis. 2020;70(1):30–9. **Baker et al. prospectively collected data on prevalence rates and timing of invasive fungal infections (IFIs), risk factors for IFIs, and data from IFIs that broke through standard antifungal prophylaxis (aerosolized amphotericin B lipid comple) during the lung transplant hospitalization at a tertiary care academic hospital. Their results showed that lung transplant recipients had high rates of IFIs, despite receiving prophylaxis. Their data suggest benefit in providing systemic antifungal prophylaxis targeting Candida for up to 90 days after transplant and extending mold-active prophylaxis for up to 180 days after surgery.**
6.•• Villalobos AP, Husain S. Infection prophylaxis and management of fungal infections in lung transplant. Ann Transl Med. 2020;8(6):414. **Villalobos et al. published a review which helps to provide an update in the current approaches for the diagnosis, management and prevention of fungal infections and complications in lung transplant patients.**
7.• Linder KA, Kauffman CA, Patel TS, Fitzgerald LJ, Richards BJ, Miceli MH. Evaluation of targeted versus universal prophylaxis for the prevention of invasive fungal infections following lung transplantation. Transpl Infect Dis. 2021;23(1):e13448. **Linder, et al compared universal with targeted antifungal prophylaxis for effectiveness in preventing IFI. Results from study showed that universal antifungal prophylaxis appears to be more effective than targeted antifungal prophylaxis for prevention of IFI after lung transplant.**
8. Arthurs SK, Eid AJ, Deziel PJ, Marshall WF, Cassivi SD, Walker RC, Razonable RR. The impact of invasive fungal diseases on survival after lung transplantation. Clin Transplant. 2010;24(3):341–8.
9. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50(8):1101–11.
10. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009;53(1):24–34.
11. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother. 2014;69(5):1162–76.
12.•• Husain S, Sole A, Alexander BD, Aslam S, Avery R, Benden C, Billaud EM, Chambers D, Danziger-Isakov L, Fedson S, et al.

The 2015 International Society for Heart and Lung Transplantation Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: executive summary. J Heart Lung Transplant. 2016;35(3):261–82. **A document created by International Society for Heart and Lung Transplantation (ISHLT) Infectious Diseases Council to help address the most relevant questions in the areas of epidemiology, diagnosis, prophylaxis, and treatment of fungal infections in adult and pediatric heart, lung, and MCSD patients.**

13.•• Shoham S, Dominguez EA. Practice tAIDCo: **Emerging fungal infections in solid organ transplant recipients: guidelines of the American Society of Transplantation Infectious Diseases Community of Practice**. Clin Transplant. 2019;33(9):e13525. **These are the most up-to date AST-IDCOP guidelines where they review the epidemiology, diagnosis, and management of emerging fungi after organ transplantation.**

14. Dhar D, Dickson JL, Carby MR, Lyster HS, Hall AV, Banner NR. Fungal infection in cardiothoracic transplant recipients: outcome without systemic amphotericin therapy. Transpl Int. 2012;25(7):758–64.

15. Park BJ, Pappas PG, Wannemuehler KA, Alexander BD, Anaissie EJ, Andes DR, Baddley JW, Brown JM, Brumble LM, Freifeld AG, et al. Invasive non-Aspergillus mold infections in transplant recipients, United States, 2001–2006. Emerg Infect Dis. 2011;17(10):1855–64.

16. Husain S, Kwak EJ, Obman A, Wagener MM, Kusne S, Stout JE, McCurry KR, Singh N. Prospective assessment of Platelia™Aspergillus galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transplant. 2004;4(5):796–802.

17. Pasqualotto AC, Xavier MO, Sánchez LB, de Oliveira Costa CDA, Schio SM, Camargo SM, Camargo JJ, Sukiennik TCT, Severo LC. Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. Transplantation. 2010;90(3):306–11.

18. Zou M, Tang L, Zhao S, Zhao Z, Chen L, Chen P, Huang Z, Li J, Chen L, Fan X. Systematic review and meta-analysis of detecting galactomannan in bronchoalveolar lavage fluid for diagnosing invasive aspergillosis. PLoS One. 2012;7(8):e43347.

19. Guo YL, Chen YQ, Wang K, Qin SM, Wu C, Kong JL. Accuracy of BAL galactomannan in diagnosing invasive aspergillosis: a bivariate metaanalysis and systematic review. Chest. 2010;138(4):817–24.

20. Prasad P, Fishman JA. Impact and cost of the serum galactomannan assay at a tertiary care facility. Transplantation. 2014;98(7):773–80.

21. Heng SC, Morrissey O, Chen SC, Thursky K, Manser RL, Nation RL, Kong DC, Slavin M. Utility of bronchoalveolar lavage fluid galactomannan alone or in combination with PCR for the diagnosis of invasive aspergillosis in adult hematology patients: a systematic review and meta-analysis. Crit Rev Microbiol. 2015;41(1):124–34.

22. Mengoli C, Cruciani M, Barnes RA, Loeffler J, Donnelly JP. Use of PCR for diagnosis of invasive aspergillosis: systematic review and meta-analysis. Lancet Infect Dis. 2009;9(2):89–96.

23. Gabe LM, Malo J, Knox KS. Diagnosis and management of coccidioidomycosis. Clin Chest Med. 2017;38(3):417–33.

24. Finkelman MA. Specificity influences in (1→3)-β-d-glucansSupported diagnosis of invasive fungal disease. J Fungi. 2021;7(1):14.

25. Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. Future Microbiol. 2012;7(5):639–55.

26. Nosotti M, Tarsia P, Morlacchi LC. Infections after lung transplantation. J Thorac Dis. 2018;10(6):3849–68.

27.•• Husain S, Camargo JF. Invasive Aspergillosis in solid-organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13544. **These updated AST-IDCOP guidelines provide information on epidemiology, diagnosis, and management of Aspergillus after organ transplantation.**

28. Singh NM, Husain S. Practice tAIDCo: Aspergillosis in solid organ transplantation. Am J Transplant. 2013;13(s4):228–41.

29. Fishman JA. Infection in organ transplantation. Am J Transplant. 2017;17(4):856–79.

30. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–60.

31.• Maertens JA, Rahav G, Lee D-G, Ponce-de-León A, Ramírez Sánchez IC, Klimko N, Sonet A, Haider S, Diego Vélez J, Raad I, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet. 2021;397(10273):499–509. **Maertens et al. conducted a randomized, prospective, double-blind, double-dummy, controlled trial aimed to assess non-inferiority of posaconazole to voriconazole for the primary treatment of invasive aspergillosis. Posaconazole was non-inferior to voriconazole for all-cause mortality up until day 42. Posaconazole was well tolerated, and participants had fewer treatment-related adverse events than in the voriconazole group. This study supports the use of posaconazole as a first-line treatment for the condition.**

32. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell ransplant recipients with graft-versus-host disease. Pharmacotherapy. 2007;27(12):1627–36.

33.• Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760–9. **The SECURE trial is a phase 3, double-blind, global multicentre, comparative-group study assessing the efficacy and safety of isavuconazole versus voriconazole in patients with invasive mold disease. Isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mold disease. Isavuconazole was well tolerated compared with voriconazole, with fewer study-drug-related adverse events. The results support the use of isavuconazole for the primary treatment of patients with invasive mold disease.**

34. Bhaskaran A, Mumtaz K, Husain S. Anti-Aspergillus prophylaxis in lung transplantation: a systematic review and meta-analysis. Curr Infect Dis Rep. 2013;15(6):514–25.

35. Husain S, Paterson DL, Studer S, Pilewski J, Crespo M, Zaldonis D, Shutt K, Pakstis DL, Zeevi A, Johnson B, et al. Voriconazole prophylaxis in lung transplant recipients. Am J Transplant. 2006;6(12):3008–16.

36. Kozuch JM, Feist A, Yung G, Awdishu L, Hays S, Singer JP, Florez R. Low dose posaconazole delayed release tablets for fungal prophylaxis in lung transplant recipients. Clin Transplant. 2018;32(8):e13300.

37. Qiao W, Zou J, Ping F, Han Z, Li L, Wang X. Fungal infection in lung transplant recipients in perioperative period from one lung transplant center. J Thorac Dis. 2019;11(4):1554–61.

38. Aslam S, Rotstein C. Practice tAIDCo: Candida infections in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13623.

39. Gadre SK, Koval C, Budev M. Candida blood stream infections post lung transplant. J Heart Lung Transplant. 2017;36(4):S241.
40. Palmer SM, Perfect JR, Howell DN, Lawrence CM, Miralles AP, Davis RD, Tapson VF. Candidal anastomotic infection in lung transplant recipients: successful treatment with a combination of systemic and inhaled antifungal agents. J Heart Lung Transplant. 1998;17(10):1029–33.
41. Chakrabarti A, Slavin MA. Endemic fungal infections in the Asia-Pacific region. Med Mycol. 2011;49(4):337–44.
42. Snydman DR, Singh N, Dromer F, Perfect JR, Lortholary O. Cryptococcosis in solid organ transplant recipients: current state of the science. Clin Infect Dis. 2008;47(10):1321–7.
43. Penumarthi LR, La Hoz RM, Wolfe CR, Jackson BR, Mehta AK, Malinis M, Danziger-Isakov L, Strasfeld L, Florescu DF, Vece G, et al. Cryptococcus transmission through solid organ transplantation in the United States: a report from the Ad Hoc Disease Transmission Advisory Committee. Am J Transplant. 2021;21(5):1911–23.
44. Baddley JW, Forrest GN. Cryptococcosis in solid organ transplantation-guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13543.
45. Singh N, Alexander BD, Lortholary O, Dromer F, Gupta KL, John GT, del Busto R, Klintmalm GB, Somani J, Lyon GM, et al. Pulmonary cryptococcosis in solid organ transplant recipients: clinical relevance of serum cryptococcal antigen. Clin Infect Dis. 2008;46(2):e12-18.
46. Husain S, Wagener MM, Singh N. Cryptococcus neoformans infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg Infect Dis. 2001;7(3):375–81.
47. Cruz MC, Del Poeta M, Wang P, Wenger R, Zenke G, Quesniaux VF, Movva NR, Perfect JR, Cardenas ME, Heitman J. Immunosuppressive and nonimmunosuppressive cyclosporine analogs are toxic to the opportunistic fungal pathogen Cryptococcus neoformans via cyclophilin-dependent inhibition of calcineurin. Antimicrob Agents Chemother. 2000;44(1):143–9.
48. Kollath DR, Miller KJ, Barker BM. The mysterious desert dwellers: Coccidioides immitis and Coccidioides posadasii, causative fungal agents of coccidioidomycosis. Virulence. 2019;10(1):222–33.
49. Miller R, Assi M. Practice tAIDCo: Endemic fungal infections in solid organ transplant recipients—guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13553.
50. Kusne S, Taranto S, Covington S, Kaul DR, Blumberg EA, Wolfe C, Green M. Coccidioidomycosis transmission through organ transplantation: a report of the OPTN Ad Hoc Disease Transmission Advisory Committee. Am J Transplant. 2016;16(12):3562–7.
51. Kuberski T, Herrig J, Pappagianis D. False-positive IgM serology in coccidioidomycosis. J Clin Microbiol. 2010;48(6):2047–9.
52. Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Geertsma F, Hoover SE, Johnson RH, Kusne S, Lisse J, MacDonald JD, et al. 2016 Infectious Diseases Society of America (IDSA) Clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016;63(6):e112-146.
53. Dierberg KL, Marr KA, Subramanian A, Nace H, Desai N, Locke JE, Zhang S, Diaz J, Chamberlain C, Neofytos D. Donor-derived organ transplant transmission of coccidioidomycosis. Transpl Infect Dis. 2012;14(3):300–4.
54. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin North Am. 2016;30(1):207–27.
55. Colombo AL, Tobón A, Restrepo A, Queiroz-Telles F, Nucci M. Epidemiology of endemic systemic fungal infections in Latin America. Med Mycol. 2011;49(8):785–98.
56. Benedict K, Mody RK. Epidemiology of histoplasmosis outbreaks, United States, 1938–2013. Emerg Infect Dis. 2016;22(3):370–8.
57. Newman SL. Cell-mediated immunity to Histoplasma capsulatum. Semin Respir Infect. 2001;16(2):102–8.
58.• Cuellar-Rodriguez J, Avery RK, Lard M, Budev M, Gordon SM, Shrestha NK, van Duin D, Oethinger M, Mawhorter SD. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. Clin Infect Dis. 2009;49(5):710–6. **Cuellar-Rodriguez et al., showed that post-transplantation histoplasmosis is rare even in endemic areas. Prognosis is good but requires lengthy treatment. Patients with latent infection did not develop post-transplantation histoplasmosis when prophylaxis was used.**
59. Wheat J, Myint T, Guo Y, Kemmer P, Hage C, Terry C, Azar MM, Riddell J, Ender P, Chen S, et al. Central nervous system histoplasmosis: multicenter retrospective study on clinical features, diagnostic approach and outcome of treatment. Medicine (Baltimore). 2018;97(13):e0245.
60. Araúz AB, Papineni P. Histoplasmosis. Infect Dis Clin North Am. 2021;35(2):471–91.
61. Mazi PB, Rauseo AM, Spec A. Blastomycosis. Infect Dis Clin North Am. 2021;35(2):515–30.
62. Grim SA, Proia L, Miller R, Alhyraba M, Costas-Chavarri A, Oberholzer J, Clark NM. A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. Transpl Infect Dis. 2012;14(1):17–23.
63. Frost HM, Novicki TJ. Blastomyces antigen detection for diagnosis and management of blastomycosis. J Clin Microbiol. 2015;53(11):3660–2.
64. Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, Kauffman CA. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(12):1801–12.
65. Rammaert B, Puyade M, Cornely OA, Seidel D, Grossi P, Husain S, Picard C, Lass-Flörl C, Manuel O, Le Pavec J, et al. Perspectives on Scedosporium species and Lomentospora prolificans in lung transplantation: results of an international practice survey from ESCMID fungal infection study group and study group for infections in compromised hosts, and European Confederation of Medical Mycology. Transpl Infect Dis. 2019;21(5):e13141.
66.• Vazirani J, Westall GP, Snell GI, Morrissey CO: Scedosporium apiospermum and Lomentospora prolificans in lung transplant patients – a single center experience over 24 years. Transplant Infect Dis, n/a(n/a):e13546. **Vazirani et al. performed a retrospective single center audit of all sputum/bronchoscopy samples for Scedosporium/Lomentospora species in LTx patients over a 24-year period. Their findings suggest the incidence of Scedosporium/Lomentospora is increasing and these organisms are typically isolated several years after LTx, and requires prolonged anti-fungal treatment that is usually associated with improved in lung function.**
67. Ramirez-Garcia A, Pellon A, Rementeria A, Buldain I, Barreto-Bergter E, Rollin-Pinheiro R, de Meirelles JV, Xisto MIDS, Ranque S, Havlicek V, et al. Scedosporium and Lomentospora: an updated overview of underrated opportunists. Med Mycol. 2018;56(suppl_1):S102–25.
68. Li JY, Yong TY, Grove DI, Coates PT. Successful control of Scedosporium prolificans septic arthritis and probable osteomyelitis without radical surgery in a long-term renal transplant recipient. Transpl Infect Dis. 2008;10(1):63–5.
69. Almyroudis NG, Sutton DA, Linden P, Rinaldi MG, Fung J, Kusne S. Zygomycosis in solid organ transplant recipients in a tertiary transplant center and review of the literature. Am J Transplant. 2006;6(10):2365–74.

70. Wand O, Unterman A, Izhakian S, Fridel L, Kramer MR. Mucormycosis in lung transplant recipients: a systematic review of the literature and a case series. Clin Transplant. 2020;34(2):e13774.
71. Steinbrink JM, Miceli MH. Mucormycosis. Infect Dis Clin North Am. 2021;35(2):435–52.
72. Furfaro E, Signori A, Di Grazia C, Dominietto A, Raiola AM, Aquino S, Ghiggi C, Ghiso A, Ungaro R, Angelucci E, et al. Serial monitoring of isavuconazole blood levels during prolonged antifungal therapy. J Antimicrob Chemother. 2019;74(8):2341–6.
73. Pilarczyk K, Haake N, Heckmann J, Carstens H, Haneya A, Cremer J, Jakob H, Pizanis N, Kamler M. Is universal antifungal prophylaxis mandatory in adults after lung transplantation? A review and meta-analysis of observational studies. Clin Transplant. 2016;30(12):1522–31.
74. Husain S, Zaldonis D, Kusne S, Kwak EJ, Paterson DL, McCurry KR. Variation in antifungal prophylaxis strategies in lung transplantation. Transpl Infect Dis. 2006;8(4):213–8.
75. Mitsani D, Nguyen MH, Shields RK, Toyoda Y, Kwak EJ, Silveira FP, Pilewski JM, Crespo MM, Bermudez C, Bhama JK, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: factors impacting levels of and associations between serum troughs, efficacy, and toxicity. Antimicrob Agents Chemother. 2012;56(5):2371–7.
76. Luong M-L, Hosseini-Moghaddam SM, Singer LG, Chaparro C, Azad S, Lazar N, Boutros PC, Keshavjee S, Rotstein C, Husain S. Risk gactors for voriconazole hepatotoxicity at 12 weeks in lung transplant recipients. Am J Transplant. 2012;12(7):1929–35.
77. Robinson CL, Chau C, Yerkovich ST, Azzopardi M, Hopkins P, Chambers D. Posaconazole in lung transplant recipients: use, tolerability, and efficacy. Transpl Infect Dis. 2016;18(2):302–8.
78.• Samanta P, Clancy CJ, Marini RV, Rivosecchi RM, McCreary EK, Shields RK, Falcione BA, Viehman A, Sacha L, Kwak EJ et al.: Isavuconazole is as effective as and better tolerated than voriconazole for antifungal prophylaxis in lung yransplant recipients. Clin Infect Dis 2020. **Samanta et al. compared effectiveness and tolerability of isavuconazole and voriconazole prophylaxis in lung transplant recipients by conducting a single-center, retrospective study of patients who received isavuconazole or voriconazole for antifungal prophylaxis. Results showed that Isavuconazole was effective and well-tolerated as antifungal prophylaxis following lung transplantation.**
79. Lo Re V 3rd, Carbonari DM, Lewis JD, Forde KA, Goldberg DS, Reddy KR, Haynes K, Roy JA, Sha D, Marks AR, et al. Oral azole antifungal medications and risk of acute kiver injury, overall and by chronic liver disease status. Am J Med. 2016;129(3):283-291 e285.
80. Wang J-L, Chang C-H, Young-Xu Y, Chan KA. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. Antimicrob Agents Chemother. 2010;54(6):2409–19.
81. Nguyen MH, Davis MR, Wittenberg R, McHardy I, Baddley JW, Young BY, Odermatt A, Thompson GR. Posaconazole serum drug levels associated with pseudohyperaldosteronism. Clin Infect Dis. 2020;70(12):2593–8.
82. Andes D, Kovanda L, Desai A, Kitt T, Zhao M, Walsh TJ. Isavuconazole concentration in real-world practice: consistency with results from clinical trials. Antimicrob Agents Chemother 2018, 62(7).
83. Borman AM, Hughes JM, Oliver D, Fraser M, Sunderland J, Noel AR, Johnson EM. Lessons from isavuconazole therapeutic drug monitoring at a United Kingdom Reference Center. Med Mycol. 2020;58(7):996–9.
84. Kosmidis C, Otu A, Moore CB, Richardson MD, Rautemaa-Richardson R. Isavuconazole therapeutic drug monitoring during long-term treatment for chronic pulmonary aspergillosis. Antimicrob Agents Chemother. 2020;65(1):e01511-01520.
85. The Sanford guide to antimicrobial therapy 2020. In. Edited by Gilbert DN, Chambers HF, Saag MS, Pavia AT. Sperryville, VA, USA: Antimicrobial Therapy, Inc.; 2020.
86. Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C, Cooper B, Dubberke ER, Engemann AM, Freifeld AG, et al. Prevention and treatment of cancer-related infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2016;14(7):882–913.
87. Dolton MJ, McLachlan AJ. Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity. Int J Antimicrob Agents. 2014;44(3):183–93.
88. Hussaini T, Rüping MJGT, Farowski F, Vehreschild JJ, Cornely OA. Therapeutic drug monitoring of voriconazole and posaconazole. Pharmacotherapy. 2011;31(2):214–25.
89. Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH, Song KH, Choe PG, Kim NJ, Jang IJ, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis. 2012;55(8):1080–7.
90. Ullmann AJ, Aguado JM, Akdagli A. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24:e1–38.
91. Saliba F, Dupont B. Renal impairment and Amphotericin B formulations in patients with invasive fungal infections. Med Mycol. 2008;46(2):97–112.
92. Botero Aguirre JP, Restrepo Hamid AM. Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. Cochrane Database Syst Rev. 2015(11).
93. Bahr NC, Rolfes MA, Musubire A, Nabeta H, Williams DA, Rhein J, Kambugu A, Meya DB, Boulware DR. Standardized electrolyte supplementation and fluid management improves survival during amphotericin therapy for cryptococcal meningitis in resource-limited settings. Open Forum Infect Dis. 2014;1(2):ofu070.
94. Cho E, Chan H, Nguyen H, Shayani S, Nakamura R, Pon D. Management of drug interaction between posaconazole and sirolimus in patients who undergo hematopoietic stem cell transplant. Pharmacotherapy. 2015;35(6):578–85.
95. Greco R, Barbanti MC, Lupo Stranghellini MT, Giglio F, Morelli M, Messina C, Forcina A, Oltolini C, Piemontese S, Scarpellini P, et al. Coadministration of posaconazole and sirolimus in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2016;51(7):1022–4.
96. Kubiak DW, Koo S, Hammond SP, Armand P, Baden LR, Antin JH, Marty FM. Safety of posaconazole and sirolimus coadministration in allogeneic hematopoietic stem cell transplants. Biol Blood Marrow Transplant. 2012;18(9):1462–5.
97. Marty FM, Lowry CM, Cutler CS, Campbell BJ, Fiumara K, Baden LR, Antin JH. Voriconazole and sirolimus coadministration after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2006;12(5):552–9.
98. Outeda Macías M, Salvador Garrido P, Elberdín Pazos L, Martín Herranz MI. Management of everolimus and voriconazole interaction in lung transplant patients. Ther Drug Monit. 2016;38(3):305–12.
99. Surowiec D, DePestel DD, Carver PL. Concurrent administration of sirolimus and voriconazole: a pilot study assessing safety and approaches to appropriate management. Pharmacotherapy. 2008;28(6):719–29.

100. Charhon N, Bernard C, Richard JC, Cordel N, Leboucher G, Broussolle C, Seve P. Off-label use of intravenous immunoglobulin therapy in the treatment of lupus myocarditis: two case reports and literature review. Rev Med Interne. 2017;38(3):204–9.
101. Billaud EM, Antoine C, Berge M, Abboud I, Lefeuvre S, Benammar M, Glotz D. Management of metabolic cytochrome P450 3A4 drug-drug interaction between everolimus and azole antifungals in a renal transplant patient. Clin Drug Investig. 2009;29(7):481–6.
102. Canafax DM, Graves NM, Hilligoss DM, Carleton BC, Gardner MJ, Matas AJ. Interaction between cyclosporine and fluconazole in renal allograft recipients. Transplantation. 1991;51(5):1014–8.
103. Torregrosa V, De la Torre M, Campistol JM, Oppenheimer F, Ricart MJ, Vilardell J, Andreu J. Interaction of fluconazole with ciclosporin A. Nephron. 1992;60(1):125–6.
104. Mañez R, Martin M, Raman D, Silverman D, Jain A, Warty V, Gonzalez-Pinto I, Kusne S, Starzl TE. Fluconazole therapy in transplant recipients receiving FK506. Transplantation. 1994;57(10):1521–3.
105. Toda F, Tanabe K, Ito S, Shinmura H, Tokumoto T, Ishida H, Toma H. Tacrolimus trough level adjustment after administration of fluconazole to kidney recipients. Transplant Proc. 2002;34(5):1733–5.
106. Cervelli MJ. Fluconazole-sirolimus drug interaction. Transplantation. 2002;74(10):1477–8.
107. Nakagita K, Wada K, Terada Y, Matsuda S, Terakawa N, Oita A, Takada M. Effect of fluconazole on the pharmacokinetics of everolimus and tacrolimus in a heart transplant recipient: case report. Int J Clin Pharmacol Ther. 2018;56(6):270–6.
108. Florea NR, Capitano B, Nightingale CH, Hull D, Leitz GJ, Nicolau DP. Beneficial pharmacokinetic interaction between cyclosporine and itraconazole in renal transplant recipients. Transplant Proc. 2003;35(8):2873–7.
109. Kramer MR, Merin G, Rudis E, Bar I, Nesher T, Bublil M, Milgalter E. Dose adjustment and cost of itraconazole prophylaxis in lung transplant recipients receiving cyclosporine and tacrolimus (FK 506). Transplant Proc. 1997;29(6):2657–9.
110. Banerjee R, Leaver N, Lyster H, Banner NR. Coadministration of itraconazole and tacrolimus after thoracic organ transplantation. Transplant Proc. 2001;33(1–2):1600–2.
111. Billaud EM, Guillemain R, Tacco F, Chevalier P. Evidence for a pharmacokinetic interaction between itraconazole and tacrolimus in organ transplant patients. Br J Clin Pharmacol. 1998;46(3):271–2.
112. Capone D, Gentile A, Imperatore P, Palmiero G, Basile V. Effects of itraconazole on tacrolimus blood concentrations in a renal transplant recipient. Ann Pharmacother. 1999;33(10):1124–5.
113. Sádaba B, Campanero MA, Quetglas EG, Azanza JR. Clinical relevance of sirolimus drug interactions in transplant patients. Transplant Proc. 2004;36(10):3226–8.
114. Romero AJ, Le Pogamp P, Nilsson LG, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther. 2002;71(4):226–34.
115. Vanhove T, Bouwsma H, Hilbrands L, Swen JJ, Spriet I, Annaert P, Vanaudenaerde B, Verleden G, Vos R, Kuypers DRJ. Determinants of the magnitude of interaction between tacrolimus and voriconazole/posaconazole in solid organ recipients. Am J Transplant. 2017;17(9):2372–80.
116. Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. Pharmacotherapy. 2007;27(6):825–34.
117. Charhon N, Valour F, Tod M: Management of drug-drug interaction between everolimus and azole antifungals in a cardiac transplant patient. In: 2017.
118. Cupri A, Leotta S, Markovic U, Camuglia MG, Milone GA, CurtoPelle A, Leotta V, Di Giorgio MA, Bulla A, Anna Lia DM, et al. Isavuconazole prophylaxis during early phases of allogeneic HSC transplantation is not associated to an increase need of cyclosporin-a dose modification. Blood. 2019;134(Supplement_1):3271–3271.
119. Kim T, Jancel T, Kumar P, Freeman AF. Drug-drug interaction between isavuconazole and tacrolimus: a case report indicating the need for tacrolimus drug-level monitoring. J Clin Pharm Ther. 2015;40(5):609–11.
120. Rivosecchi RM, Clancy CJ, Shields RK, Ensor CR, Shullo MA, Falcione BA, Venkataramanan R, Nguyen MH. Effects of isavuconazole on the plasma concentrations of tacrolimus among solid-organ transplant patients. Antimicrob Agents Chemother. 2017, 61(9).
121. Kieu V, Jhangiani K, Dadwal S, Nakamura R, Pon D. Effect of isavuconazole on tacrolimus and sirolimus serum concentrations in allogeneic hematopoietic stem cell transplant patients: a drug-drug interaction study. Transpl Infect Dis. 2019;21(1):e13007.
122. Azole-echinocandin combination therapy for invasive aspergillosis. In.: https://ClinicalTrials.gov/show/NCT04876716. Accessed 18 May 2021.
123. Evaluate F901318 treatment of invasive fungal infections in patients lacking treatment options. In.: https://ClinicalTrials.gov/show/NCT03583164. Accessed 18 May 2021.
124. Study to evaluate the efficacy and safety of ibrexafungerp in patients with fungal diseases that are refractory to or intolerant of standard antifungal treatment. In.: https://ClinicalTrials.gov/show/NCT03059992. Accessed 18 May 2021.
125. Open-label study of APX001 for treatment of patients with invasive mold infections caused by Aspergillus or rare molds. In.: https://ClinicalTrials.gov/show/NCT04240886. Accessed 18 May 2021.