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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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
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

**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. (%)
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
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                                                                        |
|                     | Choledochojunostomy 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         | Enteric drainage                                                                                     |
| pancreas-kidney     | 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].
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. neoformans*, *H. capsulatum*, *B. dermatitidis*, and *C. neoformans*.

### Table 13.4 Clinical manifestations of yeast and endemic fungal infections in SOT recipients

| IFI type  | Clinical manifestation                                                                 |
|-----------|---------------------------------------------------------------------------------------|
| *Candida* | Candidemia<br>Intra-abdominal and hepatobiliary infections<br>Sternal wound infections (heart transplants)<br>Bronchial anastomotic infections (lung transplants)<br>Urinary tract infections<br>Ureteral fungal ball<br>Vascular anastomotic infections<br>Less common: septic arthritis, chronic meningitis, endocarditis, mediastinitis<br>Cutaneous infections |
| *Cryptococcus* | Asymptomatic pulmonary infection to severe pneumonia with ARDS, respiratory failure<br>Meningitis<br>Skin infections (necrotizing cellulitis)<br>Disseminated disease<br>Fungemia<br>Osteoarticular disease<br>Immune reconstitution inflammatory syndrome |
| *Blastomyces* | Pneumonia, including fulminant multilobar pneumonia, ARDS, respiratory failure<br>Disseminated disease: cutaneous, osteoarticular, genitourinary, or CNS disease<br>Fungemia is rare |
| *Coccidioides* | Pneumonia, ranging from mild to severe, with ARDS, respiratory failure<br>Disseminated disease: meningitis, fungemia, erythema nodosum, erythema multiforme, musculoskeletal disease |
| *Histoplasma* | Pneumonia, ranging from mild to severe with respiratory failure<br>Disseminated disease: hepatosplenomegaly, gastrointestinal disease such as ileocecal ulceration and perforation, pancytopenia, weight loss, transaminitis, mucocutaneous disease, increased lactate dehydrogenase levels<br>Unusual: thrombotic microangiopathy and hemophagocytic lymphohistiocytosis (HLH) |
| *Trichosporon* | Catheter-related intravenous infections |
| *Rhodotorula* | Peritonitis, fungemia |
| *Malassezia* | Folliculitis, groin abscess |
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)                 |
| **Cryptococcos** | 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)                    |
### 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 |
|-------------------|-----------------|---------------------|----------|
| **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)
| 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 |
| 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 $\geq 25$ cm of CSF, with symptoms of ICP, do LP to relieve pressure to opening pressure $\leq 20$ 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

| Condition | Primary therapy | Alternative therapy | Comments |
|-----------|-----------------|---------------------|----------|
| 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

| Condition | Primary therapy | Alternative therapy | Comments |
|-----------|-----------------|---------------------|----------|
| 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 | Itraconazole 200 mg three times daily for 3 days and then twice daily | For at least 12 months | |
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].

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 |

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References

1. Green M. Introduction: infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):3–8.
2. Al Hammadi A, Ostrosky-Zeichner L. Epidemiology and management of Candidiasis in solid organ transplant recipients. Curr Fungal Infect Rep. 2016;10(4):147–52.
3. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50(8):1101–11.
4. Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. Future Microbiol. 2012;7(5):639–55.
5. Ramage G, Saville SP, Thomas DP, Lopez-Ribot JL. Candida biofilms: an update. Eukaryot Cell. 2005;4(4):633–8.
6. Kojic EM, Darouiche RO. Candida infections of medical devices. Clin Microbiol Rev. 2004;17(2):255–67.
7. Ison MG, Grossi P. Donor-derived infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):22–30.
8. Andes DR, Safdar N, Baddley JW, Alexander B, Brumble L, Freifeld A, et al. The epidemiology and outcomes of invasive Candida infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Transpl Infect Dis. 2016;18(6):921–31.
9. Nguyen MH, Peacock JE Jr, Morris AJ, Tanner DC, Nguyen ML, Snydman DR, et al. The changing face of candidemia: emergence of non-Candida albicans species and antifungal resistance. Am J Med. 1996;100(6):617–23.
10. Pfaffer MA, Moet GJ, Messer SA, Jones RN, Castanheira M. Candida bloodstream infections: comparison of species distributions and antifungal resistance patterns in community-onset and nosocomial isolates in the SENTRY antimicrobial surveillance program, 2008-2009. Antimicrob Agents Chemother. 2011;55(2):561–6.
11. Neofytos D, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010;12(3):220–9.
12. Lockhart SR, Wagner D, Iqbal N, Pappas PG, Andes DR, Kauffman CA, et al. Comparison of in vitro susceptibility characteristics of Candida species from cases of invasive candidiasis in solid organ and stem cell transplant recipients: Transplant-Associated Infections Surveillance Network (TRANSNET), 2001 to 2006. J Clin Microbiol. 2011;49(7):2404–10.
13. TSay S, Welsh RM, Adams EH, Chow NA, Gade L, Berkow EL, et al. Notes from the field: ongoing transmission of Candida auris in health care facilities - United States, June 2016-May 2017. MMWR Morb Mortal Wkly Rep. 2017;66(19):514–5.
14. Sun HY, Alexander BD, Lortholary O, Dromer F, Forrest GN, Lyon GM, et al. Unrecognized pretransplant and donor-derived cryptococcal disease in organ transplant recipients. Clin Infect Dis. 2010;51(9):1062–9.
15. Forrest GN, Bhalla P, DeBess EE, Winthrop KL, Lockhart SR, Mohammadi J, et al. Cryptococcus gattii infection in solid organ transplant recipients: description of Oregon outbreak cases. Transpl Infect Dis. 2015;17(3):467–76.
16. Singh N, Alexander BD, Lortholary O, Dromer F, Gupta KL, John GT, et al. Cryptococcus neoformans in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. J Infect Dis. 2007;195(5):756–64.
17. Husain S, Wagener MM, Singh N. Cryptococcus neoformans infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg Infect Dis. 2001;7(3):375–81.
18. George IA, Santos CAQ, Olsen MA, Powderly WG. Epidemiology of Cryptococcosis and Cryptococcal meningitis in a large retrospective cohort of patients after solid organ transplantation. Open Forum Infect Dis. 2017;4(1):ofx004.
19. Grim SA, Proia L, Miller R, Alhyraba M, Costas-Chavarri A, Oberholzer J, et al. A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. Transpl Infect Dis. 2012;14(1):17–23.
20. Miller R, Assi M. Endemic fungal infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):250–61.
21. Blair JE, Logan JL. Coccidioidomycosis in solid organ transplantation. Clin Infect Dis. 2001;33(9):1536–44.
22. Kubak BM, Huprikar SS. Emerging & rare fungal infections in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S208–26.
23. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357(25):2601–14.
24. Gabardi S, Kubiak DW, Chandraker AK, Tullius SG. Invasive fungal infections and antifungal therapies in solid organ transplant recipients. Transpl Int. 2007;20(12):993–1015.
25. Fishman JA, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. Infect Dis Clin N Am. 2010;24(2):273–83.
26. Nampoory MR, Khan ZU, Johny KV, Constandi JN, Gupta RK, Al-Muzairi I, et al. Invasive fungal infections in renal transplant recipients. J Infect. 1996;33(2):95–101.
27. Pirsch JD, Odorico JS, D’Alessandro AM, Knechtle SJ, Becker BN, Sollinger HW. Posttransplant infection in enteric versus bladder-drained simultaneous pancreas-kidney transplant recipients. Transplantation. 1998;66(12):1746–50.
28. Collins LA, Samore MH, Roberts MS, Luzzati R, Jenkins RL, Lewis WD, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis. 1994;170(3):644–52.
29. Patterson JE. Epidemiology of fungal infections in solid organ transplant patients. Transpl Infect Dis. 1999;1(4):229–36.
30. Silveira FP, Husain S. Fungal infections in solid organ transplantation. Med Mycol. 2007;45(4):305–20.
31. Tissot F, Pascual M, Hullin R, Yerly P, Tozzi P, Meylan P, et al. Impact of targeted antifungal prophylaxis in heart transplant recipients at high risk for early invasive fungal infection. Transplantation. 2014;97(11):1192–7.
32. Abbott KC, Hypolite I, Poropatich RK, Hshieh P, Cruess D, Hawkes CA, et al. Hospitalizations for fungal infections after renal transplantation in the United States. Transpl Infect Dis. 2001;3(4):203–11.
33. Dockrell DH, Mendez JC, Jones M, Harmsen WS, Illstrup DM, Smith TF, et al. Human herpesvirus 6 seronegativity before transplantation predicts the occurrence of fungal infection in liver transplant recipients. Transplantation. 1999;67(3):399–403.
34. Saliba F, Delvart V, Ichai P, Kassis N, Botterel F, Mihaila L, et al. Fungal infections after liver transplantation: outcomes and risk factors revisited in the MELD era. Clin Transpl. 2013;27(4):E454–61.
35. Silveira FP, Kusne S. Candida infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):220–7.
36. Peleg AY, Husain S, Kwak EJ, Silveira FP, Ndirangu M, Tran J, et al. Opportunistic infections in 547 organ transplant recipients receiving alemtuzumab, a humanized monoclonal CD-52 antibody. Clin Infect Dis. 2007;44(2):204–12.
37. Issa NC, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. Clin Infect Dis. 2009;48(6):772–86.
38. Kontoyiannis DP, Lewis RE, Alexander BD, Lortholary O, Dromer F, Gupta KL, et al. Calcineurin inhibitor agents interact synergistically with antifungal agents in vitro against Cryptococcus neoformans isolates: correlation with outcome in solid organ transplant recipients with cryptococcosis. Antimicrob Agents Chemother. 2008;52(2):735–8.
39. Levesque E, Suet G, Merle JC, Compagnon P, Amathieu R, Feray C, et al. Candida vascular complication in a liver transplant recipient due to yeast contamination of preservation solution. Transpl Infect Dis. 2014;16(5):827–9.
40. Rodrigues BF, Natario AS, Vizinho RS, Jorge CM, Weigert AL, Martinho A, et al. Candida species contamination of preservation fluid-outcome of renal transplantation in 6 patients. Transplant Proc. 2013;45(6):2215–9.
41. Albano L, Bretagne S, Mamzer-Bruneel MF, Kacso I, Desnos-Ollivier M, Guerrini P, et al. Evidence that graft-site candidiasis after kidney transplantation is acquired during organ recovery: a multicenter study in France. Clin Infect Dis. 2009;48(2):194–202.
42. Azar MM, Turbett SE, Fishman JA, Pierce VM. Donor-derived transmission of Candida auris during lung transplantation. Clin Infect Dis. 2017;65(6):1040–2.
43. Singh N, Huprikar S, Burdette SD, Morris MI, Blair JE, Wheat LJ. Donor-derived fungal infections in organ transplant recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. Am J Transplant. 2012;12(9):2414–28.
44. Shoham S, Marwaha S. Invasive fungal infections in the ICU. J Intensive Care Med. 2010;25(2):78–92.
45. Said A, Safdar N, Lucey MR, Knechtle SJ, D’Alessandro A, Musat A, et al. Infected bilomas in liver transplant recipients, incidence, risk factors and implications for prevention. Am J Transplant. 2004;4(4):574–82.
46. Kanj SS, Welty-Wolf K, Madden J, Tapsin V, Baz MA, Davis RD, et al. Fungal infections in lung and heart-lung transplant recipients. Report of 9 cases and review of the literature. Medicine (Baltimore). 1996;75(3):142–56.
47. Ciccaro G, Burke GW, Viciana AL, Ruiz P, Ginzburg E, Dowdy L, et al. Destructive allograft fungal arteritis following simultaneous pancreas-kidney transplantation. Transplantation. 1996;61(8):1172–5.
48. Dowling RD, Baladi N, Zenati M, Dummer JS, Kormos RL, Armitage JM, et al. Disruption of the aortic anastomosis after heart-lung transplantation. Ann Thorac Surg. 1990;49(1):118–22.
49. Baddley JW, Forrest GN. Cryptococcosis in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):242–9.
50. Karnak D, Avery RK, Gildea TR, Sahoo D, Mehta AC. Endobronchial fungal disease: an under-recognized entity. Respiration. 2007;74(1):88–104.
51. Osawa R, Alexander BD, Lortholary O, Dromer F, Forrest GN, Lyon GM, et al. Identifying predictors of central nervous system disease in solid organ transplant recipients with cryptococcosis. Transplantation. 2010;89(1):69–74.
52. Sun HY, Alexander BD, Lortholary O, Dromer F, Forrest GN, Lyon GM, et al. Cutaneous cryptococcosis in solid organ transplant recipients. Med Mycol. 2010;48(6):785–91.
53. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, et al. An immune reconstitution syndrome-like illness associated with Cryptococcus neoformans infection in organ transplant recipients. Clin Infect Dis. 2005;40(12):1756–61.
54. Gauthier GM, Safdar N, Klein BS, Andes DR. Blastomycosis in solid organ transplant recipients. Transpl Infect Dis. 2007;9(4):310–7.
55. Vikram HR, Blair JE. Coccidioidomycosis in transplant recipients: a primer for clinicians in nonendemic areas. Curr Opin Organ Transplant. 2009;14(6):606–12.
56. Netsvyetayeva I, Szwoboda-Kopec E, Paczek L, Fiedor P, Sikora M, Jaworska-Zaremba M, et al. Trichosporon asahii as a prospective pathogen in solid organ transplant recipients. Mycoses. 2009;52(3):265–7.
57. Potti A, Danielson B, Sen K. “True” mycotic aneurysm of a renal artery allograft. Am J Kidney Dis. 1998;31(1):E3.
58. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(3):291–322.
59. Rhie S, Turcios R, Buckley H, Suh B. Clinical features and treatment of Malassezia folliculitis with fluconazole in orthotopic heart transplant recipients. J Heart Lung Transplant. 2000;19(2):215–9.
60. Zhao HM, Ran YP, Jiang X, Zeng W, Xiong L, Dai YL, et al. Isolation of Malassezia furfur from the groin abscess of a renal transplant patient. Sichuan Da Xue Xue Bao Yi Xue Ban. 2005;36(1):6–9.
61. Al Othman A. Rhodotorula species peritonitis in a liver transplant recipient: a case report. Saudi J Kidney Dis Transpl. 2006;17(1):47–9.
62. Riedel DJ, Johnson JK, Forrest GN. Rhodotorula glutinis fungemia in a liver-kidney transplant patient. Transpl Infect Dis. 2008;10(3):197–200.
63. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813–21.
64. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Executive summary: clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):409–17.
13 Prevention and Treatment of Yeast and Endemic Fungal Infections

65. Assi M, Martin S, Wheat LJ, Hage C, Freifeld A, Avery R, et al. Histoplasmosis after solid organ transplant. Clin Infect Dis. 2013;57(11):1542–9.

66. Hage CA, Knox KS, Davis TE, Wheat LJ. Antigen detection in bronchoalveolar lavage fluid for diagnosis of fungal pneumonia. Curr Opin Pulm Med. 2011;17(3):167–71.

67. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, Garey KW, Alangaden GJ, Vazquez JA, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis. 2015;60(6):892–9.

68. Singh N, Lortholary O, Dromer F, Alexander BD, Gupta KL, John GT, et al. Central nervous system cryptococcosis in solid organ transplant recipients: clinical relevance of abnormal neuroimaging findings. Transplantation. 2008;86(5):647–51.

69. Loyse A, Moodley A, Rich P, Molloy SF, Bicanic T, Bishop L, et al. Neurological, visual, and MRI brain scan findings in 87 South African patients with HIV-associated cryptococcal meningoencephalitis. J Infect. 2015;70(6):668–75.

70. Personett HA, Laub MR. Review of infectious disease prophylaxis in solid organ transplantation. Crit Care Nurs Q. 2017;40(4):383–98.

71. Winston DJ, Limaye AP, Pelletier S, Safdar N, Morris MI, Meneses K, et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. Am J Transplant. 2014;14(12):2758–64.

72. Fortun J, Martin-Davila P, Montejo M, Munoz P, Cisneros JM, Ramos A, et al. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. Transplantation. 2009;87(3):424–35.

73. Singh N, Wagener MM, Cacciarelli TV, Levitsky J. Antifungal management practices in liver transplant recipients. Am J Transplant. 2008;8(2):426–31.

74. Cuellar-Rodriguez J, Avery RK, Lard M, Budev M, Gordon SM, Shrestha NK, et al. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. Clin Infect Dis. 2009;49(5):710–6.

75. Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(12):1801–12.

76. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807–25.

77. Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Geertsma F, Hoover SE, et al. Executive summary: 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of Coccidioidomycosis. Clin Infect Dis. 2016;63(6):717–22.

78. Pappas PG. Invasive candidiasis. Infect Dis Clin N Am. 2006;20(3):485–506.

79. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis. 2006;43(1):25–31.

80. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother. 2005;49(9):3640–5.

81. Grossi PA, Gasperina DD, Barchiesi F, Biancofiore G, Carafiello G, De Gasperi A, et al. Italian guidelines for diagnosis, prevention, and treatment of invasive fungal infections in solid organ transplant recipients. Transplant Proc. 2011;43(6):2463–71.

82. Lipp HP. Antifungal agents—clinical pharmacokinetics and drug interactions. Mycoses. 2008;51(Suppl 1):7–18.

83. Huprikar S, Shoham S. Emerging fungal infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):262–71.