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Special Article

Candida Infections in Solid Organ Transplantation

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Abbreviations: ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmB-d, deoxycholate amphotericin; BDG, 1–3 β glucan; CNI, calcineurin inhibitor; CSF, cerebrospinal fluid; 5-FC, flucytosine; GI, gastrointestinal; IFI, invasive fungal infection; LAmB, liposomal amphotericin B; LFAmB, lipid formulation of amphotericin B; PCR, polymerase chain reaction; PNA-FISH, peptide nucleic acid fluorescent *in situ* hybridization assay; TDM, therapeutic drug monitoring.

Epidemiology and Risk Factors

Infections due to *Candida* spp are the most common invasive fungal infections (IFIs) among organ transplant recipients, accounting for over half of all IFIs in this population (1). In a large prospective study, invasive candidiasis had a 12-month cumulative incidence of 1.9%, the highest of all IFIs, and occurred more frequently in small bowel, pancreas, liver, kidney, heart and lung transplant recipients, in descending order (1). Invasive candidiasis occurs earlier than other invasive mycoses, generally within the first 3 months after transplantation, and is viewed as a classic nosocomial infection (2–6). However, a substantial number of cases of invasive candidiasis, especially among liver and small bowel transplant recipients, occur well beyond this traditional risk period (1,3,4). The most common sites of infection are bloodstream infection, intra-abdominal and urinary tract infection (1,6–8).

Candida albicans is the dominant invasive pathogen, accounting for approximately 50% of isolates. *C. glabrata* is the most common non-*albicans* isolate. *C. krusei* and *C. guilliermondii*, an important pathogen in neutropenic hosts, are more common among stem cell transplant recipients, but far less common among organ transplant recipients (9), and may vary according to institution and geographic location.

Established risk factors for invasive candidiasis in the general population include age, broad spectrum antibiotic therapy, use of central venous catheter, receipt of parenteral nutrition, prolonged neutropenia, prolonged intensive care unit stay, diabetes and renal replacement therapy. Unique risk factors for invasive candidiasis in transplant recipients include the type of transplant and the surgical anastomosis (10). For instance, among liver transplant recipients, a choledocho-jejunostomy is associated with a higher risk of invasive candidiasis compared to a choledocho-choledochostomy anastomosis (11). Similarly, among pancreas transplant recipients, enteric drainage is associated with a higher risk of invasive candidiasis than bladder drainage (12). Other well established risks in transplant recipients include acute renal failure, recent CMV infection, primary graft failure, early surgical re-exploration and early colonization with *Candida* spp (13).

Diagnosis

A definitive diagnosis of invasive candidiasis is dependent on recovery of an organism from a sterile body site. Unfortunately, blood cultures are an insensitive means of identifying patients with invasive candidiasis. Even with newer blood culture techniques, the overall sensitivity of blood cultures for the isolation of *Candida* spp is estimated at 70% (14). Therefore, the development of nonculture based diagnostic methods is important. Presently, there are several FDA-approved assays available, but their use has been very limited in clinical practice. Among these, the 1–3 β-D-glucan (BDG) assay is probably the most reliable, with the sensitivity and specificity of 70% and 87%, respectively, among patients with proven invasive candidiasis (15–17). At present, this assay is only approved as an adjunct to the diagnosis of invasive candidiasis. Other newer diagnostic assays, including PCR-based multiplex assays, are in development. In a prospective study of 55 patients with invasive candidiasis, of which 20% were organ recipients, the sensitivity of BDG with a cut-off for positivity of $\geq$80 pmol/mL and PCR for invasive candidiasis was 56% and 80% and the specificity was 73% and 70%, respectively (18). The sensitivity of either test was not affected by antifungal therapy. The sensitivity of blood cultures combined with BDG

Table 1: General susceptibility patterns of *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	5FC	AmB	Echinocandins
C. albicans	S	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S	S
C.parapsilosis	S	S	S	S	S	S	S to R[1]
C. glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
C. krusei	R	S-DD to R	S	S	I to R	S to I	S
C. lusitaniae	S	S	S	S	S	S to R	S

AmB = amphotericin B; 5-FC = flucytosine; I = intermediate susceptibility; R = resistant; S = susceptible; S-DD = susceptible dose-dependent.

[1] *C. parapsilosis* isolates resistant to echinocandins are uncommon.

or PCR among patients with invasive candidiasis was 79% and 98%, respectively.

Identification of *Candida* isolates to the species level is critically important in selecting antifungal therapy, and to a lesser extent, in predicting outcome. The germ tube test is an inexpensive and specific means of identifying *C. albicans* and *C. dubiliniensis*. The peptide nucleic acid fluorescent *in situ* hybridization assay (PNA-FISH) reliably identifies *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei* in positive blood cultures (19,20). Chromogenic agar, a specialized media for *Candida* isolation and identification, is easily used and readily distinguishes *C. albicans*, *C. tropicalis* and *C. krusei* based on production of distinctive pigments (21).

Susceptibility testing for all clinically significant *Candida* isolates is not practical for many centers. Generally, antifungal susceptibility can be predicted on the basis of species and local epidemiology (see Table 1).

In a prospective study of invasive candidiasis in organ and stem cell transplant recipients fluconazole resistance was observed in 1% of *C. albicans*, *C. tropicalis* and *C. parapsilosis* isolates. Overall voriconazole resistance was observed in 3% of isolates and in 8% of *C. glabrata* isolates. Isolates that were resistant to voriconazole were also resistant to fluconazole. All isolates were susceptible to caspofungin. In multivariate analysis, among organ recipients fluconazole nonsusceptibility was independently associated with any fluconazole use within 3 months before IFI, *C. glabrata*, ganciclovir use within 3 months before the IFI, diabetes acquired because the transplant and gender (22).

Antifungal susceptibility testing is recommended for clinically significant *C. glabrata* isolates, in the clinical setting where azole resistance is strongly suspected, and in case of treatment failure (22,23) (II-3).

Treatment

The treatment of invasive candidiasis among organ transplant recipients is similar to treatment of other patients based on the recently published 2009 IDSA guidelines (23). There are no randomized studies for the treatment of invasive candidiasis among organ transplant recipients; thus, the therapeutic approach is based on large randomized studies in a heterogeneous group of patients, which include only small portion of organ recipients. A summary of the treatment recommendations is described in Table 2.

Therapeutic Drug Monitoring (TDM)

All azoles show significant drug–drug interactions, especially with calcineurin inhibitors (CNI; Ref. (24). Therefore careful monitoring of (CNI) levels is done and dose reduction of CNI is made once an azole is initiated. For patients receiving prolonged courses of voriconazole or posaconazole, TDM is recommended but there is no consensus on this topic (25,26) (III).

In a prospective study of 93-lung transplant recipients receiving voriconazole prophylaxis, patients $\geq$60 years old and cystic fibrosis patients were associated with higher and lower initial troughs, respectively. Prophylaxis was most effective with voriconazole troughs $>$1.5 μg/mL, and troughs correlated directly with aspartate transferase levels (27).

In another study of 17 cardiothoracic transplant recipients, patients with posaconazole levels consistently $>$0.5 μg/mL were more likely to have a successful outcome (28).

The main purpose of TDM is to potentially avoid toxicity that may be observed at higher serum concentrations and to reduce the risk of treatment failure at lower concentrations (29).

Specific treatment recommendations

Candidemia: The selection of any particular agent for the treatment of candidemia should take into account azole exposure within the last 90 days, a history of intolerance to an antifungal agent, the dominant *Candida* spp cultured and current susceptibility data in a particular location (30). In addition, the severity of illness, relevant co-morbidities and evidence of metastatic involvement to other organs systems are important considerations. Early initiation of therapy is critical to the successful treatment of candidemia (31,32).

Table 2: Summary of recommendations for the treatment of candidiasis (23)

Condition	Therapy		Comments
	Primary	Alternative	
Candidemia			
Nonneutropenic	Fluconazole 800 mg (12 mg/kg) load, then 400 mg (6 mg/kg) daily[1] or an echinocandin (I)	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; for *C. krusei* and flu-resistant, voriconazole-sensitive *C. glabrata*, voriconazole 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily after initial therapy with an echinocandin	Choose an echinocandin for moderate to severe illness and for patients with recent azole exposure (III). Transition to fluconazole after initial echinocandin is appropriate in many cases (II-3). Remove all intravascular catheters, if possible. Treat 14 days after first negative blood culture and resolution of signs and symptoms associated with candidemia
Neutropenic	An echinocandin or LFAmB 3–5 mg/kg daily (II-2)	Fluconazole 800 mg (12 mg/kg) load, then 400 mg (6 mg/kg) daily[1]; or voriconazole 400 mg (6mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily	An echinocandin or LFAmB is preferred for most patients. Fluconazole is recommended for patients without recent azole exposure and who are not critically ill
Urinary tract infections			
Asymptomatic	Therapy not usually indicated, unless high risk or undergoing urologic procedures		For patients undergoing urologic procedures, fluconazole, 200–400 mg (3–6 mg/kg) daily[1] or AmB-d 0.3–0.6 mg/kg daily for several days before and after the procedure is recommended
Symptomatic Cystitis	Fluconazole 200 mg (3 mg/kg) daily[1] for 2 weeks (III)	AmB-d 0.3–0.6 mg/kg for 1–7 days; or flucytosine (5-FC) 25 mg/kg four times daily[1] for 7–10 days (III). AmB-d 0.5–0.7 mg/kg daily ± 5-FC 25 mg/kg four times daily[1]	Alternative therapy is recommended for patients with fluconazole-resistant organisms. AmB-d bladder irrigation is only recommended for patients with refractory fluconazole-resistant organisms (e.g., *C. krusei*, *C. glabrata*)
Pyelonephritis	Fluconazole 200–400 mg (3–6 mg/kg) daily[1] for 2 weeks		For patients with pyelonephritis and suspected disseminated candidiasis, treat as for candidemia
Urinary fungus balls	Surgical removal strongly recommended. Fluconazole 200–400 mg (3–6 mg/kg) daily[1] or AmB-d 0.5–0.7 mg/kg daily +/–5-FC 25 mg/kg four times daily[1]		Local irrigation with AmB-d may be a useful adjunct to systemic antifungal therapy
Respiratory candidiasis	Therapy not recommended unless associated with clinical evidence of anastomotic tracheobronchitis		*Candida* lower respiratory tract infection is rare, even among lung transplant recipients, and it requires histopathologic evidence to confirm a diagnosis

[1]Doses of fluconazole and 5-FC require adjustment for renal function.

Based on data from clinical trials, fluconazole remains the standard therapy for selected patients with candidemia (33–36). Fluconazole is considered first-line among patients with mild to moderate illness, no recent azole exposure and in whom *C. glabrata* is unlikely (23) (I).

The echinocandins show rapid fungicidal activity against all *Candida* spp, and have shown approximately 75% success in randomized clinical trials (37–39). Because of their efficacy, favorable safety profile and very few drug–drug interactions, the echinocandins are favored as initial therapy for patients with a recent history of azole exposure, moderately severe to severe illness, a history of allergy or intolerance to the azoles, or high risk for infection due to *C. krusei* or *C. glabrata* (23) (III). After a short course of intravenous echinocandin therapy (3–5 days), fluconazole is a reasonable choice for step-down therapy, provided that the organism is predictably susceptible to fluconazole (*C. albicans, C. parapsilosis* and *C. tropicalis*) and the patient is clinically stable (23) (II-3). There are reports of decreased susceptibility of *C. parapsilosis* to the echinocandins, but the clinical significance of this is unknown. However, it may

be prudent to choose an alternative to an echinocandin as first line therapy for invasive infections due to this organism (40,41). The echinocandins are sufficiently similar and therefore interchangeable.

Voriconazole is approved for treatment of candidemia, but clinical trials have not shown a particular advantage compared to other agents (42). The role of voriconazole for the treatment of candidemia is limited to patients who have an infection due to a fluconazole-resistant organism, and who are ready for transition to oral therapy. Examples include infections with *C. krusei* and fluconazole-resistant but voriconazole-susceptible *C. glabrata* (23). The role for LFAmB is limited due to potential nephrotoxicity, especially in kidney transplant recipients, and is generally reserved for individuals who are intolerant or refractory to other forms of therapy.

Removal of central venous catheters, when feasible, is strongly recommended among patients with candidemia (43) (II-3). There is debate as to the necessity of removing all intravascular catheters (44), but most experts agree that removal is indicated if the source of candidemia is unclear. In addition, all patients with candidemia should have a dilated funduscopic exam to identify signs of metastatic complications to the eye, such as endophthalmitis; and repeat blood cultures at 48–72 h intervals until blood cultures are negative. The duration of therapy for treatment of candidemia without metastatic complications is generally 2 weeks after clearance of *Candida* from the bloodstream and resolution of symptoms attributable to candidemia (23). Patients with metastatic complications require longer therapy.

The treatment of candidemia in neutropenic organ transplant recipients differs somewhat from nonneutropenic patients with a greater emphasis on the use echinocandins and LFAmB (45,46) (II-2). Most clinicians prefer these agents over fluconazole based on persistent concerns that a fungicidal agent (such as echinocandin or LFAmB) is preferred over a fungistatic agent (fluconazole or voriconazole), although there are few data to support this approach.

Urinary Tract Infections

In the absence of fever or other evidence of systemic infection, candiduria in the organ transplant recipient does not generally necessitate treatment (47,48). There are no prospective and comparative trials comparing treatment versus nontreatment in this group, thus treatment in this setting is largely driven by anecdotal experience and personal preference. For purposes of determining selection of an agent and duration of therapy, it is helpful to divide organ recipients with candiduria into asymptomatic and symptomatic categories. Treatment of asymptomatic candiduria is generally discouraged unless the patient is undergoing a urologic procedure or is neutropenic (23). Imaging of the kidneys and collecting system is prudent to exclude abscess, fungus ball or urologic abnormality.

Among symptomatic patients with candiduria and suspected disseminated candidiasis, it is appropriate to treat as for candidemia (see above). For patients with cystitis due to a fluconazole-susceptible *Candida* spp, oral fluconazole 200–400 mg (pediatric dosing 3–6 mg/kg/dose) daily for 2 weeks is advisable (23) (III). For patients with fluconazole-resistant organisms, LFAmB or oral flucytosine 25 mg/kg four times daily are recommended (23) (III). Flucytosine may cause diarrhea and bone marrow suppression, especially in individuals with baseline renal insufficiency, and side effects must be monitored carefully. If prolonged use is expected, flucytosine drug level monitoring is indicated to avoid dose-related toxicity. AmB-d bladder irrigation is generally not recommended, but might be useful for patients with fluconazole-resistant *Candida* spp, especially *C. glabrata* (49). For patients with pyelonephritis, treatment with fluconazole is indicated for fluconazole-susceptible organisms. For fluconazole-resistant organisms, AmB-d possibly with flucytosine, or flucytosine alone can be offered for at least 2 weeks (23) (III). Echinocandins are normally avoided due to poor urinary concentration.

Pulmonary Candidiasis

Isolation of *Candida* spp from the respiratory tract rarely indicates invasive candidiasis and generally is not treated with antifungal therapy (50–52). An exception exists for lung transplant recipients in whom anastomotic tracheobronchitis due to *Candida* is a concern. Evidence of *Candida* tracheobronchitis is based on visual inspection and histologic confirmation, usually accompanied by a positive culture from an appropriate specimen. Selection of a specific agent could be based on the same principles as for selecting an agent for treatment of candidemia. There are no specific studies to guide duration of therapy, but it is reasonable to continue treatment until there is clinical resolution of the infection.

Prophylaxis

Identifying patients at the highest risk of infection is crucial to the development of effective approaches to antifungal prophylaxis. The major points that need to be addressed when deciding if antifungal prophylaxis is warranted include: (1) general prophylaxis versus targeted prophylaxis; (2) selection of an appropriate agent and (3) the duration of prophylaxis.

The prophylactic approach implies that an antifungal agent is administered to all transplant recipients, whereas *targeted* prophylaxis applies to the use of an antifungal agent in a subgroup of transplant recipients with predisposing conditions that place them at higher risk of developing

Table 3: Risk factors for *Candida* infection and recommended prophylactic strategies

Organ	Risk factors	Antifungal prophylaxis	Duration
Liver	Prolonged or repeat operation Retransplantation Renal failure Choledocho-jejunostomy *Candida* colonization High transfusion requirement	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	Up to 4 weeks or Until resolution of risk factors
Small bowel	Graft rejection/dysfunction Enhanced immunosuppression Anastomotic dysruption Abdominal reoperation Multivisceral transplantation	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	At least 4 weeks Until healing of anastomosis and absence of rejection
Pancreas	Enteric drainage Vascular thrombosis Postperfusion pancreatitis	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	At least 4 weeks

[1]If high rates of non-*albicans* spp or risk factors for *Aspergillus*.

invasive candidiasis. If high-risk patients can be easily identified, and if it is shown that withholding prophylaxis in patients considered low-risk is not associated with a high incidence of invasive candidiasis, then the targeted approach is preferred.

The ideal antifungal agent used for prophylaxis is one that is efficacious, safe to the allograft and other organs, with predictable or no drug interactions, ease to administer, with minimal/manageable side effects, and affordable. It is also important to determine if the patient at risk for *Candida* infection is also at risk for mold infections, particularly due to *Aspergillus*, so an agent with good anti-mold activity can be selected.

Duration of antifungal prophylaxis is not clearly defined, but as a general rule, prophylaxis should be maintained for at least 14 days posttransplantation, and longer if predisposing comorbidities persist. Because the risk factors and best choice of antifungal agent vary according to the transplanted organ, each organ will be discussed separately and recommendations are summarized on Table 3.

Liver transplantation

Antifungal prophylaxis against *Candida* should be given to all adult liver transplant recipients at high risk for development of invasive candidiasis; i.e. those with $\geq$2 of the following risk factors: prolonged or repeat operation; retransplantation; renal failure; high transfusion requirement, i.e., transfusion of $\geq$40 units of cellular blood products including platelets, packed red blood cells and auto transfusion; choledocho-jejunostomy and *Candida* colonization in the peri-operative period (1,4) (II-1). Liver transplant candidates are highly colonized with *Candida* spp in their gastrointestinal (GI) tract (53). Duration of prophylaxis is not clearly determined, and has ranged from 5 days to 10 weeks in clinical trials. Duration of up to 4 weeks, or for the duration of persistent risk factors, seems reasonable. The use of fluconazole as a prophylactic antifungal agent should be limited only to patients at high risk for invasive candidiasis. Liver transplant recipients at risk for both candidiasis and aspergillosis should receive an agent with anti-*Aspergillus* activity.

Three prospective randomized controlled trials in adults have shown the efficacy of antifungal prophylaxis of invasive candidiasis. In one study, fluconazole 100 mg/day was compared to oral nystatin in 143 liver transplant recipients. Prophylaxis was given for 4 weeks after liver transplantation. Fluconazole was associated with a reduction in *Candida* colonization and superficial infections, as well as a trend toward reduction of invasive infections (54). In the second trial, fluconazole 400 mg/day or placebo were administered for 10 weeks after liver transplantation. Antifungal prophylaxis with fluconazole compared to placebo resulted in a decreased rate of proven fungal infection (43% vs. 9%) and invasive infection (23% vs. 6%; Ref.55). Overall survival was not improved. In the third study, itraconazole was compared to placebo, and showed a decrease in the rate of candidiasis from 24% to 4% (56).

Studies with LFAmB, including LAmB and ABLC, have used different doses for variable periods of prophylaxis. Risk factors for IFI were also not uniform in these trials. These studies have shown that low dose of liposomal amphotericin B (1 mg/kg/day), administered for as few as 5 days, is associated with a significant reduction in invasive candidiasis (57–59).

Caspofungin given for at least 21 days was shown to be an efficacious and well-tolerated antifungal regimen in high-risk liver transplant recipients in a recent multicenter, non-comparative, open-label trial (60). Its use as a prophylactic agent seems promising due to lack of significant drug interactions with tacrolimus, lack of nephrotoxicity and activity against non-*albicans Candida*. A randomized controlled trial of anidulafungin versus fluconazole for the prevention of

fungal infections in liver transplant recipients is currently ongoing.

A recent meta-analysis showed that antifungal prophylaxis in liver transplant recipients significantly reduced the total episodes of superficial and IFI, as well as mortality attributable to fungal infections; however it did not affect overall mortality or the need for empirical antifungal treatment (61). Compared to controls, patients receiving antifungal prophylaxis experienced a higher proportion of non-*albicans Candida* infections.

Observing liver transplant recipients at low risk for IFIs without antifungal prophylaxis is safe, as shown by a recent multicenter, prospective, observational study, in which 200 liver transplant recipients at low risk for IFIs did not receive antifungal prophylaxis. In this trial only 7% of the 193 eligible patients developed an IFI at 100 days posttransplantation (62). Of those, only 2% were due to *Candida* spp and potentially preventable by the use of fluconazole prophylaxis. The use of nonabsorbable agents such as nystatin, clotrimazole and amphotericin B to achieve selective decontamination of the GI tract and oral cavity has shown inconsistent results and not proven to be useful (63–66).

Intestinal (small bowel) transplantation

Despite an absence of clinical trials in this patient population, antifungal prophylaxis in small bowel adult transplant recipients is routinely practiced and justified by the high rate of *Candida* infections. Rates of invasive candidiasis have been described to be as high as 28% in small case series (67,68). Patients at high risk are those with graft rejection or dysfunction, enhanced immunosuppression, anastomotic disruption, abdominal reoperation or multivisceral transplantation. Fluconazole is an acceptable agent. However, LFAmB should be utilized in patients where there is high suspicion of non-*albicans Candida* spp. Prophylaxis is usually administered for a minimum of 4 weeks, until anastomosis has completely healed, and rejection is not present (II-3).

Pancreas and kidney transplantation

The risk factors for candidiasis among pancreas transplant recipients include enteric drainage, vascular thrombosis and postperfusion pancreatitis (12). The use of prophylactic fluconazole should be considered whenever one of these risk factors is identified. LFAmB is preferred in centers with a high prevalence of non-*albicans* species. Duration of prophylaxis will depend on reduction of risk factors (II-3). The risk of invasive candidiasis is too low after isolated kidney transplantation to warrant prophylaxis.

Lung, heart–lung and heart transplantation

Candida is commonly isolated from the respiratory tract of lung and heart–lung transplant recipients. The highest risk for *Candida* infection is in the first 30 days posttransplantation, and risk factors include the use of broad spectrum antibiotics, duration of antibiotic use, presence of central venous catheters and need for renal replacement therapy (3,4). There is a wide variation in the practice of antifungal prophylaxis in lung and heart–lung transplant recipients, not only in terms of the antifungal agent, but also on its mode of administration, timing and duration. Because of the high rates of *Aspergillus* infection after lung and heart–lung transplantation, antifungal prophylaxis should be directed towards the prevention of invasive aspergillosis, and prophylaxis with an agent without adequate anti-*Aspergillus* activity is not appropriate (II-1). *Candida* infections are infrequent after heart transplantation, and antifungal prophylaxis is not routinely recommended for these patients (III).

Infection Control Issues

There are no infection control measures specifically targeted towards prevention of *Candida* infections. Measures to reduce the incidence of these infections should include adequate hand hygiene, judicious use of antibiotics and frequent assessments to determine the need for intravascular and urinary catheters.

Future Research

Invasive candidiasis has been associated with increased length of hospitalization and increased mortality. Despite recent advances in microbiology techniques, the sensitivity of blood cultures is still poor. Future research should focus on better diagnostic methods. Randomized controlled trials are also needed to determine the best agent and duration of antifungal prophylaxis in organ transplant recipients.

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