Prevention and Treatment of Yeast and Endemic Fungal Infections

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Abbreviations

5-FC	Flucytosine
ABLC	Amphotericin B lipid complex
AmB	Liposomal amphotericin B
AmB-d	AmB deoxycholate
ARDS	Acute respiratory distress syndrome
ATG	Antithymocyte globulin
BAL	Bronchoalveolar lavage
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
CrAg	Cryptococcal antigen
CSF	Cerebrospinal fluid
CVC	Central venous catheter
EIA	Enzyme immune assay
G-CSF	Granulocyte colony-stimulating factor
HD	Hemodialysis
HHV-6	Human herpesvirus 6
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
IC	Invasive candidiasis
ICP	Intracranial pressure

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IDSA	Infectious Diseases Society of America
IFI	Invasive fungal infection
IFN-γ	Recombinant interferon-gamma
IRIS	Immune reconstitution inflammatory syndrome
KOH	Potassium hydroxide
L-AmB	Liposomal amphotericin B
LFAmB	Lipid formulation of amphotericin B
MALDI-TOF	Matrix-assisted laser desorption ionization-time-of-flight mass spectrometry assay
MELD	Model of end-stage liver disease
MIC	Minimal inhibitory concentration
MSK	Musculoskeletal system
PCR	Polymerase chain reaction
PNA-FISH	In situ hybridization assay
SOT	Solid organ transplantation
TRANSNET	Transplant-Associated Infection Surveillance Network
VAD	Ventricular assisted devices
βDG	1,3-β-D-glucan

13.1 Introduction

Solid organ transplantation (SOT) for the treatment of end-organ disease has increased over the last three decades. While novel immunosuppressive regimens have improved allograft survival and function, combined with surgical complications, these predispose transplant recipients to infectious complications [1, 2]. Invasive fungal infections (IFIs) are particularly concerning in this population due to the associated high morbidity and mortality [1]. The most common IFIs in SOT recipients are candidiasis, aspergillosis, cryptococcosis, and those caused by endemic fungi such as *Blastomyces*, *Coccidioides*, and *Histoplasma* [3]. The incidence of IFIs varies according to type of organ transplant, and the risk of infection changes over time based on host state of immunosuppression and many fungal factors (e.g., virulence and resistance of fungi) [2, 4]. In this chapter, we review epidemiology, clinical presentation, diagnosis, and treatment of fungal infections due to yeast and endemic fungi in SOT recipients.

13.2 Epidemiology

The data from the US Transplant-Associated Infection Surveillance Network (TRANSNET) estimated that invasive candidiasis (IC) was the most common (53%) IFI, followed by invasive aspergillosis (19%) in most organ transplants. The exception was for lung transplants where aspergillosis was more common than IC. Cryptococcosis (8%) was the third most common IFI, and endemic fungi

Table 13.1 Frequency of yeast and endemic fungal infections by type of transplant from the TRANSNET study [3]

IFI type	Liver (n = 378)	Kidney (n = 332)	Lung (n = 248)	Pancreas (n = 128)	Heart (n = 99)	Small bowel (n = 22)
Candidiasis	255 (68)	164 (49)	56 (23)	97 (76)	48 (49)	19 (85)
Cryptococcosis	24 (6)	49 (15)	6 (2)	6 (5)	10 (10)	1 (5)
Endemic mycoses	17 (5)	33 (10)	3 (1)	8 (6)	3 (1)	0 (0.0)
Other yeast	9 (2.4)	6 (1.8)	0 (0.0)	5 (3.9)	0 (0.0)	1 (5)
Unspecified yeast	5 (1.3)	3 (0.9)	6 (2.4)	1 (0.8)	0 (0.0)	1 (5)

No. (%)

accounted for 5.3% of IFIs, whereas other yeasts accounted for less than 3% of the IFIs (Table 13.1) [3].

Candida is a normal commensal of humans and becomes pathogenic when the host immune system is compromised. *Candida* colonization and biofilm formation on human tissues, intravascular catheters, implants, and prosthetic material support IC [5, 6]. Donor-derived infections by *Candida* have been reported [7]. Among infections caused by *Candida* species in SOT recipients, *C. albicans* was the most common isolate (46.3%), followed by *C. glabrata* (24.4%) and *C. parapsilosis* (8.1%) [8]. Resistance to azoles and echinocandins is increasing, and previous data suggested that prior exposures to azole or echinocandins lead to the development resistance and increased incidence of infections due to non-*albicans Candida* in SOT recipients [9–12]. *C. auris* is an emerging multidrug-resistant yeast in the healthcare settings in the USA and other parts of the world (Spain, South America, and Asia) [13].

Cryptococcal infections occur due to the inhalation of the aerosolized basidiospores from soil or avian excreta, although rarely it can be transmitted from donor organs and tissue grafts [14]. Most infections are caused by *C. neoformans* although infections due to *C. gattii* have emerged in North America since 1999 where it was in the past more typical of tropical and subtropical areas [15]. Cryptococcosis causes approximately 8% of IFIs in SOT recipients [3] and has an overall mortality of 14% at 90 days after diagnosis in this population [16]. The median time to cryptococcosis ranges between 16 and 21 months posttransplantation, although time to onset was earlier (<12 months) in liver and lung transplant recipients possibly related to the more intense immunosuppression they receive compared to other types of transplants [16, 17]. A recent multicenter study suggested that lung transplant recipients are at highest risk of cryptococcosis [18]. When infection occurs in the first 30 days posttransplantation, donor-derived cryptococcosis should be considered [14].

Endemic fungal infections can occur in patients who reside or have resided in endemic areas and occur posttransplantation with a median time of 343 days. Histoplasmosis is caused by *H. capsulatum* and is endemic to the Ohio and the Mississippi River valleys in the USA and has been isolated in many parts of the world particularly around river valleys. Blastomycosis, caused by *B. dermatitidis*, is

also seen in the Ohio-Mississippi River Valley. Histoplasmosis or blastomycosis occurs only in about 0.5% of transplant patients in endemic areas [19]. Coccidioidomycosis is endemic in the Southwestern United States, New Mexico, western Texas, and some parts of Central and South America [20] and is caused by two species: *C. immitis* and *C. posadasii*. The disease may be primary or secondary to reactivation of a latent infection [20] and may occur in up to 8% of transplant patients in endemic areas [21]. Other yeasts or endemic fungi that have been rarely reported in SOT recipients include *Trichosporon*, *Rhodotorula*, *Malassezia*, *Hansenula*, and paracoccidioidomycosis [22].

13.3 Timing and Risk Factors for Fungal Infections

The timing of IFIs posttransplantation is typically divided into three intervals based on the risk and type of IFIs: early (0–1 month), intermediate (1–6 months), and late (>6 months). Infections in the early interval are similar to that in non-immunocompromised patients postoperatively, usually due to surgical complications, nosocomial, or donor-derived infections [3]. *Candida* species are the common cause of IFIs in the early period. The intermediate interval has the most frequent IFIs as immunosuppression plays a major role, while the effects of surgical and nosocomial factors decrease. IC is less common, while mold infections due to aspergillosis, mucormycosis, scedosporiosis, or other molds predominate [3]. By late stage when 80% of SOT recipients are maintained on minimal chronic immunosuppression, the risk of IFIs declines [2]. The predominant fungal pathogens in this interval are *Cryptococcus* and endemic fungi, but mold infections such as aspergillosis and mucormycosis are possible and may occur at any time posttransplantation [3, 17].

The net state of immunosuppression is an important determinant of the overall risk of infection and involves a number of host and environmental factors. Host factors include underlying immune defects; extrinsic factors such as loss of integrity of mucocutaneous barriers and surgical complications; dose, duration, and sequence of immunosuppressive therapy; and environmental exposures to specific pathogens (Table 13.2) [23, 24]. Other risk factors that are specific to the type of organ transplant include the type of anastomosis or drainage, intensity of immunosuppression especially in the immediate posttransplantation period, and postoperative complications (anastomotic leak, ischemia, thrombosis, fluid collection, and the presence of foreign bodies) (Table 13.3) [2, 23–36].

Several immunosuppressive agents are used in SOT recipients including cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, as well as antithymocyte globulin (ATG) or monoclonal antibodies such as alemtuzumab, basiliximab, or rituximab in order to avoid or minimize the use of glucocorticoids [36, 37]. Calcineurin inhibitors (CNIs) (such as cyclosporine and tacrolimus) have synergistic antifungal activity against *C. neoformans* isolates, and thus, cryptococcal disease in SOT recipients manifests with skin and soft tissue disease rather than CNS disease owing to the antifungal activity of tacrolimus at 37–39 °C and the lower skin

Table 13.2 Risk factors of yeast and endemic fungal infections in SOT recipients and "net state of immunosuppression" [23, 24]

Immunosuppression and immunosuppressive therapy	
– Dose and duration of current and past immunosuppressive agents	
– Previous use of chemotherapy	
– Antibody or complement deficiency and other immune disorders	
Healthcare related	
– Prolonged use of empiric antibiotics	
– Prolonged intensive care unit stay and mechanical ventilation	
– Use of prophylactic agents with myelosuppressive side effects (e.g., trimethoprim-sulfamethoxazole, valganciclovir, ganciclovir, dapsone)	
– Acquired myelosuppression, neutropenia, and/or lymphopenia	
– Total parental nutrition, renal replacement therapy	
Underlying immune disorders	
– Autoimmune disorders (e.g., systemic lupus erythematosus)	
Loss of mucocutaneous barriers/integrity	
– Drains, lines, catheters	
– Ischemic tissue, fluid, or blood collections	
Metabolic conditions (cirrhosis, diabetes mellitus, malnutrition, uremia)	
Chronic viral infections	
– CMV, herpes simplex virus, human herpesvirus 6 (HHV-6)	
Environmental and new technologies	
– Travel to endemic areas or transplantation in endemic areas	
– Occupational or recreational exposures, marijuana use	
New technologies	
– Use of ventricular assisted devices (VAD) (heart transplants)	
– Reperfusion injury and bronchiolitis obliterans (lung transplants)	
Risk assessment	
Greater risk of infection • Active/latent donor/recipient infection • Early graft rejection • Graft dysfunction • High-dose corticosteroids • High rejection risk • Induction therapy – lymphocyte depletion • Plasmapheresis • Technical complications – Anastomotic leak, bleeding, prolonged intubation/intensive unit care. Drains and catheters, wound infection/poor wound healing	*Lower risk of infection* • Appropriate surgical prophylaxis • Appropriate vaccination • Effective antiviral prophylaxis • Good graft function Good HLA match • Immunologic tolerance • PCP prophylaxis • Technically successful surgery

temperatures [38]. Episodes of rejection pose a particular risk for IFIs as patients receive pulse doses of glucocorticoids, intensified immunosuppressive therapy, ATG, and monoclonal antibodies as well as they experience high rates of cytomegalovirus (CMV) reactivation which can contribute to IFIs and immunosuppression [37].

Table 13.3 Specific risk factors of yeast and endemic fungal infections per type of solid organ transplant [3, 23, 26–36]

Transplant type	Specific factors
Heart	Active CMV infection Antilymphocyte globulins Central venous catheters Colonization of VAD Extracorporeal membrane oxygenation Hemodialysis (HD) Prolonged use of broad-spectrum antibiotics Reoperation Treatment for rejection
Kidney	Alemtuzumab Chronic allograft rejection and intense immunosuppression therapy Corticosteroids Diabetes mellitus Indwelling venous catheters Prolonged dialysis before transplant Requirement for HD posttransplant
Liver	Active CMV infection Allograft failure Baseline creatinine >3.0 mg/dL Choledochojejunostomy anastomosis (Roux-en-Y) Early colonization Hepatic dysfunction HHV-6 Intraoperative requirement of >40 blood products Model of end-stage liver disease (MELD) score > 20, major if >30 Operative time ≥ 11 h Renal dysfunction requiring HD Retransplantation
Lung or lung-heart	Antibody deficiency (hypogammaglobulinemia) Damage of local pulmonary defenses by transplant Intense immunosuppression Ischemia of anastomosis
Pancreas or pancreas-kidney	Enteric drainage Preoperative peritoneal dialysis Postreperfusion pancreatitis Retransplantation or laparotomy after transplantation Vascular graft thrombosis
Small bowel	Abdominal reoperation Graft rejection or dysfunction Intense immunosuppression Multivisceral transplantation Small bowel anastomotic leaks

Donor-derived yeast infections have been reported due to *Candida* and *Cryptococcus* among other fungi. Also, *Candida* contamination of preservation fluid has been associated with posttransplantation infections in renal and liver transplant recipients [39, 40]. In a study of graft-site infections in renal transplant recipients, the incidence was 1 case per 1000 grafts [41]. A recent case of *C. auris* was

transmitted during lung transplantation [42]. Of note, early cases of cryptococcosis were reported posttransplantation especially in liver transplant recipients that were attributed to unrecognized pretransplant or donor-derived infections [14]. Donor-derived infections due to *Histoplasma* and *Coccidioides* but not *Blastomyces* have been reported [43].

13.4 Clinical Manifestations

13.4.1 Infections Due to *Candida*

Candida colonizes skin, respiratory, gastrointestinal, and genitourinary tracts. Colonization usually precedes IC, and the infection depends on the breach of integrity of mucocutaneous barriers, the virulence of infecting strain, and the intensity of immunosuppression [4]. Candidemia is the most common form of IC in SOT recipients (64%), followed by urinary tract infections (11%) and peritonitis (9%) [3, 11]. Candidemia may occur due to translocation across damaged intestinal barriers or from central venous catheters (CVC) [2, 44]. Intra-abdominal infections are particularly common among liver, pancreas, and small bowel transplant recipients [3]. Intra-abdominal manifestations include biliary, perirenal, and peritoneal infections. Bilomas, in liver transplant recipients, may result from *Candida* and can lead to the loss of liver transplant function [4, 45].

Candida may cause anastomotic tracheobronchitis in lung transplant recipients and sternal wound infections in heart and lung transplant recipients [46]. Asymptomatic *Candida* colonization is common in renal transplant recipients; however, the need for indwelling catheters can result in ascending renal parenchymal infection or ureteral fungal balls due to *Candida* species [26]. Of note, infections of allograft vascular anastomosis have been reported in renal [41], pancreatic [47], heart, and lung transplants [48].

13.4.2 Infections Due to *Cryptococcus*

The two major sites of cryptococcosis in SOT recipients are the lungs and the central nervous system (CNS). Other sites that can be involved include the skin and soft tissues, bones, joints, liver, kidney, and prostate [49]. Isolated pulmonary infection is seen in 33% of SOT recipients [16]. Lung disease ranges from asymptomatic colonization to pneumonia leading to respiratory failure [49]. Endobronchial disease is an increasingly recognized disease [50]. Extrapulmonary dissemination was seen in 61% of SOT recipients, and liver transplant recipients have a sixfold higher risk for dissemination [16]. Cryptococcal meningitis was seen in 44% of SOT recipients with cryptococcosis and had a mortality of 26% [18]. Predictors of CNS involvement in SOT recipients include late-onset disease >24 months posttransplantation, altered mental status, and serum cryptococcal antigen (CrAg) titer >1:64 [51].

Skin manifestations are diverse and may include nodules, papules, pustules, abscess, and necrotizing cellulitis commonly in the lower extremities [52]. The use

of calcineurin inhibitors is associated with fewer CNS infections and more cutaneous manifestations [17]. Immune reconstitution inflammatory syndrome (IRIS) is an uncommon manifestation and results from rapid reduction of immunosuppressive therapy when initiating antifungal therapy in SOT recipients and mimics worsening cryptococcosis or antifungal failure [53]. It may present as lung nodules, hydrocephalus, cerebral mass lesions, aseptic meningitis, lymphadenitis, or cellulitis [52, 53].

13.4.3 Infections Due to Endemic Fungi

Infections due to endemic fungi result from environmental exposures and enter into the body through the lungs. Pneumonia is common, and fulminant multilobar pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure are feared complications [20]. The most common presentation of blastomycosis in SOT is pneumonia, but extrapulmonary dissemination of the skin, musculoskeletal system (MSK), genitourinary, or CNS disease is seen in almost 50% of SOT recipients [3, 19, 54]. Clinical manifestations of coccidioidomycosis range from pneumonia to disseminated disease. Extrapulmonary disseminated disease in SOT recipients involves the skin, MSK, and CNS and occurs in about 1–5% [55]. Those of African, Filipino, or Native American descent, males, pregnant women, and immunosuppressed are at increased risk [55]. Histoplasmosis can involve any organ but most commonly presents with disseminated disease in SOT patients. Clinical findings usually underestimate the severity and burden of disease [19].

13.4.4 Infections Due to Other Yeasts

Other yeasts that are rare in SOT recipients include *Trichosporon*, *Rhodotorula*, and *Malassezia*. *T. asahii* is associated with intravenous catheter-related infections [56]. *Rhodotorula* and *Malassezia* have been associated with fungemia and disseminated disease [22]. Table 13.4 outlines the clinical manifestations of yeast infections in SOT recipients [3, 14, 17–20, 52, 53, 57–62].

13.5 Diagnosis and Monitoring

Diagnosis of IFIs in SOT recipients is challenging due to their nonspecific signs and symptoms owing to impaired inflammatory responses as a result of immunosuppression and the lack of highly sensitive and specific diagnostic modalities. Early diagnosis is key to successful outcomes, and physicians should have a high index of suspicion based on risk factors and epidemiology of these pathogens [23]. IFIs are categorized into proven, probable, and possible based on specific cytologic/histopathologic findings and host, clinical, radiographic, and microbiological criteria [63].

Table 13.4 Clinical manifestations of yeast and endemic fungal infections in SOT recipients [3, 14, 17–20, 52, 53, 57–62]

IFI type	Clinical manifestation
Candida	Candidemia Intra-abdominal and hepatobiliary infections Sternal wound infections (heart transplants) Bronchial anastomotic infections (lung transplants) Urinary tract infections Ureteral fungal ball Vascular anastomotic infections Less common: septic arthritis, chronic meningitis, endocarditis, mediastinitis Cutaneous infections
Cryptococcus	Asymptomatic pulmonary infection to severe pneumonia with ARDS, respiratory failure Meningitis Skin infections (necrotizing cellulitis) Disseminated disease Fungemia Osteoarticular disease Immune reconstitution inflammatory syndrome
Blastomyces	Pneumonia, including fulminant multilobar pneumonia, ARDS, respiratory failure Disseminated disease: cutaneous, osteoarticular, genitourinary, or CNS disease Fungemia is rare
Coccidioides	Pneumonia, ranging from mild to severe, with ARDS, respiratory failure Disseminated disease: meningitis, fungemia, erythema nodosum, erythema multiforme, musculoskeletal disease
Histoplasma	Pneumonia, ranging from mild to severe with respiratory failure Disseminated disease: hepatosplenomegaly, gastrointestinal disease such as ileocecal ulceration and perforation, pancytopenia, weight loss, transaminitis, mucocutaneous disease, increased lactate dehydrogenase levels Unusual: thrombotic microangiopathy and hemophagocytic lymphohistiocytosis (HLH)
Trichosporon *Rhodotorula* *Malassezia*	Catheter-related intravenous infections Peritonitis, fungemia Folliculitis, groin abscess

Histopathological demonstration of tissue invasion by fungal elements helps to establish proven disease, and special stains may be utilized. Isolation of *Candida* from blood cultures (which has a sensitivity of 50–70% [35]) or sterile sites is indicative of true infection, while *Candida* isolated from nonsterile sites usually represents colonization which could indicate infection in the right context but also is a risk factor for future invasive candidiasis [41]. Diagnosis of anastomotic tracheobronchitis in lung transplant recipients is to be based on direct visual examination, histopathological confirmation, and positive cultures [64]. Otherwise, the recovery of *Candida* species in sputum rarely indicates disease in the lungs [35, 64]. Isolation of other yeasts such as *C. neoformans*, *H. capsulatum*, *B. dermatitidis*, *and C.*

immitis even without clinical findings suggests disease and calls for additional testing. SOT recipients suspected to have cryptococcosis should undergo evaluation with a lumbar puncture (LP), blood and urine cultures, and bronchoalveolar lavage (BAL) with or without biopsy [58]. Species identification and drug susceptibilities help to decide on antifungal therapy and to predict clinical outcomes.

Sensitivity of *Histoplasma* urine and serum antigen exceeds 90% in immunocompromised patients with disseminated disease and is at least 59% in pulmonary disease [65]. Similarly, *Blastomyces* Ag detection assays in urine, blood, or BAL have a sensitivity of >90%. Ag detection assays for *Histoplasma* and *Blastomyces* in BAL may cross-react with each other [66]. IgM (detected by tube precipitin method, immunodiffusion, latex agglutination, and enzyme immune assay (EIA)) and IgG complement-fixing antibody serology tests for *Coccidioides* are very sensitive and specific to diagnose coccidioidomycosis and to define the severity of disease [55]. Diagnosis and management of suspected meningeal coccidioidomycosis require an LP and cerebrospinal fluid (CSF) analysis for CSF complement-fixing IgG antibodies [20]. Table 13.5 shows the different laboratory and radiographic diagnostic modalities for yeast infections [20, 35, 49, 58, 64, 67–69].

Table 13.5 Diagnosis of yeast and endemic fungal infections in SOT recipients [20, 35, 49, 58, 64, 67–69]

IFI type	Diagnostic tests
Candida	*Commonly used* Blood cultures (sensitivity 50–70%) or smear (yeast, hyphae, pseudohyphae) and cultures of sterile sites 1,3-β-D-glucan (βDG) detection assays Matrix-assisted laser desorption Ionization-time-of-flight mass spectrometry assay (MALDI-TOF) *Not commonly used* Polymerase chain reaction (PCR) T2 magnetic resonance Species identification: peptide nucleic acid fluorescent In situ hybridization assay (PNA-FISH)
Cryptococcus	Blood cultures Serum cryptococcal antigen testing BAL with or without biopsy (stains for yeast, culture) Lumbar puncture (opening pressure, Gram's stain, CSF cultures, cell count, protein, glucose, and cryptococcal antigen testing) Tissue biopsy and cultures Brain imaging: basal ganglia and midbrain lesions, hydrocephalus, single or multiple nodules with or without enhancement, dilated Virchow-Robin spaces, pseudocysts, masses, gyral enhancement, cryptococcomas, lacunar and cortical infarcts
Blastomyces	Direct microscopy (Gram, Giemsa, and potassium hydroxide (KOH)/calcofluor stains) Tissue cultures Antigen testing (urine, serum, BAL)

Table 13.5 (continued)

IFI type	Diagnostic tests
Coccidioides	Direct microscopy (Gram, Giemsa, and KOH/calcofluor stains): visualization of spherules containing endospores Tissue culture PCR of respiratory specimens or CSF Antigen enzyme immunoassay (EIA) test (urine, serum, BAL) Serum IgM detection (tube precipitin method, immunodiffusion, latex agglutination, and EIA Complement-fixing IgG antibodies (helps to quantify severity and monitor infection) Lumbar puncture (opening pressure, Gram's stain, CSF cultures cell count, protein, glucose, and complement-fixing IgG antibodies)
Histoplasma	Direct microscopy (Gram, Giemsa, hematoxylin, and eosin, Wright-Giemsa and KOH/calcofluor stains) in tissue, blood, or bone marrow Tissue culture Histoplasma antigen test (urine, serum, BAL)
Trichosporon *Rhodotorula* *Malassezia*	Blood cultures; smear shows hyaline septate fungal hyphae and pseudohyphae Budding yeast in tissue KOH preparation or culture

13.6 Treatment and Prevention

13.6.1 Prophylaxis and Prevention

Preventive strategies have been developed in SOT patients at high risk of opportunistic IFIs [70]. There is no current recommendation to start universal prophylaxis to prevent IC in SOT recipients, and a targeted approach is based on type of transplant and other risk factors [35]. Similarly, there is no recommendation to start primary antifungal prophylaxis for cryptococcosis. However, secondary prophylaxis is recommended in some cases [49]. Primary or secondary antifungal prophylaxis for blastomycosis in SOT recipients is not currently recommended [20]. Table 13.6 shows different antifungal prophylaxis recommendations in SOT recipients [20, 35, 71–77].

13.6.2 Treatment of Yeast and Endemic Fungal Infections in SOT Recipients

The choice of antifungal therapy in the treatment of candidemia should be based on the *Candida* species in cultures and their susceptibilities, azole exposure in the last 90 days, and history of intolerance to antifungal agents [78]. Early antifungal therapy for suspected candidemia has been associated with better outcomes in patients with candidemia [79, 80]. Fluconazole can be used as first-line in patients with

Table 13.6 Antifungal prophylaxis of yeast and endemic fungi recommendations in SOT recipients [20, 35, 71–77]

Organism/transplant type	Antifungal drug	Alternatives	Duration	Note
Candida				
Kidney	No prophylaxis			
Liver	Fluconazole 400 mg daily	LFAmB[a] 3–5 mg/kg/day[b]	Up to 4 weeks or until risk factors resolve	Possible role of anidulafungin or caspofungin
Pancreas or pancreas-kidney	Fluconazole 400 mg daily	LFAmB[a] 3–5 mg/kg/day[b]	At least 4 weeks	
Small bowel	Fluconazole 400 mg daily	LFAmB[a] 3–5 mg/kg/day[b]	Until healing of anastomosis and absence of rejection	
Lung or lung-heart	No specific prophylaxis for yeast or endemic fungi			
Heart	No prophylaxis			
Secondary cryptococcal prophylaxis after initial 12 months treatment • In patients needing increased immunosuppression (e.g., treatment of rejection) • Renal transplant patients who can have a hemodialysis bridge may be considered for transplantation if received a year of antifungal therapy, have no signs of active cryptococcosis, and have negative cultures from the site of infection • For renal transplant patients with graft failure where hemodialysis bridging cannot be done, at least 1 year of secondary prophylaxis with fluconazole is considered • Retransplantation can be considered after receiving induction therapy, clearance of positive cultures, and decline of CrAg				
Blastomycosis Primary or secondary prophylaxis is not recommended				
Coccidioidomycosis • All patients undergoing SOT in endemic areas without active disease should receive an oral azole (e.g., fluconazole 200 mg daily) for at least 6–12 months • Secondary lifelong prophylaxis after controlling active infection to prevent relapse				
Histoplasmosis • SOT patients who recovered from active disease with or without treatment during the 2 years before transplantation should receive itraconazole 200 mg daily (duration unknown). Monitoring for relapse during immunosuppression with serial urinary antigen is recommended • Detection of *H. capsulatum* in explanted organs or donor tissue especially lung transplants should be considered for antifungal prophylaxis				

[a]LFAmB (lipid formulation of amphotericin B includes liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC))

[b]If high rates of non-*albicans Candida* species or risk of *Aspergillus*

mild-moderate disease and who are unlikely to have infections with fluconazole-resistance *Candida* species [64]. The use of an echinocandin is now strongly recommended in the treatment of candidemia [64], especially in SOT patients with hemodynamic instability or with previous exposures to azoles or colonized with Candida species resistant to azoles [81]. Liposomal amphotericin B (AmB) or an azole should be used when other IFIs are suspected due to the limited activity of echinocandins, but the use of AmB is limited but its toxicities. Monitoring drug levels is important as azoles are potent inhibitors of liver cytochrome P-450 CYP3A4 and can increase the levels of CNIs, everolimus, and sirolimus [35, 82]. Patients with candidemia should have repeated blood cultures every 48–72 h until it is cleared, and central venous catheters should be removed as soon as possible. It is also strongly recommended to do a dilated fundoscopic exam in these patients [64]. Management of anastomotic tracheobronchitis should include using inhaled or systemic AmB. Treatment of other manifestations of IC is outlined in Table 13.7.

Table 13.7 Recommendations for the treatment of yeast and endemic fungal infections in SOT recipients [20, 35, 49, 58, 64, 75–77, 83]

Condition	Primary therapy	Alternative therapy	Comments
Candidemia			
Nonneutropenic	Echinocandin or fluconazole 800 mg (12 mg/kg) load and then 400 mg (6 mg/kg) daily	LFAmB 3–5 mg/kg/day for intolerant patients or non-susceptible *Candida* species. Fluconazole initially if not critically ill and low risk of azole resistance	Step-down to fluconazole. Voriconazole step-down recommended for *C. krusei.* Remove all CVC and obtain a dilated eye examination for all patients. Treat for at least 2 weeks after clearance of candidemia and resolution of symptoms
Neutropenic	Echinocandins or LFAmB 3–5 mg/kg/day. Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses and then 200–300 mg (3–4 mg/kg) twice daily for additional mold coverage or for *C. krusei*	Fluconazole 800 mg (12 mg/kg) load and then 400 mg (6 mg/kg) daily for less critically ill patients and no azole exposure	Step-down to fluconazole 400 mg daily or voriconazole. Remove all CVC and obtain a dilated eye examination for all patients. Treat for at least 2 weeks after clearance of candidemia and resolution of symptoms. Granulocyte colony-stimulating factor (G-CSF) can be used in persistent candidemia with protracted neutropenia

(continued)

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Intra-abdominal infections	Treat as candidemia		Duration determined by source control and clinical response
Urinary tract infections			
Asymptomatic candiduria	Not necessary unless high risk for dissemination. Fluconazole 400 mg (6 mg/kg) daily, for several days before and after urological procedures	AmB deoxycholate (AmB-d) 0.3–0.6 mg/kg daily for several days before and after urological procedures	Remove indwelling bladder catheters
Symptomatic cystitis	Fluconazole 200 mg (3 mg/kg) daily for 2 weeks	AmB-d 0.3–0.6 mg/kg daily for 1–7 days or flucytosine (5-FC) 25 mg/kg four times daily for 1–7 days	AmB-d IV or bladder irrigation indicated for fluconazole-resistant *C. glabrata* or *C. krusei*. Remove indwelling bladder catheters
Pyelonephritis	Fluconazole 200–400 mg (3–6 mg/kg) daily for 2 weeks	AmB-d 0.3–0.6 mg/kg daily for 1–7 days with or without 5-FC 25 mg/kg four times daily or 5-FC alone for 2 weeks	AmB-d with or without 5-FC or 5-FC alone for 2 weeks in *C. glabrata* and AmB-d alone for 1–7 days for *C. krusei*. Eliminate urinary obstruction, and consider removing or replacing nephrostomy tubes and stents. Treat for candidemia if suspected
Urinary fungus balls	Surgical removal strongly recommended. Antifungal therapy as for cystitis or pyelonephritis		Local irrigation with AmB-d through nephrostomy tube, if present, is recommended

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Cryptococcal meningoencephalitis			
Induction	L-AmB 3–4 mg/kg daily or ABLC 5 mg/kg daily plus 5-FC 25 mg/kg four times daily for 2 weeks	L-AmB 6 mg/kg daily, ABLC 5 mg/kg daily, or AmB-d 0.7 mg/kg daily all for 4–6 weeks	Give induction for 4–10 weeks if persistent infection. Can increase induction dose of L-AmB to 6 mg/kg daily or AmB-d to 1 mg/kg daily. If intolerant to polyene, consider fluconazole ≥800 mg daily plus 5-FC 25 mg/kg four times daily. If intolerant to 5-FC, consider AmB-d 0.7 mg/kg daily plus fluconazole 800 mg (12 mg/kg) daily. Intrathecal or intraventricular AmB-d use is discouraged and is rarely necessary. Check minimal inhibitory concentrations (MIC) for fluconazole in persistent or relapsed infections
Consolidation	Fluconazole 400–800 mg daily for 8–12 weeks	Consider salvage consolidation in relapses for 10–12 weeks with fluconazole 800–1200 mg daily, voriconazole 200–400 mg twice daily, or posaconazole 200 mg four times daily or 400 mg twice daily	
Maintenance	Fluconazole 200–400 mg daily for 6–12 months		
Mild-moderate non-CNS disease	Fluconazole 400 mg (6 mg/kg) daily for 6–12 months		Also applies to mild-moderate isolated pulmonary disease

(continued)

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Moderately severe-severe non-CNS or disseminated disease without CNS involvement	Treat the same as CNS disease		Also applies to isolated severe pulmonary disease
Management of cryptococcal complications – Elevated CSF pressure: If CSF opening pressure ≥25 cm of CSF, with symptoms of ICP, do LP to relieve pressure to opening pressure ≤20 cm of CSF. Repeat LP daily until CSF pressure and clinical symptoms have stabilized for >2 days, or consider temporary percutaneous lumbar drains or ventriculostomy if daily LP is required. Permanent ventriculoperitoneal (VP) shunt only if other measures failed to control elevated ICP. Continue concomitant antifungal therapy – IRIS: Minor IRIS resolves spontaneously in days to weeks. For major cases with CNS inflammation and increased ICP, consider prednisone 0.5–1.0 mg/kg daily and possibly dexamethasone for severe CNS signs and symptoms. Taper over 2–6 weeks. Continue concomitant antifungal therapy			
Blastomycosis			
Mild-moderate disease	Itraconazole 200 mg three times daily for 3 days and then twice daily		Give at least for 6–12 months
Moderately severe-severe disease	LFAmB 3–5 mg/kg/day or AmB-d 0.7–1 mg/kg/day		Give at least for 2 weeks or until clinical improvement is noted
Coccidioidomycosis			
Mild-moderate disease	Fluconazole 400–800 mg daily or itraconazole 200 mg twice daily		For at least 6–12 months, followed by chronic suppressive therapy
Moderately severe- severe disease	AmB-d 0.5–1.5 mg/kg/day or LFAmB 2–5 mg/kg/day		For at least 2 weeks or until clinical improvement is noted and then step-down to oral azoles
Meningeal disease	Fluconazole 800–1000 mg daily and itraconazole 400–600 mg daily	Itraconazole 400–600 mg daily, intrathecal amphotericin B	Lifelong suppression for meningeal disease
Pretransplant or donor infection	Fluconazole 200–400 mg daily		For at least 6–12 months
Histoplasmosis			
Mild-moderate disease	Itraconazole 200 mg three times daily for 3 days and then twice daily		For at least 12 months

Table 13.7 (continued)

Condition	Primary therapy	Alternative therapy	Comments
Moderately severe- severe disease	L-AmB 3 mg/kg daily for 1–2 weeks and then itraconazole 200 mg three times daily for 3 days and then twice daily	AmB-d 0.7–1 mg/kg daily	For at least 12 months
Trichosporon	Azoles	Amphotericin B	
Rhodotorula	Amphotericin B	Posaconazole	
Malassezia	Topical preparation of clotrimazole 1% and selenium sulfide lotion	Oral fluconazole for superficial infections	Catheter removal and fluconazole for disseminated infections

Guidelines for the treatment of cryptococcosis in SOT patients are mostly based on clinical trial data among HIV patients [49, 58]. In order to choose the right antifungal therapy, it is essential to define the extent and severity of disease as well as the net state of immunosuppression. Identifying localized pulmonary from disseminated disease and sites of involvement including CNS helps to define the extent of disease. When meningeal disease is suspected, an LP should be done for CSF analysis, CSF CrAg, and opening pressure. This can also have therapeutic implications to relieve elevated intracranial pressure (ICP) to ≤20 cm.

Patients with localized pulmonary cryptococcal disease, even if asymptomatic, should be treated with fluconazole for 6–12 months. Treatment of severe, diffuse pulmonary disease or disseminated disease should follow the treatment of cryptococcal meningoencephalitis [49]. Similar to cryptococcosis, treatment for blastomycosis [75], coccidioidomycosis [77], and histoplasmosis [76] is based on IDSA guidelines and is based on the site of involvement and severity of disease. Table 13.7 shows the treatment recommendations of IFIs in SOT recipients [20, 35, 49, 58, 64, 75–77, 83].

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