38
Yeast Infections After Solid Organ Transplantation

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38.1 Candida

38.1.1 Epidemiology

Candida is a genus of yeast found in abundance worldwide. There is a wide variety of species found throughout the environment, however only about 15 of these are commonly pathogenic in humans. In addition to causing disease, the yeast can be found throughout the body as a part of the normal human microbial environment.

The Transplant-Associated Infection Surveillance Network (TRANSNET) study reported in 2010 that *Candida* comprised more than half of all documented invasive fungal infections in SOT recipients [1]. *Candida albicans* was the predominant species, however was the etiologic pathogen in approximately 50% of *Candida* cases. *C. glabrata* comprised a quarter while the remaining cases were primarily caused by *C. parapsilosis*, *C. tropicalis,* and *C. krusei*. Polymicrobial infection occurred in almost 10%. The Prospective Antifungal Therapy (PATH) registry followed a broader group of patients and saw a similar distribution of species overall, however when looking at solely solid organ transplant recipients, observed *C. glabrata* to be the most common species at nearly 40% [2]. They also demonstrated similar findings of *Candida* being the most common cause of fungal infection in solid organ transplant (SOT) recipients [3]. A follow-up study from the PATH registry looking solely at non-albicans species observed *C. glabrata* to cause over 60% of non-albicans candidiaisis (Table 38-1) [4]. A similar population-based monitoring program, the SENTRY Antimicrobial Surveillance Program, demonstrated *C. albicans* as the most common with *C. glabrata* second, however at a lower frequency (less than 20%) compared to TRANSNET and PATH Alliance [5]. One key difference between the studies, however, is that while TRANSNET and PATH were confined to North America, SENTRY was a worldwide study. The SENTRY breakdown by region shows their North America rates by species to be similar to the other studies, with much lower rates of *C. glabrata* in the other parts of the world [6]. *C. parapsilosis* supplants *C. glabrata* as the second most common species in their Latin America isolates.

38.1.2 Pathogenesis

As the most common species, the majority of work looking at pathogenesis and virulence has focused on *C. albicans. C. albicans* has an ability to exist along a spectrum from budding yeast to a walled hyphal structure [7]. One primary mode of virulence is the ability of the yeast to adhere to surfaces, including human cells, and convert to the hyphal form for the purposes of invading tissue [7]. Indeed, altering genetics to prevent the transition from yeast to hyphal phase has been shown to decrease pathogenicity [8]. The ability to adhere to surfaces is also an important contributor to human disease with the ability to form biofilms on prosthetic surfaces, including a concurrent upregulation of resistance mechanisms [9]. The adherence of fungal cells to a surface and formation of a biofilm prompt the development of "persister cells" that are highly resistant to antifungals [10].

38.1.3 Clinical Manifestations

38.1.3.1 Superficial Infections

As SOT recipients have their immune system influenced by pharmacologic immunosuppression, in particular glucocorticosteroids, *Candida* is presented with the opportunity to transform from commensal to pathogen. The spectrum of superficial disease ranges from cutaneous to mucous membrane and can occur in a variety of sites. Additional co-morbid conditions can contribute to the development of oropharyngeal thrush or vaginitis, such as concurrent antibiotic use (e.g., prophylaxis) and diabetes. Oropharyngeal thrush can progress to a more invasive form of mucosal disease, specifically,

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Table 38-1. Species distribution in candidemia among patients with solid organ transplants

	TRANSNET	PATH alliance
Species	*N*=264	*N*=292
C. albicans	131 (50%)	97 (33%)
C. glabrata	78 (30%)	112 (38%)
C. parapsilosis	23 (9%)	33 (11%)
C. tropicalis	12 (5%)	16 (5%)
C. krusei	14 (5%)	8 (3%)

Candida esophagitis. A more severe infection such as this must be dealt with promptly as potential complications ranging from stricture to perforation and death have been reported [11, 12].

38.1.3.2 Candidemia

Candidemia is the most common manifestation of invasive candidiasis amongst transplant recipients based on data from the TRANSNET cohort [1, 13]. The following risk factors are well understood to place patients at risk for invasive candidiasis: neutropenia, chemotherapy, colonization with *Candida*, broad-spectrum antibiotics, central venous catheter, hemodialysis or renal failure, critical illness, parenteral nutrition, mechanical ventilation, surgery, and advanced age [14]. It is not uncommon for the SOT recipient to meet one or more of these factors.

Liver transplant recipients are at particularly increased risk of candidemia with a variety of potential factors taking into account pre- and post-transplant variables. Using a focused algorithm of creatinine greater than 3 mg/dL, transplant operative time greater than or equal to 11 h, retransplantation, receipt of more than 40 units of blood products, or early fungal colonization, the presence of two or more factors identified a group of patients in whom 67% developed an invasive fungal infection with *Candida* being the most common genus [15]. Since the establishment of the Model for End-stage Liver Disease (MELD), this has now been evaluated for its contribution to predicting infectious complications [16, 17]. In multivariate analysis including other known risk factors for invasive fungal infections (IFIs), an elevated MELD score has been shown to have increased odds for developing all types of IFIs including invasive candidiasis and candidemia [17].

38.1.3.3 Urinary Tract Infection

Candida is an uncommon pathogen in the urinary tract; however, it is a frequent colonizer in certain patients. Patients with urinary catheters, diabetes, on broad-spectrum antibiotics, or prolonged hospitalization are all prone to *Candida* isolation from urine culture specimens. Renal transplant recipients, in particular, pose a dilemma over what to do with positive culture results in the setting of manipulation of the urinary tract and possibly the placement of a ureteral stent. Prosthetic materials are one of the situations where *Candida* can evolve from colonizer to pathogen. Studies to determine the true incidence of candiduria in renal transplant recipients are inconclusive, however it probably approximates 10%, not dissimilar to the hospitalized population as a whole [18, 19]. These studies have failed to show a substantial benefit to treating a positive *Candida* urine culture in the absence of symptomatic probable or proven disease. Infection can be severe with pyelonephritis having been reported [20, 21].

38.1.3.4 Intra-Abdominal

Candida has long been known to be a colonizer of the gastrointestinal tract, and therefore controversy has persisted over whether its presence in peritoneal culture represents colonization versus invasive infection [22]. In particular, complicated nosocomial peritonitis appears to be an instance of true infection [23]. Liver, small bowel, and pancreas transplant recipients can be of increased risk and, if certain criteria are met, may warrant fluconazole prophylaxis to prevent invasive candidiasis. This will be discussed in more detail below.

38.1.3.5 Pulmonary

Candida as a cause of primary pneumonia is exceptionally rare. While pulmonary disease does occur, it is generally in the form of hematogenous spread from other sources. This generally appears radiographically as septic emboli. *Candida* frequently occurs as a colonizer either of the respiratory tract or, in the mechanically ventilated, the endotracheal tube given the organism's propensity to adhere to surfaces. Studies have failed to find an association between microbiologic growth of *Candida* from bronchoscopic specimens and an impact mortality or other outcomes [24, 25]. An exception to this statement is limited to anastomotic tracheobronchitis in lung transplant recipients. This is a well-described entity and can be caused by a wide variety of organisms, including *Candida* [26]. A single center study looking at the causes of tracheobronchitis in 272 heart–lung or lung recipients found 15 anastomotic infections, of which *Candida* was the most common pathogen, having been diagnosed in eight of the patients [27].

38.1.3.6 Ocular

Involvement of the eye is an uncommon but well-recognized complication of disseminated invasive candidiasis. Clinical manifestations range from chorioretinitis to full-blown endophthalmitis. Rates as high as 26% for ocular spread associated with candidemia have been reported. Historically *C. albicans* is more likely than other species to cause ocular involvement based on its innate invasive potential, while *C. parapsilosis* is the least likely compared to other species [28, 29]. There are no prospective studies looking at rates of ocu-

lar candidiasis in solid organ transplant recipients; however, it has been reported in the SOT population [26, 30, 31]. It does appear to be an uncommon complication, as one series reporting all ocular infections from a cohort of heart transplant recipients had no cases caused by *Candida* [32].

38.1.3.7 Donor-Derived

Presence of *Candida* in the gastrointestinal tract raises the potential for transmission in the process of the intra-peritoneal organs [33]. Additionally, the presence of candidemia prior to or at the time of death of the donor would raise the potential for transmission. While not strictly a donor-derived complication, there are numerous case reports of *Candida* contaminating the preservation fluid in transport from donor to recipient [34–39]. A study of graft-site candidiasis deriving from organ recovery in renal transplant recipients found renal arteritis to be the most common complication [40].

38.1.4 Diagnosis

Culture is currently the gold standard of diagnosis. While it is difficult to interpret a culture positive for *Candida* species from a non-sterile site, sterile cultures are indicative of an invasive process and should be treated with the utmost urgency. Given the benefits of early and effective treatment and the variation of anti-fungal sensitivities based on species, efforts are underway to develop more reliable means of rapid diagnosis and species identification.

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) is one means of rapid identification that can lead to faster adjustment of antifungal treatment. MALDI-TOF has been shown to identify *Candida* species with accuracy equal to or greater than conventional methods [41]. Additionally, the technology has been shown to drastically decrease time to identification, in particular for the non-albicans *Candida* species [42]. To run the assay, a pure culture specimen must undergo preparation specific to the brand of MALDI-TOF in use. While this earlier identification can be beneficial in making empiric adjustments in treatment, it does not impact the time to diagnosis of invasive candidiasis since it still requires a positive culture.

Peptide nucleic acid fluorescent in situ hybridization (PNA-FISH) can be performed directly from a positive blood culture bottle prior to being plated for isolation of pure colonies with a very high level of sensitivity and specificity for *C. albicans* [43]. Commercially available multi-species kits now exist but have some limitations in their ability to distinguish completely to the species level with pairing of species to a single color fluorescence [44]. The test can be run directly from positive blood culture bottles or from subcultured colonies. While this has the potential to provide some identification data even faster than MALDI-TOF, it is still reliant on *Candida* growing in culture.

Table 38-2. Performance of non-culture based diagnostic assays for candidemia and/or invasive candidiaisis

Assay	Sensitivity	Specificity
(1 → 3)-β-D-glucan	57–97%	44–93%
PCR	73–93%	90–96%
T2Candida®	88–94%	98.9–99.9%

The most recent technology to become available is the T2Candida® assay. Based on magnetic resonance technology, the assay is able to identify to a paired species level (*C. albicans/C. tropicalis*, *C. krusei/C. glabrata*, and *C. parapsilosis*) from a whole blood specimen without waiting for a positive culture [45]. The technology can identify a positive signal within hours of the obtaining the whole blood specimen, thus having the potential to identify candidemia much sooner and lead to earlier initiation of appropriate therapy. Additionally it has an excellent negative predictive value for candidemia which could be used to de-escalate or stop unnecessary anti-fungal therapy very quickly (Table 38-2).

Non-fungemic invasive candidiasis remains a challenge to diagnose [46]. An assay to detect (1 → 3)-β-D-glucan (BDG), a component of the *Candida* cell wall, in serum or plasma has been shown in a meta-analysis to have a sensitivity of 76.8% and specificity of 85.3% for proven or probable invasive fungal infections from any organism [47]. Studies restricted to candidiasis have sensitivities ranging from 57% to 97% while the specificity was 44% to 93% [48]. Part of the variation in specificity is due to the presence of the protein in the cell wall of most fungi, not solely *Candida*. Thus, the assay is less specific than some other assays and is considered to be "pan-fungal" by many experts. One study restricted to liver transplant recipients showed improved performance with a sensitivity of 83% and specificity of 89% [49]. Conversely, the test performs poorly in lung transplant recipients with one study having a sensitivity of 71 and 59%, noting mold colonization of the lungs and hemodialysis raised levels of BDG [50]. A meta-analysis of polymerase chain reaction (PCR) for the diagnosis of candidiasis has shown good performance characteristics in the blood culture negative population with sensitivity ranging from 73% for culture negative candidiasis to 93% for proven/probable candidiasis [51]. Specificity for both groups was over 90%.

38.1.5 Treatment

Multiple guidelines exist to assist the clinician with ensuring appropriate treatment across the spectrum of invasive candidiasis [52–55]. Overall, treatment of the solid organ transplant is the same as treatment for the non-transplant patient. As such, the focus here will be on selected types of infection.

Candidemia initial regimen should be based on both severity of illness and the potential for a resistant isolate, in particular *C. glabrata* and *C. krusei*, but most experts agree that

echinocandins are preferred as initial therapy for most patients with candidemia [55]. For empiric therapy, echinocandins are generally preferred in the critically ill, those with a recent history of or present fluconazole use, or colonization with a resistant isolate. The TRANSNET study, performed between 2000 and 2006, documented an overall fluconazole resistance rate at that time of 16%, with *C. glabrata* and *C. krusei* comprising 30% of all isolates [13]. Lacking those risk factors, fluconazole is a reasonable option for empiric therapy in the non-acutely ill person. Once the species and susceptibilities are determined, targeted therapy can be chosen. Treatment should continue for at least 14 days from the first negative culture with an attempt to influence source control, in particular the removal of intravascular catheters [55].

For candiduria, the decision to treat should be on the basis of symptoms and/or findings consistent with a urinary tract infection. If the patient is asymptomatic but neutropenic or undergoing a urologic procedure, then treatment is warranted. The kidney(s) should be assessed for the presence of a fungal ball and surgical removal of the obstruction pursued if found. Echinocandins are poorly excreted into the urine, therefore fluconazole is the treatment of choice for most *Candida* urinary tract infections. If a fluconazole-resistant isolate is isolated, then a lipid amphotericin-B preparation can be used, with or without flucytosine [55].

Ocular candidiasis is another circumstance where echinocandins fall short in their ability to penetrate a particular tissue. Again, lipid amphotericin-B products and fluconazole are the agents of choice. Consultation with ophthalmology should be obtained early to assess the need for aggressive surgical intervention with vitrectomy [55].

Treatment of end-organ infection, such as pulmonary, intra-peritoneal, or cardiovascular candidiasis should be driven by species identification and susceptibilities. Duration of therapy will need to be tailored to the individual patient on the basis of ability to drain the infected material and reverse the source of contamination.

There is emerging evidence of the development of resistance to echinocandins, in particular in *C. glabrata. C. parapsilosis* has been noted to have, on average, higher minimum inhibitory concentrations against the echinocandins, but there is little correlation to these values and clinical response to therapy with echinocandins [56–60]. Rates of resistance appear to vary significantly across centers. The presence of azole and/or echinocandin resistance should be explored among patients failing to respond as expected to either of these therapies.

The other aspect of treatment is monitoring for drug–drug interactions (DDIs). While the echinocandins have minimal DDIs, fluconazole and other azole agents are well documented to have many potential DDIs, and care should be taken to adjust immunosuppressant dosing, especially with use of the calcineurin inhibitors, cyclosporine and tacrolimus, and the mTOR inhibitors, everlimus and sirolimus [61, 62].

38.1.6 Prophylaxis

There is a subset of intra-abdominal transplant patients who are high risk for invasive candidiasis. Criteria to determine high-risk is best established in liver transplant recipients; defined as *Candida* colonization, 40 or more units of cellular blood products transfused, retransplantation, choledochojejunostomy, and prolonged operation, having two or more of these factors warrants prophylaxis [54]. Additionally, a MELD score >30 has been shown to increase the odds of a post-transplant infection of any type [63]. There were few documented fungal infections in this study; however, the broader use of MELD has overlapped with the growing use of anti-fungal prophylaxis. This confounds the assessment of the value of MELD as a predictor of invasive fungal infection (IFI), but nevertheless, a high MELD score should be considered a risk factor for IFI and taken into consideration when deciding to give anti-fungal prophylaxis in the early post-transplant period.

A meta-analysis of antifungal prophylaxis of any sort demonstrated a decrease in all types of candidiasis and improvement of mortality attributable to fungal infections, but without an impact on overall mortality [64]. Fluconazole has been shown to be superior to both nystatin and placebo in preventing infections caused by *Candida* and is well tolerated [65, 66]. Caspofungin has demonstrated efficacy but has not been studied in a randomized, comparative trial [67]. Anidulafungin has been shown to be equally effective for antifungal prophylaxis when compared to fluconazole in a randomized, controlled trial of 200 liver transplant recipients that met the criteria for needing prophylaxis [68]. A 2008 survey of liver transplant centers in North America showed three quarters of programs used targeted prophylaxis among high-risk recipients, and fluconazole was the most commonly used agent [69]. Prophylaxis should be discontinued no more than 4 weeks after transplant unless there are ongoing concerns for invasive candidiasis.

There are no clinical trials to assess the role of antifungal prophylaxis in small bowel transplants; however given its presence as a colonizer in the gastrointestinal tract and high rate of infection, fluconazole is commonly used for this purpose [70]. Pancreatic transplantation also carries a high rate of fungal infection with one study showing the benefit of fluconazole prophylaxis on decreased candidiasis and infection free survival [71].

38.2 Cryptococcus

38.2.1 Epidemiology

Cryptococcus is an encapsulated budding yeast capable of causing a disease with a variety of manifestations. *Cryptococcus neoformans* has long been the predominant disease causing species, but the emergence of *Cryptococcus gattii* throughout the world is becoming a formidable challenge.

Originally recognized in Australia and Papua New Guinea, *C. gattii* has now been reported across the globe [72].

Comprising 8% of all IFIs in the TRANSNET dataset, the 146 cases of cryptococcosis were the third most common fungal pathogen in solid organ transplant (SOT) recipients [1]. The incidence of cryptococcosis in that study was approximately 0.2% of all solid organ transplant patients. Literature reviews of reported cases have shown a much higher incidence in SOT recipients, ranging from 1.56 to 2.8, but these represent cumulative estimates, whereas the TRANSNET data are based on calculated annual incidence [73, 74]. Cryptococcosis is rare in stem cell transplant recipients. The TRANSNET study identified only 6 cases among 16,200 enrolled stem cell transplant recipients [75]. While infection can occur any time after transplant, multiple studies show a median time to infection of 19–21 months post-transplantation [1, 74, 76]. Infection in the first month raises the possibility of pre-existing infection in the recipient or donor-derived infection [77, 78].

38.2.2 Pathogenesis

Primary infection in humans occurs through inhalation of infectious particles, though uncertainty remains over just what type of particle begins the cascade that ultimately leads to active disease. Current data suggests humans are exposed at a high rate at a young age with the organism remaining dormant for a prolonged period of time before later causing disease [79–81]. This is not uniform worldwide, however, as a study of exposure rates in children from the Philippines and two regions of New York demonstrated high variability in serologic positivity among children from the Bronx, NY, Dutchess County, NY and the Philippines [82]. A study to determine pre-transplant exposure to *Cryptococcus* in SOT recipients who were diagnosed with disease exhibited evidence of antibody responses in 52% [83]. That group also developed cryptococcosis much earlier in the post-transplant period, 5.6 months from the time of transplant rather than 40.6 months in the group that did not have evidence of pre-transplant antibodies against *Cryptococcus*. These data suggest that most cases of post-transplantation cryptococcosis are due to a reactivation event.

The polysaccharide capsule plays a key role in its ability to cause disease and evade the host immune system. It has been shown to inhibit phagocytosis and reduce the production and effectiveness of the innate immune response, including cytokines and the complement pathway [84]. Once phagocytosed and intracellular, the capsule enhances the ability of the yeast to survive oxidative stress [85]. Inoculation of a mouse with a capsule deficient strain of *Cryptococcus* leads to an increased inflammatory response and minimal production of invasive disease compared to a capsular *Cryptococcus* strain [86]. Further evidence of the importance of the capsule in the virulence of *C. neoformans* is found in the animal model. When one deletes the *CAP59* gene responsible for capsule formation, this causes a loss of virulence in a mouse model of cryptococcal meningitis; the transformation of the avirulent strain with a plasmid containing the *CAP59* gene restores its virulence in this model [87].

38.2.3 Clinical Manifestations

Cryptococcus causes a variety of clinical syndromes. In the solid organ transplant population, there is a higher frequency of isolated pulmonary disease when compared to the human immunodeficiency virus (HIV) population [88]. Disseminated disease remains a frequent occurrence with the bloodstream, central nervous system (CNS), skin and soft tissue, and urinary tract as potential sites of disease.

38.2.3.1 Pulmonary

As the primary site of most infections, the lungs are the most common site of disease, and patients can present either with primary or reactivation disease. Pulmonary disease in the SOT population can range from an asymptomatic nodular infiltrate to lobar consolidation, a mass-like infiltrate, cavitary disease, or diffuse nodular infiltrates [89, 90]. Studies of cryptococcosis in SOT recipients have found that 25–39% of cases will have disease limited to the lungs [1, 88, 89]. Higher doses of steroids have been associated with a higher rate of symptomatic and disseminated diseases [89, 91]. Duration of symptoms prior to diagnosis spans a wide range, with one study of solid organ transplant recipients reporting the presence of symptoms from 1 to 97 days [92]. Severity of illness can range from asymptomatic disease to fulminant respiratory failure [93]. Compared to HIV patients, SOT recipients have a higher rate of pulmonary disease with less CNS involvement [88]. However, the diagnosis of pulmonary disease should prompt a search for infection elsewhere, in particular a lumbar puncture to assess for involvement of the CNS [94].

38.2.3.2 Central Nervous System

As noted above, central nervous system involvement occurs at a lower frequency in SOT patients compared to HIV patients, but it remains the most common site of extrapulmonary involvement among SOT patients with cryptococcosis, occurring in 44–62% of these patients [1, 88, 95, 96]. While presenting symptoms vary, asymptomatic meningeal disease likely occurs rarely, patients can present acutely with symptoms occurring for only 2 days to several weeks [97]. Abnormal mental status, fungemia, late-onset disease (defined as more than 24 months post-transplant), and a serum cryptococcal antigen titer >1:64 have been found to be associated with an increased risk of CNS involvement [95].

Focal parenchymal lesions with or without evidence of meningitis may occur in SOT recipients [98]. Focal parenchymal lesions without meningitis are an uncommon manifestation of disease in this population. In one study, 10% of patients had focal parenchymal lesions while 13% had meningeal enhancement. Additionally, the presence of a focal meningeal lesion was associated with higher CSF cryptococcal antigen titers compared to parenchymal lesions [98]. Finally, among those with CNS infections, the presence of abnormal neuroimaging findings at diagnosis was more likely to meet the diagnostic criteria for immune reconstitution inflammatory syndrome later in their treatment course [99].

38.2.3.3 Bloodstream Infection

Rates of blood culture positivity indicating disseminated disease vary, in part due to a lack of consistent collection of the blood cultures. One study of 178 cases had 38% of blood cultures grow *Cryptococcus*, however cultures were only collected on 39 patients [74]. Other studies have shown lower rates of bloodstream infection, with the Cryptococcal Collaborative Transplant Study Group showing 21% overall but significantly more common in CNS disease with 36% of patients who were fungemic [76, 98]. Positive blood cultures were also associated with increased 90-day mortality [76]. A separate single-center study of cryptococcal meningitis in SOT recipients demonstrated similar observations with 39% of patients with CNS disease having positive blood cultures [97].

38.2.3.4 Skin and Soft Tissue

Cutaneous and subcutaneous infection is the third most common form of cryptococcosis in the SOT population, comprising 10–18% of cases [88, 100]. Appearance varies greatly, from cellulitis to abscess and ulcer formation to deep nodular and panniculitis lesions having been reported in a variety of anatomic locations [100]. Clues that should make the clinician suspect cryptococcosis rather than a bacterial etiology should include the following: bilateral or disseminated lesions, a nodular component to palpation or appearance, atypical anatomic location, tissue necrosis, and failure to respond to conventional anti-bacterial agents.

38.2.3.5 Urinary Tract

The prostate and urinary tract are known reservoirs for fungal infections, however reports of cryptococcal infection there in SOT patients are rare. Involvement of the prostate and the kidney have both been reported [101, 102].

38.2.4 Diagnosis

Multiple reliable means of establishing a diagnosis of cryptococcosis exist: cryptococcal antigen assay of bodily fluid (primarily serum and cerebral spinal fluid), routine and fungal culture, and characteristic findings on histopathology and/or cytology of pathologic samples.

38.2.4.1 Cryptococcal Antigen

A variety of types of antigen assays to detect the capsular polysaccharide antigen exist. The most experience has been developed with latex agglutination and enzyme immunoassays, although more recently a lateral flow assay with potential utility as a point-of-care test has been developed [103–105]. All methods display a high degree of sensitivity and specificity, approaching 100% depending on the sample type and clinical syndrome. One group in whom the assay performs less well is the lung transplant population, where the serum assay may have decreased sensitivity [89, 106].

38.2.4.2 Culture

Cryptococcus species do not require specialized media for reliable culture, growing readily on standard bacterial media such as blood agar as well as standard fungal media such as Sabouraud's dextrose agar [107]. Certain types of media can be used to increase the sensitivity of culture, with brain heart infusion agar potentially improving the yield [108]. The organism can be cultured from tissue or bodily fluid collected at the site of disease, whether it be a tissue biopsy, blood culture, pulmonary specimen, cerebral spine fluid, or urine. The time to positive culture result for *Cryptococcus* tends to be slower than for bacterial or other yeast organisms, usually 3–5 days before growth is evident [107].

38.2.4.3 Histopathology

Microscopic examination of specimens, either of tissue or fluid, can be an important addition to prompt diagnosis and determining sites of involvement. Several stains can be helpful to distinguish *Cryptococcus* from other fungal infections. India ink has classically been used to highlight the capsule of these yeasts in cerebrospinal fluid. The potential difficulty with this simple test is in successfully identifying the yeast from CSF lymphocytes [107]. With increasing use of easier to perform and interpret antigen tests, however, the India ink is being used less frequently. Gomori methanamine silver (GMS) stain is positive but non-specific for most fungal organisms, and mucicarmine stain of tissue is useful in highlighting the capsule and distinguishing *Cryptococcus* from *Histoplasma, Blastomyces*, and *Candida*.

38.2.4.4 Species Identification

With the increasing recognition of *C. gattii* as a cause of human disease and the comparative difficulties in treating this organism, attention must also be placed on proper species identification with the diagnosis of cryptococcosis. The two main species can be differentiated when grown on agar that is supplemented with L-canavanine, glycine, and

bromthymol blue (CGB agar). *C. gattii* isolates turning the agar blue, while the agar remains yellow with *C. neoformans* isolates [109]. Genetic typing to determine *C. neoformans* or *C. gattii* is generally used with more specialized labs being able to determine the specific subtype of *C. gattii* for epidemiologic purposes and potentially tracing acquisition to a particular exposure [108].

38.2.5 Management

The management of cryptococcosis in SOT recipients is largely based on more recent data generated from the HIV epidemic which has been extrapolated to the SOT population, and abundant retrospective studies specific to post-organ transplantation. Once the diagnosis of cryptococcosis is established, the extent of the infection should be established, in particular to discern whether there is CNS involvement. A lumbar puncture to measure opening pressure and collect cerebrospinal fluid for microbiologic diagnosis is essential in all patients with proven or suspected cryptococcosis. Elevated opening pressure is frequent but not universal. As discussed above, cerebrospinal fluid can be tested for the presence of cryptococcal antigen, stained and microscopically examined for the presence of yeast, and cultured. The presence or absence of involvement in the CNS guides the type and duration of antifungal therapy.

Early studies in HIV patients suggested that amphotericin-B and fluconazole as monotherapy were similar in treating cryptococcal meningitis, however later studies have shown that the combination of amphotericin-B with flucytosine shortens time to sterilization of the CSF and improves outcomes when compared to other interventions [110–112]. Additionally, a prospective study in solid organ transplant recipients noted improved mortality in transplant recipients with cryptococcal meningitis when a lipid formulation of amphotericin was used rather than amphotericin-B deoxycholate [113]. Disseminated disease and fungemic patients also benefit from initial therapy with amphotericin-B, however no specific trials have investigated this. Treatment of isolated, extra-neural disease can be monotherapy with fluconazole, depending on disease severity, with an avoidance of the potential nephrotoxic consequences of amphotericin-B. Similarly, duration of therapy depends on disease location and severity. When amphotericin-B products are being used for induction of disseminated, CNS, or severe disease it should be in conjunction with flucytosine for a minimum of 2 weeks if this regimen can be tolerated [94, 114]. This could potentially be extended if the patient is slow to respond and still with significant symptoms or evidence of disease at 2 weeks. If amphotericin is given without flucytosine, induction should continue for at least 4 weeks [94, 114]. Following the completion of induction therapy, the patient can be transitioned to a fluconazole consolidation phase for 8–10 weeks dosed at 6–12 mg/kg (generally 400–800 mg) daily though dose adjusted, if needed, for renal function [94, 114]. Finally, therapy can be completed with a further 6–12 months of fluconazole maintenance at a lower dose of 200–400 mg daily. For mild to moderate, localized, extra-neural disease that does not require amphotericin-B induction, fluconazole should be given for 6–12 months at 400 mg daily [94, 114].

Other potential options for treatment that have been studied in some fashion are the extended-spectrum triazoles including voriconazole, posaconazole, and isavuconazole, however there are insufficient clinical data to support their use in this setting.

Calcineurin pathways exist in *Cryptococcus* as a means for governing growth and are key in allowing the fungus to grow at higher temperatures, such as that of the human body [115]. Blocking this pathway via the addition of the calcineurin-inhibitors cyclosporine and tacrolimus has been shown to eliminate the ability of *Cryptococcus* to grow at higher temperatures [116]. Indeed, these calcineurin-inhibitors have been shown to act in a synergistic manner with anti-fungal agents against *Cryptococcus* isolates obtained from clinical cases [117]. Additionally, SOT patients with a calcineurin-inhibitor as part of their immunosuppressive regimen appear to have a lower risk of mortality and possibly less CNS involvement in the setting of cryptococcosis compared to those not receiving one of those agents [76].

Another aspect of treatment that should be considered is the potential for drug–drug interactions, in particular with the azole agents. Calcineurin inhibitors require their doses to be decreased when co-administered with azoles [62]. Similarly, mTOR inhibitors also require dose decreases however in an even greater magnitude that can completely restrict their concurrent use [61]. The presence of a an opportunistic infection such as cryptococcosis generally leads to a reduction of the overall immunosuppression as allowed and these interactions require careful monitoring to ensure that goal is met safely.

The European Society for Clinical Microbiology and Infectious Diseases, the Infectious Diseases Society of America, and the American Society for Transplantation have developed recommendations to guide treatment each with specific guidance for SOT patients. These recommendations vary based on the extent of the infection [52, 94, 114].

38.2.6 Complications

One of the hallmarks of CNS cryptococcosis is elevated intracranial pressure. This problem is generally relieved by drainage of fluid via lumbar puncture. If increased pressure persists in spite of drainage, this can lead to a need for more continuous diversion of cerebrospinal fluid. In particular, ventriculoperitoneal shunting has been shown to be safe and effective in managing this issue [118, 119]. A trial to assess the potential of acetazolamide in HIV patients with CNS cryptococcosis to reduce intracranial pressure was terminated early due to serious adverse events and a lack of benefit [120]. There are no studies designed to examine a benefit to steroids for the con-

trol of increased intracranial pressure in the setting of cryptococcal meningitis. One HIV treatment trial did track high dose steroid usage and showed worse mortality and clinical response in those that received steroids compared to those that did not [121]. The Infectious Diseases Society of America guidelines for *Cryptococcus* has specifically recommend against the use of steroids in this setting [114].

With reductions in total immunosuppression in the face of an opportunistic infection, the potential exists to develop immune reconstitution inflammatory syndrome (IRIS). This has been reported in the SOT population [122, 123]. The occurrence of IRIS has been associated with an increased risk of allograft loss in renal transplant recipients [124]. A lack of inflammation in the CSF (fewer than 20 WBCs) at the time of diagnosis has been shown to be a risk factor for the development of IRIS in the HIV population [125]. In the SOT population, discontinuation of calcineurin inhibitors and CNS disease were associated with an increased risk of IRIS, however it did not appear to increase the risk of death [99]. There are no trials to assess potential benefit of steroids or other therapy for IRIS. Anecdotal evidence to support the use of steroids exists and guidelines suggest their use as a component of the treatment of severe IRIS with complications [94, 114, 122].

38.2.7 Mortality

Estimates of mortality at 90 days range from 14% to 21% amongst all SOT patients with cryptococcosis of any type [76, 88, 96]. The TRANSNET study found a 27% mortality at 1 year following infection [1]. Mortality rates appear similar when compared to HIV patients [88, 96].

38.2.8 Prophylaxis

While secondary prophylaxis following cryptococcosis can be considered, there have been no trials to assess for a benefit related to this. Relapse has been reported as rare when patients are appropriately treated [126]. There have been no trials to assess for the potential benefit of primarily prophylaxis in the SOT population.

38.3 Other Yeasts

38.3.1 Trichosporon

Trichosporon is a basidiomycetous yeast found worldwide and in the same family as *Cryptococcus* [127]. The most common species in clinical disease are *T. asahii*, *T. mucoides*, and *T. asteroides* [127]. It has generally been associated with hematologic malignancies, but is reported in a variety of forms in solid organ transplant recipients [128, 129]. Similar to other yeasts as well as bacteria, it can form biofilms on prosthetic surfaces and broadly increase its resistance to anti-fungal agents [130]. The most common forms of invasive disease are fungemia, urinary tract infections, peritonitis, and endocarditis [127]. *Trichosporon* is notable in particular for the poor treatment activity of the echinocandin class of anti-fungal agents [131]. This should be kept in mind in cases of breakthrough yeast infection while patients are being treated with an echinocandin [132]. The activity of the triazoles and amphotericin-B vary according to species, indicating a need to ensure full identification of the organism to allow for optimal treatment [133].

38.3.2 Rhodotorula

Rhodotorula is also a basidiomycetous yeast with a predominance for Asia and the regions of the Pacific [134]. The yeast produces carotenoid pigments and colonies can appear salmon to pink depending on the species isolated [135]. The most common species causing pathogenic disease in humans are *R. mucilaginosa* and *R. glutinis* [136, 137]. The most common form of invasive disease is fungemia, however reports of endocarditis, endophthalmitis, and peritonitis also exist [134, 136, 138]. Reports indicate an association with hematologic malignancies and the presence of a central venous catheter, however it has also been reported in SOT recipients [137–139]. The triazoles have generally poor in vitro activity versus *Rhodotorula* species, but amphotericin-B MICs are generally acceptable [140]. *Rhodotorula* species demonstrate in vitro resistance to the echinocandins, and these agents should be avoided to treat these organisms [138].

38.4 Other Considerations

Dimorphic fungi can appear as yeast forms in tissue specimens and blood cultures. This includes *Histoplasma*, *Blastomyces*, *Coccidioides*, and *Paracoccidioides* as the most common agents. Similarly, patients with fungemia due to one of these organisms are usually initially identified simply as "yeasts," and very often patients are begun on an echinocandin therapy based on an assumption that the organism is a *Candida* species. Echinocandins have little in vitro activity versus the endemic mycoses and *Cryptococcus* species, and should be avoided in these circumstances. Rather, in the proper clinical setting, these organisms should be suspected and thoroughly evaluated through a thoughtful diagnostic work-up and treatment adjusted appropriately. Another potential confounding organism is *Fusarium*, which in spite of being a mold may initially appear as a yeast on blood culture broth, leading to the mistaken impression of a diagnosis of candidemia [141].

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