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REVIEW

Invasive fungal infections and antifungal therapies in solid organ transplant recipients

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Summary

This manuscript will review the risk factors, prevalence, clinical presentation, and management of invasive fungal infections (IFIs) in solid organ transplant (SOT) recipients. Primary literature was obtained via MEDLINE (1966–April 2007) and EMBASE. Abstracts were obtained from scientific meetings or pharmaceutical manufacturers and included in the analysis. All studies and abstracts evaluating IFIs and/or antifungal therapies, with a primary focus on solid organ transplantation, were considered for inclusion. English-language literature was selected for inclusion, but was limited to those consisting of human subjects. Infectious complications following SOT are common. IFIs are associated with high morbidity and mortality rates in this patient population. Determining the best course of therapy is difficult due to the limited availability of data in SOT recipients. Well-designed clinical studies are infrequent and much of the available information is often based on case-reports or retrospective analyses. Transplant practitioners must remain aware of their therapeutic options and the advantages and disadvantages associated with the available treatment alternatives.

Introduction

Solid organ transplant (SOT) is a widely accepted treatment modality for end-stage organ disease. Advances in organ procurement, surgical techniques, immunosuppression and post-transplant care have improved allograft and patient survival. Despite this, the incidence of infectious complications post-transplant continues to be high. In SOT recipients, invasive fungal infections (IFIs) are aggressive and associated with high mortality rates [1–3]. The occurrence of IFIs is influenced by several factors, including the type of organ transplanted and degree of immunosuppression.

The prevalence of IFIs has declined over the past decade, due in large part to improvements in transplant surgical methods (i.e. reduced surgical complications, shortened duration of most transplant procedures) [4]. During this time period, we have seen a reduction in the number of infections caused by *Candida* but a rise in infection caused by *Aspergillus* and other less common fungi (i.e. *Fusarium*, Zygomycetes) [3–8]. Overall, *Candida* and *Aspergillus* account for more than 80% of IFIs in SOT [3–5].

Fungal infections pose a great challenge to practitioners, due to the lack of reliable diagnostic tests; making it increasingly more difficult to quickly and accurately identify IFIs [9–12]. Successful therapy hinges on prompt and precise identification of the fungal pathogen and appropriate selection of antifungal therapy [9]. The introduction of new triazoles and the glucan-synthesis inhibitors

has transformed medical management of IFIs. In general, antifungals must be selected cautiously in SOT recipients due to the potential for drug misadventures.

Epidemiology

Invasive fungal infections can be categorized into two types, opportunistic infections and geographically restricted mycoses. Opportunistic infections rarely cause disease in immunocompetent patients and include *Candida*, *Aspergillus*, *Cryptococcus*, and the Zygomycetes [13–15]. The geographically restricted mycoses cause primary or reactivation infections in patients living in or visiting endemic areas [13–15]. Table 1 outlines the incidence of major IFIs among SOT recipients.

Treatment decisions are often complicated due to difficulty in distinguishing between fungal colonization, contamination or infection [1–3,16,17]. Risk factors for colonization include broad-spectrum antibiotic use, environmental exposure, immunosuppression, and the presence of indwelling catheters [1–3,8,16–18]. Fungal overgrowth is also influenced by these factors and may predispose patients to IFIs [1,3,9]. Positive fungal cultures in SOT recipients must always be viewed judiciously. Overall, the severity of disease usually varies according to the pathogen and type of organ transplanted.

Risk factors

The occurrence of IFIs in transplant recipients depends predominantly on degree of risk. Risk factors vary in their capacity to influence the development of fungal infections. Identification of patient-specific risk factors allows practitioners to choose appropriate candidates for targeted prophylaxis [1]. Several categories of risk are discussed below and in Table 2.

Environmental

Certain geographic locations carry higher risk for development of IFIs [2,19–21]. Patients living in or visiting endemic areas should be advised about ways to reduce their risks of developing infection. Transplant recipients should be educated about potential hazards of occupational and recreational activities (i.e. farming, landscaping, gardening). Construction also plays a role in the development of IFIs, as it has been seen that construction in or around the hospital or patients' homes increases the risk of mould infections.

Table 1. Incidence of invasive fungal infections among transplant recipients [1–3,33,121].

Type of transplant	Incidence of IFIs (%)	Usual etiologic pathogen(s)
Heart	3–21	70–90% *Aspergillus*
Liver	4–42	35–91% *Candida* 9–34% *Aspergillus*
Lung and heart/lung	10–44	43–72% *Candida* 25–50% *Aspergillus*
Pancreas	6–38	97–100% *Candida*
Renal	1–14	50–80% *Candida* 7–19% *Aspergillus*
Small bowel	40–59	90% *Candida*

IFIs, invasive fungal infections.
The prevalence figures come from several sources and have a wide range. This is due, in most part, to geographic differences from reporting institutions and differences in IFIs rates over time. These figures also do not take into account the use of antibiotic prophylaxis, which may be used at some institutions but not at others.

Table 2. Risk factors associated with invasive fungal infections in solid organ transplant recipients [1–3,125].

Environmental
Hospital exposures/adjacent construction/contaminated ventilation systems and water supplies
Prolonged ICU requirement/mechanical ventilation
Agricultural, occupational, and recreational activities (i.e. gardening, horticultural activities, farming, landscaping, spelunking)
Poor hand washing/hygiene by health care providers
Marijuana use
Acquired myelosuppression
Diabetes mellitus
Malnutrition/debilitation
Ventricular assist device (heart transplants)
Reperfusion injury and bronchiolitis obliterans (lung transplant)
Travel to endemic areas
Immunosuppression/other medications
Pretransplant immunosuppression
Chronic graft dysfunction/chronic graft rejection and multiple courses of immunosuppression
Prolonged use of broad spectrum antibiotics
Prophylactic antimicrobials with myelosuppressive adverse events (i.e. co-trimoxazole, dapsone, valganciclovir, ganciclovir)
High dose corticosteroids
Use of lymphocyte depleting agents (antithymocyte globulin horse and rabbit, OKT3 and Campath-1H)
Surgical
Primary allograft dysfunction, nonfunction and retransplantation
Prolonged operative duration, reoperation and high intraoperative blood transfusions
Multivisceral transplantation
Small bowel transplant with colonic segment
Contaminated donor allograft
Surgical drains, catheters and surgical stents
Viral
Immunomodulating viruses (CMV, HSV, HHV-6, HHV-7, HCV)

CMV, cytomegalovirus; HSV, herpes simplex virus; HHV-6, human herpes virus-6; HHV-7, human herpes virus-7; HCV, hepatitis C virus.

Immunosuppression

Immunosuppression is an inescapable risk factor for infectious complications post-transplant. The extent of immunosuppression is greatly influenced by the number, dosage and mechanism of immunosuppressive medications employed. The risk for most IFIs is highest in the early post-transplant period, when immunosuppression is greatest [21,22]. In general, the degree of immunosuppression is reduced with time. However, some transplant recipients will develop rejection and require high-dose corticosteroid and/or antilymphocyte antibody (ALAs) therapy. Conversely, some immunosuppressants have antifungal properties and may aid in the prevention of post-transplant IFIs. Table 3 outlines the impact of the immunosuppressants on IFIs.

Surgical procedures

Transplant surgery and post-transplant care can influence the potential for IFIs. Integument barriers [i.e. skin, gastrointestinal (GI) and genitourinary (GU) tracts] are nonspecific defense mechanisms against infection. Disruptions of these barriers predispose patients to infection. To this end, fluid collections (i.e. blood, biliary leakage), surgical drains and catheters provide a source for fungal growth, but are all unavoidable aspects of transplantation.

A contaminated allograft may also be the nidus for infection. It is nearly impossible to exclude fungal colonization or subclinical infection in allografts, making the possibility of this mode of transmission real, yet rare. Reports of transplants from donors with infections caused by *Histoplasma*, *Cryptococcus*, and *Aspergillus* have all been reported [23–25].

Viral infections

Certain viral infections pose a unique risk factor for fungal infections. For example, cytomegalovirus (CMV) can generate allograft injury and rejection, which may necessitate added or enhanced immunosuppression. Some viruses induce systemic immunosuppression [i.e. CMV, human herpes virus-6 (HHV-6), human herpes virus-7 (HHV-7), hepatitis C] and increase the risk for co-infection by fungal pathogens [5,26–30].

Table 3. Impact of immunosuppressants on invasive fungal infections (IFIs).

Agent(s)	Clinical effect
Immunosuppressants with antifungal properties	
Calcineurin inhibitors	Calcineurin phosphatase plays an important role in growth, morphology and virulence of several pathogenic fungi and the antifungal activity of the calcineurin inhibitors is mediated through inhibition of this enzyme. These agents have been shown to possess potent anticryptococcal properties, but also have some activity against both *Candida* and *Aspergillus* [126]
Mycophenolic acid	It appears that mycophenolic acid has activity against *Pneumocystis jiroveci*, most likely through inhibition of inosine monophosphate dehydrogenase. This agent does not appear to have activity against other pathogenic fungi [126]
Sirolimus	TOR inhibitors have potent antifungal characteristics. TOR kinases have been identified in several fungi and promote cell proliferation. Sirolimus appears to have activity against those fungi that are dependent on TOR activity, which include *Candida*, *Cryptococcus*, *Fusarium*, *Penicillium*, *Saccharomyces*, and *Schizosaccharomyces* [126]
Immunosuppressants that increase the risk for IFIs	
ALAs	The use of lymphocyte depleting agents for both induction therapy and treatment of acute rejection have been found to be an independent risk factor for the development of fungal infections, particularly invasive aspergillosis [8,17,127]
Corticosteroids	A direct relationship between high-dose steroid administration, exposure to *Aspergillus* conidia and subsequent development of *Aspergillus* infections has been reported. Corticosteroids suppress macrophage function against *Aspergillus*, increasing the risk of tissue invasion [6,128]
Medications with myelosuppressive properties (miscellaneous)	Neutropenia is a common complication after organ transplant due to the myelosuppressive effects of induction and maintenance immunosuppressive therapies and prophylactic antibiotics (i.e. co-trimoxazole, valganciclovir). It is also a major risk factor for the development of IFIs [22]. Monitoring neutrophil counts is a vital step in decreasing patients' infection risk.

ALAs, antilymphocyte antibodies; TOR, target of rapamycin.

Timing of fungal infections

The post-transplant course can be divided into three periods for infection risk: the first month, months one through six and >6 months post-transplantation. Table 4 details the timing of IFIs.

Fungal pathogens

This section will discuss pertinent information regarding several fungal pathogens. It should be noted that the prevalence and mortality estimates come from several sources and have a wide range. This is due, in most part, to geographic differences from reporting institutions and differences in IFIs rates over time. These data also do not take into account the use of antibiotic prophylaxis, which may be used at some institutions but not at others. Also, diagnostic procedures are not explicitly detailed in this review; however, Table 5 outlines some general diagnostic strategies for some of the common fungal pathogens.

Candida

Candida, a yeast, is the most common cause of opportunistic fungal infections. *Candida* is normal flora of the skin, GI and GU tracts and is a frequent colonizer of mucous membranes. There are more than 150 species of *Candida* [1,15,28,31]. The incidence of *Candida* infections after SOT ranges from 1% to nearly 60%, with the highest prevalence seen in abdominal transplant recipients [1–3]. Overall, *Candida* infections are decreasing in transplant recipients; however, infections by non-*albicans* species of *Candida* are on the rise [1,2]. The non-*albicans* species are more common in patients who have received antifungal prophylaxis and are associated with higher mortality rates compared to *Candida albicans* [32]. In general, the crude mortality rate associated with *Candida* infections in SOT recipients ranges from 5% to 77% [1–3].

Candida produces a variety of infectious complications and distinguishing between colonization and infection is challenging. Invasive candidiasis is the most prevalent type of *Candida* infection in the transplant population and can present in many ways, which usually overlap [1–3,15]. Table 6 describes the characteristics of the most common manifestations. Cutaneous candidiasis and infection of mucosal surfaces are also seen in SOT recipients and typically present as oropharangeal candidiasis, esophagitis or vulvovaginitis [1,3,15].

Aspergillus

Aspergillus is usually isolated from soil, decaying vegetation and water. Inhalation of *Aspergillus* conidia is common; however, infection in the immunocompetent host is rare [15]. In SOT recipients, the incidence of *Aspergillus* infection ranges from 1% to 15% [1,3,33]. The mortality rate for invasive aspergillosis is related to the type of transplant and is often >55% [1,3,8,17,18,33–36]. There are over 300 species of *Aspergillus*, with *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger* being the most problematic in the immunocompromised [15,33]. Of these, *A. fumigatus* and *A. flavus* account for nearly 90% of infections in SOT recipients [8,17,18,33–36].

The principal manifestations of *Aspergillus* in SOT recipients are tracheobronchitis, bronchial anastomotic aspergillosis, pulmonary aspergilloma and invasive aspergillosis. *Aspergillus* infections can also rarely present as otomycosis, exogenous endophthalmitis, allergic fungal sinusitis and urinary tract aspergillomas [15,33].

Table 4. Timing of invasive fungal infections post-transplantation [1–3].

Timing	Comments
<1 month	Wound infections and rarely invasive infections due to *Candida* may develop during this time period
	Infections by other fungi are rare; however, aspergillosis may occur in patients colonized prior to the transplant (i.e. lung transplant recipients with cystic fibrosis)
Months 1–6	*Candida* infections are less common during this time period unless drains or indwelling catheters are present
	Infection by *Aspergillus* or the geographically restricted mycoses is most common between months one and six post-transplant
>6 months	At this point, only patients who have required a higher-degree of immunosuppression or those with complications that require subsequent trips to the operating room or the use of indwelling catheters or drains are at risk for opportunistic infection or endemic mycoses
	Cryptococcus neoformans is an exception, as kidney, heart and liver transplant recipients are more likely to develop this infection >6 months after transplantation

Table 5. Laboratory methods used for the diagnosis of invasive fungal infection.

Conventional microbiologic methods	Direct microscopy* (Gram, Giemsa, and KOH/calcofluor stains)
	Culture†
	Identification
	Susceptibility testing
Histopathologic methods	Conventional microscopy
	Direct immunofluorescence
	In situ hybridization
Immunologic and biochemical methods	Histoplasma antigen test
	Cryptococcal antigen test
	Galactomannan test‡
	(1 → 3)β-d-glucan test§,¶
Chromogenic and molecular methods	Direct detection
	PCR**
	Identification, e.g. PNA FISH test for *Candida* sp.††

*Direct microscopy can often only provide an etiologic diagnosis of infection caused by *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis (posadasii)*, *Pneumocystis jiroveci (carinii)*, or *Penicillium marneffei*.

†Fungi have longer generation times than most bacteria, and may test negative even when disseminated disease is present.

‡Galactomannan (GM) is a cell-wall polysaccharide specific to aspergillus species that is detectable in serum and other body fluids, reported as optical density an index value of >0.49 is positive. False-positive GM assay results have been reported for patients receiving piperacillin-tazobactam and amoxicillin-clavulanate.

§(1 → 3)β-d-glucan (BG) is a cell wall constituent of many pathogenic fungi, including *Aspergillus* and *Candida* species, this is not expressed in *Cryptococcus* species or Zygomycetes, serum levels of ≥80 pg/ml are consider positive. Since BG is ubiquitous in the environment, false positive results may be caused by poor specimen handling, hemodialysis using certain cellulose membranes, exposure to certain types of gauze, recent receipt of albumin or immunoglobulin products.

¶To date, this assay has not been evaluated in pediatric or solid organ transplant populations.

**Despite promising reports, PCR for the diagnosis of IFI has not been widely used in the clinical setting.

††*Candida albicans* peptide nucleic acid (PNA) fluorescence *in situ* hybridization (FISH) test.

Cryptococcus

Cryptococcus is an encapsulated yeast found in soil. There are 37 species of *Cryptococcus*, with *Cryptococcus neoformans* being the major human pathogen [37]. The incidence of cryptococcosis accounts for only about 3% of IFIs in SOT recipients, but is associated with a mortality rate of approximately 40% [38–42]. Most cases of cryptococcosis occur more than 1-year post-transplant, with one analysis reporting the median time to occurrence being 1.6 years after SOT [38].

The central nervous system (CNS) is the most frequent site of infection in SOT recipients, accounting for 55% of cryptococcosis, with meningitis being the most frequent clinical manifestation of CNS cryptococcosis [38]. Cutaneous disease accounts for 13% of cryptococcal infections in transplant recipients and generally affects the skin or soft tissue [38].

Endemic dimorphic fungi

Blastomyces

In North America, *Blastomyces dermatitidis* is endemic to the southeastern and south central United States [43]. The infection is acquired after inhalation and presents 30–45 days later as an acute pulmonary disease, indistinguishable from bacterial pneumonia. Nearly 50% of primary infections are asymptomatic. Outside the lungs, blastomycosis affects the skin, bones and GU tract [43]. *Blastomyces* infections among SOT recipients appears to be uncommon [31,44].

Coccidiodes

Coccidiodes immitis is only endemic to the Western Hemisphere. including the southwestern United States, northern Mexico and parts of Central America [45]. Coccidioidomycosis is acquired after spore inhalation, with an acute respiratory infection ensuing 1–3 weeks later. This disease usually resolves rapidly, but may cause a chronic pulmonary condition or disseminate to the CNS, bones, joints, and skin. Approximately 25% of patients with disseminated disease have meningitis [45]. In endemic areas, the incidence of coccidioidal infection after SOT is 4–8% [46,47]. Coccidioidomycosis generally occurs within the first year post-transplant and is usually a reactivation infection [3,46,47].

Histoplasma

Histoplasma capsulatum var. capsulatum is endemic to the central United States and other North American countries [48]. Histoplasmosis is the most prevalent endemic mycosis in the Americas. Most infections are asymptomatic, but pulmonary disease can occur [48]. Dissemination commonly occurs in immunocompromised individuals [48]. The overall incidence of histoplasmosis in SOT recipients has not been established; however, one case-series reports an incidence of 1.9% and crude mortality rate of 11% among renal transplant recipients living in endemic areas [49].

Rare fungi

Fusarium

Fusarium spp., filamentous fungi found mostly in tropical and subtropical areas, contains over 20 species, with *Fusarium solani*, *Fusarium oxysporum*, and *Fusarium*

Table 6. The clinical characteristics of invasive *Candida* infections [129].

Form	Characteristics
Catheter-related candidemia	Invasive candidiasis is most commonly due to infection of a vascular catheter Catheter removal drastically improves the outcomes. However, drug therapy is still recommended to eradicate any local infection and to clear any undetected *Candida* in the blood
Acute disseminated candidiasis	Classically defined as candidemia with organ involvement The nidus of the infection may have been a vascular catheter; however, the catheter now represents only a minor element of the overall disease Treatment involves removal of any identifiable cause of the infection, sepsis symptom management and antifungal therapy
Chronic disseminated candidiasis	This form (i.e. hepatosplenic candidiasis) occurs almost exclusively after a prolonged episode of myelosuppression associated with therapy for hematological malignancies Infection of the liver, spleen and kidneys, are common
Deep organ candidiasis	All organs are susceptible to hematologic spread of *Candida* Chronic disseminated candidiasis (listed above) is also a type of deep organ candidiasis, the etiology of chronic disseminated candidiasis distinguishes it from deep organ candidiasis

chlamydosporus being most common. Cutaneous manifestations are typical, with dissemination generally occurring in neutropenic patients [50,51]. In SOT recipients, *Fusarium* infections have a propensity to remain localized and are associated with improved outcomes compared to fusariosis in patients with hematological malignancies [50].

Phaeohyphomycosis

Phaeohyphomycosis refers to infections caused by darkly pigmented moulds. These dematiaceous fungi are found worldwide, but are most prevalent in tropical and subtropical areas. *Exophiala* spp. and *Alternia* spp. account for the majority of phaeohyphomycosis and typically present with subcutaneous and CNS manifestations [52]. Several case reports of phaeohyphomycosis in SOT recipients exist [52–57]. One study describes phaeohyphomycosis accounting for nearly 10% of all IFIs in liver and heart transplant recipients [55].

Zygomycosis

Zygomycosis refers to infections produced by the Zygomycetes, which consists of *Absidia corymbifera*, *Cunninghamella bertholletiae, Rhizomucor pusillus*, and *Rhizopus arrhizus*, among others. Zygomycetous fungi are ubiquitous to the environment and are typically found in soil. The estimated prevalence of zygomycosis in SOT recipients is 1–9% [58–60]. In one case-series, zygomycosis was highly associated with corticosteroids and diabetes [60]. Zygomycosis typically presents as rhino-sinusitis, or pulmonary, GI or cutaneous disease at a median of 60 days post-transplant [60]. In one analysis, the overall mortality rate of zygomycosis in SOT recipients was approximately 50%, although the majority of patients in this analysis had cutaneous disease [59]. Looking specifically at patients with disseminated disease, the mortality rate was 100% [59].

Antifungal therapies

There are few well-designed studies specifically addressing management of IFIs in transplant recipients. Consequently, a consensus on the most appropriate therapeutic options for these infections does not exist. In order for transplant practitioners to make informed decisions about the most appropriate antifungal agents to use in their patients they must have a basic understanding of these medications' spectrum of activity, mechanism of action and potential for drug misadventures. The different antifungal classes are reviewed below and in Tables 7 and 8.

Allylamines

These agents reduce ergosterol biosynthesis, making them theoretically similar to the triazole antifungals [61,62]. Terbinafine is the most utilized allylamine and is a squalene epoxidase inhibitor. Several case reports outline the effectiveness of terbinafine for the treatment of both localized and systemic fungal infections in SOT recipients [62–68].

Antimetabolites

Flucytosine is the only antimetabolite antifungal. This agent is converted to fluorouracil, subsequently interfering

Table 7. Antifungal spectrum of activity of selected antifungal agents [62].

	Antifungal agents						
Organism	AmB*	Flu	Itra	Vori	Posa	Echino†	Flucyto
Aspergillus	+	–	+	+	+	+	–
A. flavus	±	–	+	+	+	+	–
A. fumigatus	+	–	+	+	+	+	–
A. niger	+	–	+	+	+	+	–
A. terreus	–	–	+	+	+	+	–
Candida	+	+	+	+	+	+	+
C. albicans	+	+	+	+	+	+	+
C. glabrata	+	±	±	+	+	+	+
C. krusei	+	–	±	+	+	+	±
C. lusitaniae	–	+	+	+	+	+	+
C. parapsilosis	+	+	+	+	+	+	+
C. tropicalis	+	+	+	+	+	+	+
Cryptococcus	+	+	+	+	+	–	+
Coccidioides	+	+	+	+	+	±‡	–
Blastomyces	+	+	+	+	+	±‡	–
Histoplasma	+	+	+	+	+	±‡	–
Fusarium	±	–	–	+	+	–	–
Zygomycetes	±	–	–	–	+	–	–

AmB, amphotericin B; Flu, fluconazole; Itra, itraconazole; Vori, voriconazole; Posa, posaconazole; Echino, echinocandins; Flucyto, flucytosine.

Plus signs (+) indicate that the antifungal agent has activity against the organism specified. Minus signs (–) indicate that the antifungal agent does not have activity against the organism specified. Plus-minus signs (±) indicate that the agent has variable activity against the organism specified.

Adapted with permission from Dodds Ashley *et al.* [62].

*Includes lipid formulations.

†Includes caspofungin, micafungin, and anidulafungin.

‡*In vitro* data show that the echinocandins (specifically, micafungin) may have variable activity against the dimorphic fungi, depending on whether they are in the mycelial or yeast-like form. To date, there has been one case report of successful therapy with caspofungin for *Coccidiodes immitis* infection.

with fungal RNA and protein synthesis [61,62]. Flucytosine has proven useful in combination therapy for treatment of several IFIs in transplant recipients [40,41,69–72].

Glucan synthesis inhibitors (echinocandins)

These agents exhibit their fungicidal activity by inhibiting β-1,3-glucan synthase with a subsequent reduction in glucan biosynthesis. Glucan is a key component of the fungal cell wall [61,62]. The echinocandin class is composed of caspofungin, micafungin, and anidulafungin. Although very appealing due to their low-risk of drug misadventures, the glucan synthesis inhibitors have not been well studied in SOT recipients, though case reports exist [73–75].

Polyenes

The polyenes bind to ergosterol in the fungal cell membrane and alter its permeability causing leakage of cellular components resulting in cell death [61,62]. This class is composed of amphotericin B deoxycholate [conventional amphotericin B (CAB)] and the lipid formulations of amphotericin B. Nystatin is also a polyene antifungal, but due to its lack of a safe systemic dosage form, it will not be discussed further. CAB has long been used for management of IFIs in SOT recipients. However, its potential to induce nephrotoxicity, especially, when used in conjunction with calcineurin inhibitors has limited its use [61,62,76]. Use of the lipid-based amphotericin B formulations and novel routes of administration (i.e. nebulization) have sparked further evaluation of the polyenes in SOT recipients [77–82].

Triazoles

The triazoles reduce ergosterol synthesis by inhibiting fungal cytochrome P450 enzymes, particularly, 14-α-demethylase, which results in impaired cell membrane formation [61,62]. The triazoles include fluconazole, itraconazole, voriconazole, and posaconazole.

Table 8. Pharmacologic characteristics of the antifungals [61].

Drug class/drug	Common dosing*	Renal/hepatic dosing adjustments	Therapeutic drug monitoring	Adverse events
Antimetabolites				
Flucytosine	25–150 mg/kg/day given in 4 divided doses (every 6 h)	**Renal**: GFR = 10–50 ml/min increase dosing interval to 12–24; GFR < 10 ml/min increase dosing interval to every 24–48 h **Hepatic**: no adjustments necessary	Yes – serum sample should be drawn two hours after dose with a target range of <100 μg/ml	**Common** *Dermatologic*: rash *GI*: N, V, D *Hepatic*: elevated liver enzymes *Neurologic*: confusion, HA, somnolence *Psychiatric*: hallucinations **Serious** *Cardiovascular*: cardiotoxicity *Hematologic*: myelosuppression
Glucan synthesis inhibitors				
Anidulafungin	50–200 mg/day *Comments*: loading dose is required; preparation contains alcohol; rate of infusion should not exceed 1.1 mg/min to avoid infusion reactions	**Renal**: no adjustments necessary **Hepatic**: no adjustments necessary	No	**Common** *GI*: N, D *Metabolic*: hypokalemia **Serious** *Cardiovascular*: deep venous thrombosis, hypotension *Hematologic*: myelosuppression *Hepatic*: elevated liver enzymes
Caspofungin	50–70 mg/day *Comments*: loading dose is required.	**Renal**: no adjustments necessary **Hepatic**: moderate insufficiency, aspergillosis = 70 mg load, then 35 mg daily; esophageal and/or oropharyngeal candidiasis = 35 mg daily	No	**Common** *Dermatologic*: swelling, pruritus, rash *GI*: N, V, D *Neurologic*: HA *Other*: fever, thrombophlebitis **Serious** *Hematologic*: myelosuppression *Hepatic*: elevated liver enzymes
Micafungin	50–150 mg/day	**Renal**: no adjustments necessary **Hepatic**: no adjustments necessary	No	**Common** *Cardiovascular*: phlebitis *Dermatologic*: rash *GI*: abdominal pain, N, V, D *Neurologic*: HA *Other*: fever, rigor **Serious** *Hematologic*: myelosuppression *Hepatic*: elevated liver enzymes

Triazoles				
Fluconazole	*Neutropenic*: 6–12 mg/kg/day *Non-neutropenic*: 200–800 mg/day *Comments*: oral and IV doses are equivalent	**Renal**: GFR < 50 ml/min reduce the dose by 50% **Hepatic**: no adjustments necessary	No	**Common** *Dermatologic*: pruritus, rash *GI*: N, V *Hepatic*: elevated liver enzymes *Neurologic*: HA
Itraconazole	100–800 mg/day given in one to four divided doses *Comments*: capsules have a poor bioavailability compared to solution	**Renal**: no adjustments necessary; however, the intravenous dosage form should not be used in patients with a GFR < 30 ml/min due to potential for accumulation of its vehicle (hydroxypropyl-β-cyclodextran) **Hepatic**: no adjustments necessary	Yes – serum trough concentrations should be drawn 1 week after therapy with a target trough of >0.5 μg/ml	**Common** *Dermatologic*: rash *GI*: N, V, D (increased diarrhea with the solution due to the cyclodextran component) *Metabolic*: hypokalemia **Serious** *Cardiovascular*: Congestive heart failure and peripheral edema (IV formulation only) *Dermatologic*: Stevens-Johnson syndrome *Hematologic*: myelosuppression *Hepatic*: hepatotoxicity
Posaconazole	600–800 mg/day given in one to three divided doses *Comments*: currently available only as an oral solution	**Renal**: no adjustments necessary **Hepatic**: no adjustments necessary	No	**Common** *GI*: abdominal pain, N, V, D **Serious** *Cardiovascular*: prolonged QT interval *Hepatic*: cholestasis, hyperbilirubinemia, elevated liver enzymes, liver failure *Metabolic*: adrenal insufficiency *Neurologic*: seizure
Voriconazole	IV: 6 mg/kg every 12 h × 2 doses, then 3–4 mg/kg every 12 h PO: 200–300 mg every 12 h for patients weighing >40 kg; 100–150 mg every 12 h for patients < 40 kg	**Renal**: no adjustments necessary; however, the intravenous dosage form should not be used in patients with a GFR < 50 ml/min due to potential for accumulation of its vehicle (sulfobutyl ether beta-cyclodextrin) **Hepatic**: Mild–moderate hepatic insufficiency, administer the standard loading dose and reduce maintenance doses by 50%; Severe hepatic insufficiency, this agent should be avoided	Yes – serum trough concentrations should be drawn 1 week after therapy with a target trough range of 2–6 μg/ml	**Common** *Cardiovascular*: peripheral edema *Dermatologic*: rash *GI*: N, V, D *Neurologic*: HA *Ophthalmic*: visual disturbance *Other*: fever **Serious** *Dermatologic*: Stevens-Johnson syndrome *Hepatic*: liver failure

Table 8. (*Continued*)

Drug class/drug	Common dosing*	Renal/hepatic dosing adjustments	Therapeutic drug monitoring	Adverse events
Polyenes				
CAB	0.25–1.5 mg/kg/day *Comment*: doses are given over 2–6 h, some continuous infusion data shows a safety benefit, but efficacy of this method has not been evaluated [130–132]	**Renal**: GFR < 10 ml/min consider increasing dosage interval (every 36 h) **Hepatic**: no adjustments necessary	No	**Common** *GI*: N, V, D, indigestion, loss of appetite *Metabolic*: weight loss *Other*: infusion-related reactions (malaise, chills, fever, headache, rigors) **Serious** *Cardiovascular*: cardiac dysrhythmia, hypotension, thrombophlebitis *Hematologic*: myelosuppression *Metabolic*: hypokalemia, hypomagnesemia *Neurologic*: seizure *Ophthalmic*: blurred vision, diplopia *Renal*: nephrotoxicity *Respiratory*: tachypnea
ABCD	3–7.5 mg/kg	**Renal**: no adjustments necessary **Hepatic**: no adjustments necessary	No	**Common** *Cardiovascular*: hypotension *Metabolic*: hypokalemia, hypomagnesemia *Other*: infusion-related reactions (malaise, chills, fever, headache, rigors) **Serious** *Hematologic*: myelosuppression *Renal*: nephrotoxicity
ABLC	3–5 mg/kg	**Renal**: no adjustments necessary **Hepatic**: no adjustments necessary	No	**Common & Serious** *See ABCD*
L-AmB	1–6 mg/kg/day	**Renal**: no adjustments necessary **Hepatic**: no adjustments necessary	No	**Common & Serious** *See ABCD*

*All doses depend on the pathogen, severity of illness and dosage form utilized.

ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; CAB, conventional amphotericin B; D, diarrhea; GFR, glomerular filtration rate; GI, gastrointestinal; HA, headache; IV, intravenous; L-AmB, liposomal amphotericin B; N, nausea; V, vomiting.

Table 9. Summary of prophylaxis recommendations [1].

Type of transplant	Fungal pathogen targeted	High-risk characteristic(s)	Antifungal agent(s)	Suggested duration
Heart	*Aspergillus* or *Candida*	Reoperation, post-transplant renal failure or CMV disease (*Aspergillus*); VAD (*Candida*)	Routine prophylaxis not recommended	N/A
Liver	*Aspergillus*	Post-transplant renal failure, retransplantation, fulminant hepatic failure prior to transplantation and post-transplant infection by CMV or HHV-6	Lipid-AmB 2.5–5 mg/kg/day	≥4 weeks
Liver	*Candida*	Repeated operation, higher intraoperative transfusion requirement, longer operation time and renal failure	Fluconazole 400 mg/day	≥4 weeks
Lung	*Aspergillus*	Airway specimen cultures positive for *Aspergillus,* increased immunosuppression, CMV infection and obliterative bronchiolitis	Voriconazole 6 mg/kg IV × 2 doses, then 200 mg po bid, [89] itraconazole or echinocandins ± nebulized CAB or lipid-AmB	4–6 months
Lung	*Candida*	Airway specimen cultures positive for *Candida,* increased immunosuppression, CMV infection and obliterative bronchiolitis	Fluconaozole 400 mg/day	4–6 months
Pancreas	*Candida*	Enteric drainage procedure, pancreas transplantation after kidney transplantation, preoperative peritoneal dialysis, pancreatitis after reperfusion and retransplantation	Fluconazole 400 mg/day	≥4 weeks
Renal	*Candida*	CMV disease, excessive immunosuppression and candiduria	Routine prophylaxis not recommended	N/A
All organs	*Coccidioides immitis*	History of coccidioidal pulmonary infection or reactive coccidioidal serology before transplantation	Triazole antifungal	Prolonged or perhaps indefinite

AmB, amphotericin B; bid, twice daily; CAB, conventional amphotericin B; CMV, cytomegalovirus; HHV-6, human herpes virus-6; IFIs, invasive fungal infections; IV, intravenous; po, by mouth; VAD, ventricular assist device.

These antifungals have been studied in SOT recipients for prophylaxis [34,35,83–91]. Also, several case studies and small-scale clinical studies have proven these agents to be effective in the treatment of IFIs in this population [72,92–97].

Appropriate treatment modalities

Prophylaxis

With well-designed studies lacking, it is difficult to provide practitioners with universally accepted, evidence-based recommendations on antifungal prophylaxis in organ transplant recipients. The protection garnered by antifungal prophylaxis is a direct function of the spectrum of activity of the agent used and also the specific target population. One concern with the use of anti-infectives is the potential for resistance. This is also true with the antifungal agents, as resistance concerns exist with regards to the *Candida* spp. As discussed earlier, there has been a shift to non-*albicans Candida* as the causative organisms of invasive candidiasis rather than *C. albicans*. Reports of resistance of *Candida* to the triazoles exist in abundance and many practitioners have attributed this shift to inappropriate dosing strategies and increased use of triazole prophylaxis [1].

The American Society of Transplantation and American Society of Transplant Surgeons have organized a set of organ-specific prophylaxis recommendations [1]. Together with these guidelines, newer studies and case reports, allograft-specific prophylaxis options are reviewed. Table 9 summarizes these recommendations.

Heart transplant

Invasive fungal infections are infrequent in heart transplantation, occurring in approximately 3–21% of patients [1–3,18,98]. Aspergillosis is the most common IFI in this population, occurring in 1–14% of patients [3,18]. *Aspergillus* and *Candida* infections have a median time to occurrence of 23 and 44 days post-transplantation, respectively [99,100]. One analysis cites reoperation, post-transplant renal failure or development of CMV disease to be independent risk factors for an increased incidence of invasive aspergillosis in heart transplant recipients [34].

In patients supported by a ventricular assist device (VAD), the risk for development of IFIs is much higher

[101–103]. The most likely offending organism in VAD-patients is *Candida*, with an incidence of 28–55% [102,103]. The common sites for candidal infection in VAD-patients include the bloodstream and in and around the VAD itself [102,103].

Recommendations for prophylaxis

Antifungal prophylaxis after heart transplantation is not commonplace. However, one study demonstrated the benefit of inhaled CAB [77]. A second study established that prophylaxis with itraconazole (400 mg/day for 3–6 months post-transplant) had an independent protective value (RR = 0.2%) against development of IFIs [34]. This study also showed that patients receiving itraconazole had an improved 1-year graft survival versus patients not receiving prophylaxis [34]. Based on these data, antifungal prophylaxis in high-risk heart transplant recipients is reasonable.

In patients with a left VAD receiving broad-spectrum antibiotics or colonized with *Candida*, fluconazole is effective at preventing invasive candidiasis [102]. For patients that develop an infection within the VAD, surgical exchange of the infected component is warranted [102,103]. If this cannot be accomplished, antifungal therapy should be initiated and continued until transplantation. These patients should be monitored for symptoms of dissemination, sepsis, and VAD dysfunction. Antifungal therapy is recommended to continue after transplantation, although the length of therapy has not been defined [102].

Liver transplant

In liver transplant recipients, IFIs are reported to occur in 4–42% of patients [1,2,33]. *Candida* (35–91%) and *Aspergillus* (9–34%) account for nearly all IFIs in liver transplant recipients [1,3,33]. Attributable mortality is high with both pathogens (*Aspergillus* = 87–100%; *Candida* = ~70%) [3,33]. In liver transplantation, there are precise and validated risk factors for development of aspergillosis, which include renal failure, retransplantation, fulminant pretransplant hepatic failure, and post-transplant infection with CMV or HHV-6 [104,105]. Need for renal replacement therapy increases the risk for development of invasive aspergillosis 15- to 25-fold [104,105]. Patients requiring retransplantation are at a 30-fold higher risk for *Aspergillus* infections [104,105]. In particular, late retransplantation (>30 days postprimary transplant) is a significant risk for disseminated aspergillosis with CNS involvement and the mortality rate in these patients is much higher compared to early retransplant patients [104,105].

Aspergillosis in liver transplant recipients has generally been thought of as an infection that occurs in the early post-transplant period. However, newer data suggest that nearly 55% of invasive aspergillosis cases occur more than 90 days post-transplant [106]. Liver transplant recipients are uniquely vulnerable to disseminated aspergillosis. Nearly 60% of *Aspergillus* infections in this population result in disseminated disease, a rate even higher than in stem-cell transplant recipients [33].

Recommendations for prophylaxis

Most experts recommend antifungal prophylaxis for liver transplant recipients, especially, those at high-risk for aspergillosis. A recent meta-analysis reviewed six studies (698 patients) using fluconazole, itraconazole or liposomal amphotericin B for prophylaxis in liver transplant recipients [91]. In this analysis, prophylaxis reduced the rate of total proven fungal infections (RR = 0.31), IFIs (RR = 0.33) and attributable mortality (RR = 0.30). However, prophylaxis did not reduce overall mortality (RR = 1.06) or requirement for empiric antifungal therapy (RR = 0.80). This analysis suggests that 12 patients need prophylaxis to prevent one IFI and 89 patients need prophylaxis to prevent empiric therapy in one patient. Overall, it demonstrated that prophylaxis reduced *C. albicans* infections and its attributable mortality. However, there was a higher rate of *Candida* non-*albicans*, particularly *Candida glabrata*, in patients receiving prophylaxis (56%) versus patients not receiving prophylaxis (32%). No reduction in aspergillosis was seen [91].

For those patients with risk factors for infection by *Aspergillus*, targeted prophylaxis should be instituted. Lipid formulation of amphotericin B, dosed at 2.5–5 mg/kg/day have demonstrated efficacy in lowering the incidence of mould infections in this population [16,107,108]. All authors concluded that in high-risk patients, prophylaxis should be utilized and continued for approximately 4 weeks, or for a period determined by the persistence of risk factors or complications [16,107,108].

Lung transplant

Invasive fungal infections occur in 10–44% of lung transplant recipients and are a significant cause of morbidity and mortality [1,3,33,109]. Lung transplant candidates are uniquely vulnerable to fungal colonization due to parenchymal changes accompanying chronic pulmonary disease and its associated treatments [1,110–112].

Aspergillus is the most problematic fungal pathogen, with invasive disease occurring in nearly 9% of lung transplant recipients [3,29,33,36]. Typically, *Aspergillus* infections are asymptomatic or minimally symptomatic, and can be localized or present as pulmonary disease. Most *Aspergillus* infections following lung transplant are tracheobronchitis or bronchial anastomotic infections,

Table 10. Potential treatment options for various fungal pathogens.

Pathogen	Treatment options
Candida spp. [129]	Fluconazole 400–800 mg/day; or
C. albicans	Caspofungin 70 mg on day 1, 50 mg/day thereafter;
C. tropicalis	micafungin 100 mg/day; anidulafungin 200 mg on day
C. glabrata	1, 100 mg/day thereafter
C. parapsilosis	Comments:
C. krusei	*C. krusei:* fluconazole resistant treat with an echinocandin,
C. lusitaniae	voriconazole or posaconazole
	C. parapsilosis: avoid echinocandins due to emerging resistance. Treat with an azole and follow susceptibilities
Aspergillus spp. [133]	Voriconazole 6 mg/kg IV × 2 doses, then 4 mg/kg twice daily IV,
A. fumigatus	can convert to 200 mg twice daily by mouth (posaconazole
A. flavus	has also demonstrated potent activity against clinical
A. niger	isolates of *Aspergillus* species, but is not currently FDA approved for this indication); or
	Lipid-AmB 5 mg/kg/day; or
	Caspofungin 70 mg on day 1, 50 mg/day thereafter; micafungin 100–150 mg/day (due to their incomplete fungicidal activity in *Aspergillus*, the echinocandins are rarely recommended as monotherapy for aspergillosis)
Cryptococcus neoformans [134]	Fluconazole 400–800 mg/day or itraconazole 200–400 mg/day; or Lipid-AmB 5 mg/kg/day with flucytosine 100 mg/kg/day for 2 weeks followed by fluconazole 400 mg/day
Blastomyces [135]	Itraconazole 200–400 mg/day or fluconazole 400–800 mg/day; or CAB 0.25–1 mg/kg/day or lipid-AmB 5 mg/kg/day
Coccidiodes [136]	Fluconazole 400 mg/day or utraconazole 400 mg/day; or CAB 0.5–0.7 mg/kg/day
Histoplasma [137]	Itraconazole 200–400 mg/day or voriconazole; or Lipid-AmB 3–5 mg/kg/day
Fusarium	Voriconazole (standard dosing) [138–140] or posaconazole 800 mg/day [141]; or Lipid-AmB 5–15 mg/kg/day
Phaeohyphomycosis [142]	Fluconazole 400 mg/day or voriconazole 400 mg/day [143]; or CAB 0.7 mg/kg/day [144]
Zygomycetes	Posaconazole 800 mg/day [145]; Lipid-AmB 5–15 mg/kg/day [146,147]

AmB, amphotericin B; CAB, conventional amphotericin B; IV, intravenous.

accounting for approximately 60% of all aspergillosis in this population [33,113,114]. Tracheobronchitis or anastomotic infections tend to occur within 3 months post-transplantation and generally present as dehiscence or vascular erosion of the anastomosis, ulceration, necrosis or pseudomembrane formation at the anastomotic site. The most common risk factors for bronchial anastomotic infections are bilateral lung transplants and use of ALAs or sirolimus early post-transplant [113,114]. Invasive pulmonary aspergillosis accounts for more than 30% of *Aspergillus* infections in lung transplant recipients [33]. Only 10% of lung transplant recipients develop disseminated infections, with the CNS the most common dissemination site [33]. Both invasive pulmonary aspergillosis and disseminated disease tend to occur late, >3 months post-transplant [36].

Candidiasis is also a concern in lung transplant recipients. Candidal colonization of the anastomotic site may cause tracheobronchitis [113,115]. Although *Candida* is often isolated from respiratory tract specimens, *Candida* pneumonia is rare but may present in patients with chronic ischemic injury or bronchiolitis [111].

Recommendations for prophylaxis

The high prevalence of IFIs after lung transplantation has led many institutions to utilize prophylaxis. In several case-series, itraconazole has been successful in preventing infections in lung transplant recipients colonized with *Aspergillus* prior to transplantation [17,35,85,116]. However, not all patients who develop aspergillosis are colonized prior to transplantation.

Table 11. Pharmacokinetic and pharmacodynamic of the antifungals and maintenance immunosuppressants [61,135,148,149].

Drug class/drug	Pharmacodynamic interactions*	Pharmacokinetic interactions†
Antimetabolites		
Flucytosine	*Hematologic*: flucytosine could worsen the myelosuppression induced by the immunosuppressants or prophylactic antibiotics‡	*CyA/TAC*: medications that reduce glomerular filtration may prolong 5-FC elimination; therefore, there may be a theoretic interaction between flucytosine and the calcineurin inhibitors§
Glucan synthesis inhibitors		
Anidulafungin	*Cardiovascular*: both anidulafungin and sirolimus have been associated with deep venous thrombosis. Co-administration of these two medications may increase the risk for thrombolic events‡ *Hematologic*: anidulafungin could worsen the myelosuppression induced by the immunosuppressants or prophylactic antibiotics‡ *Hepatic*: co-administration of CyA, TAC or sirolimus and anidulafungin may increase the risk for hepatic insufficiency‡	no PK interactions reported with the immunosuppressants
Caspofungin	*Hematologic*: caspofungin could worsen the myelosuppression induced by the immunosuppressants or prophylactic antibiotics‡ *Hepatic*: clinical studies involving the co-administration of caspofungin and CyA revealed transient increases in liver transaminases. However, two retrospective analyses suggest that there is not a significant risk of clinically relevant hepatotoxicity with concomitant use of caspofungin and CyA [150,151]	*Corticosteroids*: combined use of caspofungin and dexamethasone may result in a significant reduction in caspofungin plasma levels. This is based on regression analyses of PK data *CyA*: CyA increases the AUC of caspofungin by approximately 35% *TAC*: caspofungin reduced the AUC of tacrolimus by approximately 20%, C max by 16% and trough concentration by 26% in healthy subjects
Micafungin	*Hematologic*: micafungin could worsen the myelosuppression induced by the immunosuppressants or prophylactic antibiotics‡ *Hepatic*: co-administration of CyA, TAC or sirolimus and micafungin may increase the risk for hepatic insufficiency‡	*CyA*: micafungin appears to be a mild inhibitor of cyclosporine metabolism [152] *Sirolimus*: sirolimus AUC is increased by 21% when co-administered with micafungin
Triazoles		
Fluconazole	*Hepatic*: co-administration of CyA, TAC or sirolimus and fluconazole may increase the risk for hepatic insufficiency‡	*Corticosteroids*: concomitant use of fluconazole and prednisone can result in an increase prednisone concentrations [153] *CyA*: CyA AUC is roughly doubled when co-administered with fluconazole *Sirolimus*: a case report has documented the drug-interaction between fluconazole and sirolimus, however, quantification of the effects on PK parameters have not been formally assessed [154] *TAC*: TAC AUC is roughly doubled when co-administered with fluconazole

Itraconazole	*Cardiovascular*: congestive heart failure and peripheral edema have been reported with the use of IV itraconazole. These effects may be worsened by the sodium and water retention properties of the corticosteroids‡ *Hepatic*: co-administration of CyA, TAC or sirolimus and itraconazole may increase the risk for hepatic insufficiency‡	*Corticosteroids*: itraconazole has been shown to increase the concentrations of methylprednisolone, dexamethasone and prednisolone when given concomitantly [155–160] *CyA*: CyA AUC is roughly doubled when co-administered with itraconazole *Sirolimus*: studies and/or case-reports are lacking to support a sirolimus-itraconazole drug interaction; however, given the metabolism of sirolimus and the drug-interaction profile of itraconazole an interaction resulting in increased sirolimus concentrations should be anticipated§ *TAC*: with itraconazole doses of 200–400 mg/day, TAC AUC is roughly doubled; with itraconazole doses of 600 mg/day, TAC AUC is increased nearly fivefold [161]
Posaconazole	*Metabolic*: adrenal insufficiency has been rarely reported with anidulafungin. Concomitant use of this agent with the corticosteroids could increase the risk for or worsen this adverse event‡ *Neurologic*: co-administration of posaconazole with either CyA or TAC has resulted in seizures in two patients. No additional convulsions were reported following the discontinuation of posaconazole [162] *Hepatic*: co-administration of CyA, TAC or sirolimus and posaconazole may increase the risk for hepatic insufficiency‡	*CyA*: posaconazole increased CyA trough concentrations in one study in heart transplant recipients. Reductions in CyA dose of up to 29% were necessary in this analysis [163] *Sirolimus*: studies and/or case-reports are lacking to support a sirolimus-posaconazole drug interaction; however, given the metabolism of sirolimus and the drug-interaction profile of posaconazole an interaction resulting in increase sirolimus concentrations should be anticipated§ *TAC*: TAC AUC is increased by 4.5-fold when co-administered with posaconazole [162,163]
Voriconazole	*Hepatic*: co-administration of CyA, TAC or sirolimus and voriconazole may increase the risk for hepatic insufficiency‡	*Corticosteroids*: prednisolone AUC is increased 13–30% when co-administered with voriconazole [160,164] *CyA*: CyA AUC is increased an average of 1.7 times in renal transplant recipients, however some patients had AUC levels increase by as much as threefold [165] *Sirolimus*: sirolimus AUC is increased by 11-fold when co-administered with voriconazole. Due to this drug interaction, concomitant use of sirolimus and voriconazole is currently contraindicated. However, one study noted that an initial reduction in sirolimus levels by 90% prior to the initiation of voriconazole will prevent a rise in sirolimus trough concentrations [166] *TAC*: TAC AUC is increased by 3-fold when co-administered with voriconazole

Table 11. (Continued)

Drug class/drug	Pharmacodynamic interactions*	Pharmacokinetic interactions†
Polyenes		
CAB and lipid-based AmB	*Nephrotoxicity:* additive nephrotoxicity when combined with CyA or TAC *Metabolic:* additive water retention when combined with the corticosteroids	no PK interactions reported with the immunosuppressants

*Additive, synergistic or antagonistic interactions that can affect efficacy or toxicity.
†Interactions that result in one drug altering the absorption, distribution, metabolism or excretion or another drug.
‡Literature is not available for these pharmacodynamic drug interactions; however an interaction can be theorized based off of their mechanisms of toxicity.
§Literature is not available for these pharmacokinetic drug interactions; however an interaction can be theorized based off of the pharmacokinetic profiles of the given agents.
5-FC, 5-flucytocine; AmB, amphotericin B; AUC, overall exposure; CAB, conventional amphotericin B; Cmax, maximum concentration after administration; CyA, cyclosporine; TAC, tacrolimus.

Voriconazole has been evaluated as prophylaxis in a single center, nonrandomized, retrospective study comparing voriconazole (6 mg/kg IV × 2 doses followed by 200 mg orally twice daily; $n = 65$) versus targeted prophylaxis ($n = 35$; itraconazole ± inhaled CAB in patients colonized with *Aspergillus*) [89]. Voriconazole decreased the odds of developing a fungal infection to 0.08 (95% CI 0.01–0.63). However, tolerability was a major concern. In voriconazole-treated patients, 14% discontinued therapy versus 8% in the control group. Most voriconazole discontinuations were secondary to hepatic insufficiency. The authors noted that significant tacrolimus dose reductions were necessary to achieve target concentrations [89].

As *Aspergillus* infections are usually acquired via inhalation, administration of aerosolized antifungals makes sense for prevention of tracheobronchial and pulmonary disease. Trials using nebulized CAB for prophylaxis have shown significant reductions in *Aspergillus* infections [77,80,82]. Unfortunately, consensus on the appropriate dose, frequency and duration for aerosolized CAB has not been established. Aerosolized lipid-based amphotericin B preparations have shown similar safety in comparison to nebulized CAB [79,80,117]. However, none of these studies was powered to detect a difference in efficacy.

Pancreas transplant

The rates of IFIs after pancreas transplantation are similar to those in liver transplantation (6–38%) [3,118–121]. *Candida* is the primary fungal pathogen in this population, responsible for 97–100% of all IFIs and >40% of all infections [120–122]. In this setting, *Candida* typically presents as a superficial, deep wound, intraabdominal or urinary tract infection, peritonitis or fungemia. Intraabdominal infections have a significant impact on patient and graft survival [119]. *Candida*-associated mortality rates in pancreas transplantation is reported to be >25% [3,118].

Pancreas-transplant-related risk factors include the type of implantation process (i.e. enteric drainage worse than bladder), vascular graft thrombosis, older recipient age, retransplantation, immunosuppression prior to transplant (i.e. pancreas after kidney) and accumulation of pancreatic fluid in the peritoneal cavity [3,32,118–120,123]. Thrombocytopenia has been described as a risk factor, although it may just serve as a marker for infection [6].

Recommendations for prophylaxis

Fluconazole should be considered for prophylaxis in pancreas transplant recipients at high-risk of fungal infections [1,121]. In centers with a high incidence of *Candida* non-*albicans*, other triazoles, echinocandins or the lipid-based

amphotericin B formulations should be considered [1,121].

Renal transplant

Invasive fungal infections in renal transplant recipients are rare, occurring in only 1–14% of transplant recipients [3,99,109]. The most common fungal pathogen in these patients is *Candida*, accounting for 76–95% of all IFIs. The urinary tract is the most frequent site of infection [27,31]. Candiduria can lead to an ascending infection, which may manifest as a ureteral obstruction. Less frequently, ascending infections result in candidal pyelonephritis, which can impact graft function [27]. Due to the risk of ascending infection, some practitioners argue that repeated episodes of candiduria should be treated [1]. Although, one retrospective analysis in renal transplant recipients with asymptomatic candiduria showed similar rates of progression to candidal infections compared to candiduria in the general population [124].

Diabetes is considered the greatest risk factor for the development of IFIs in renal transplant recipients [125]. Other risk factors include cadaveric transplantation, retransplantation, high-dose/prolonged corticosteroid use, CMV disease, bladder catheters, anatomic abnormalities of the urinary tract and disruption of urine flow [125].

Recommendations for prophylaxis

Prophylaxis against IFIs in renal transplant is not routinely recommended [1].

Treatment of IFIs

Well-designed efficacy analyses for the treatment of IFIs in SOT recipients are lacking; therefore, it is difficult to make universal recommendations for treatment. Treatment of IFIs in the SOT population should be based on the isolated pathogen, hospital-specific susceptibility patterns and the patient's clinical picture. Table 10 reviews potential pathogen-specific treatment options. Antifungal use in patients with organ dysfunction is challenging due to the potential for dose adjustments based on renal and hepatic function. Also, most antifungal agents have significant pharmacokinetic and pharmacodynamic drug-interactions (Table 11) that require intense monitoring.

Management of patients that develop an IFI either during or after receiving antifungal prophylaxis is challenging. Prophylaxis failure may be the result of several factors, including insufficient intake (i.e. noncompliance), reduced absorption (i.e. GI adverse events from the immunosuppressants), insufficient dosage of the prophylactic agent, inefficient spectrum of activity and resistance of the infectious agent against the antifungal drug. Whatever the reason, treating these patients may be more difficult due to the potential for resistance or selection of fungi that were not covered by the prophylactic agent used. Although studies specifically addressing this issue in SOT do not exist, aggressive management of these patients is warranted. Some practitioners would recommend drug class rotation (i.e. prophylaxis with a triazole and treatment with an echinocandin or polyene in patients that breakthrough) to overcome the potential for resistance.

Conclusion

Organ transplantation is no longer an esoteric exercise. Several advances in the field of transplant surgery and pharmacology have improved survival and quality of life. Nonetheless, infectious complications remain a significant post-transplant impediment. Although the incidence of IFIs after SOT is lower than that of bacterial or viral infections, IFIs are associated with a higher degree of morbidity and mortality. The high morbidity and mortality rates associated with IFIs in SOT recipients are due to several factors that include difficulty in diagnosis, immunosuppression, the presence of comorbid disease states and the severity of antifungal adverse events and drug-interactions with immunosuppressants.

Determining the best course of therapy is difficult due to the limited data available on the efficacy and safety of antifungal medications in SOT recipients. Transplant practitioners must remain aware of their therapeutic options and the risks and benefits associated with different treatment modalities.

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