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Epidemiology and Management of Candidiasis in Solid Organ Transplant Recipients

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Abstract
Purpose of Review Invasive candidiasis (IC) is the leading cause of fungal infections in solid organ transplant recipients (SOT). In this article, we aim to review the epidemiology, risk factors, presentation, and management of IC in this population.
Recent Findings Certain risk factors have been associated with IC in SOT recipients. Targeted antifungal prophylaxis for SOT recipients at the highest risk of infection is currently recommended although the choice and duration of antifungal agents remain controversial. Early diagnosis and monitoring of IC in SOT recipients are critical to achieve better outcomes and prevent serious complications. Non-culture-based diagnostic modalities have been introduced to aid in earlier and more accurate diagnosis.
Summary The use of azoles for prophylaxis or treatment in SOT recipients allowed for selection of resistance and increased the incidence of non-*albicans Candida*. Drug–drug interactions, cost, and risk of resistance are to be considered when using more potent or newer antifungal agents.

Keywords Invasive candidiasis · Transplantation · Epidemiology · Management · Solid organ transplant · *Candida*

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Introduction

Advanced surgical techniques and novel immunosuppressive regimens have increased the use of solid organ transplantation (SOT) as the preferred treatment of choice for end organ disease and many malignancies [1, 2]. However, potential complications related to surgical techniques and the use of immunosuppressive medications predispose transplant recipients to post-transplant infectious complications [3••]. Invasive fungal infections (IFI) are of a concern in SOT recipients even though bacterial and viral infections are more common in this population. This is owing to the high morbidity and mortality associated with IFIs despite newer prophylactic antifungal regimens [4, 5]. Among SOT recipients, the most commonly reported IFIs are invasive candidiasis (IC) and invasive aspergillosis [6•, 7–18]. The incidence of invasive fungal infections varies based on the type of organ transplant. Patients who receive the liver, lung, pancreas, and small bowel are more at risk of IFIs than patients who receive kidney or heart transplants. Infections due to *Candida* species account for about 50% of IFIs in SOT recipients [6•, 19••, 20]. They are particularly predominant after transplant of abdominal organs, whereas the main pathogens in thoracic organ transplants are *Aspergillus* species. The Transplant-Associated Infection Surveillance Network (TRANSNET) data showed that infections due to other fungi such as endemic dimorphic fungi, filamentous mold such as *Fusarium*, and zygomycosis are less common and make less than 20% of invasive fungal infections in SOT recipients [6•, 20].

The incidence of IC in an American series of SOT has been estimated to be around 2%, including pediatric cases [6•, 21]. Infections due to *Candida* species can range from mucosal colonization to disseminated disease. Of *Candida* species, *Candida albicans* is the predominant isolate and accounts for about 50% of isolates while *C. glabrata* is the most

common non-*albicans Candida* isolates besides *C. tropicalis* and *C. parapsilosis*. On the other hand, *C. guilliermondii* is seen more frequently in stem cell transplant recipients than in SOT recipients [19••]. The wide use of azoles for treatment or prophylaxis has allowed for selection of resistance to azoles and increased the incidence of non-*albicans Candida* species [22–25].

Risk Factors and Timing for IC in SOT Recipients

Risk factors of IC in the general population include total parenteral nutrition, broad-spectrum antibiotics, prolonged neutropenia, the use of central venous catheters for a long duration, long stay in the intensive care unit, diabetes mellitus, renal replacement therapy, and colonization with *Candida* [19••, 26, 27•]. In addition, SOT recipients have unique risk factors for IC such as the type of organ transplant, surgical anastomosis, number of cellular products transfused during transplant, and acute renal failure. Other risk factors also include early colonization, early surgical intervention or retransplantation, graft failure, and recent CMV infection [10, 19••, 21, 27•, 28, 29]. Liver transplant recipients have more risk of developing IC compared to other organs, and the risk is higher when a choledochojejunostomy rather than a choledostomy anastomosis is used [19••, 30]. Also, bladder drainage of pancreatic transplants has less risk than enteric drainage due to the high levels of colonization with *C. albicans* and complications related to surgery in the gut and biliary tree [2, 19••, 31–34]. In addition, many factors contribute to the level of immunosuppression including immunosuppressive agents and operative complications (ischemia, anastomotic leak, fluid collection, thrombosis, and presence of foreign bodies).

The timing of fungal infections after SOT is divided into early (0–30 days), intermediate (1–6 months), and late (>6 months). Infections seen in the early phase are commonly similar to those seen in immunocompetent postoperative patients, and endogenous *Candida* species are the most common cause of fungal infections in this stage [13]. *Candida* infections may also be derived from the transplant donor and result from contamination of preservation fluid or can be hospital acquired [34–36]. The intermediate stage has the highest rates of IFIs with the level of immunosuppression being the major player in the development of opportunistic infections. IC remains the most common of IFIs while the incidence of *Aspergillus* infections increases [20, 37]. By late stage, the risk of infections decreases as about 80% of SOT recipients achieve a satisfactory result from transplantation and are maintained on minimal long-term immunosuppression. Patients in the late stage are more likely to develop infections due to CMV, aspergillosis, or endemic fungi or undergo organ rejection [20, 34, 38].

Diagnosis and Monitoring of *Candida* Infections in SOT Recipients

Pathogenesis and Clinical Forms of *Candida* Infections

C. albicans colonizes the skin and the gastrointestinal and genitourinary tracts while non-*albicans Candida* can also colonize mucocutaneous surfaces [39, 40•]. IC is frequently preceded by colonization, and it depends on the virulence of the organisms, the disruption of mucocutaneous barriers, and the intensity of immunosuppression [2, 41, 42]. Infections due to *Candida* species can involve the skin, the esophagus, the urinary tract, and surgical sutures lines. Candidemia may result from central venous access or from translocation across damaged intestinal barriers [41]. Following intra-abdominal organ transplantation especially liver transplants, intra-abdominal candidiasis can be seen in the form of peritoneal, perinephric, and biliary infections. Biloma, an infected hepatic fluid collection, is a serious complication of liver transplants and can lead to transplant failure [42–47].

Diagnosis and Monitoring of *Candida* Infections in SOT

Diagnosis of IC depends on the growth of *Candida* species from a sterile body site. The sensitivity of blood cultures to diagnose IC is around 50–70% [19••, 48]. Other non-culture-based rapid diagnostic methods such as antigens, antibodies, 1,3-β-D-glucan (βDG) detection assays, and polymerase chain reaction (PCR) are now being used as an adjunct to cultures. *Candida* antigen and anti-*Candida* assays are approved for use in Europe, but not in the USA. The best studied model is a combined mannan antigen/anti-mannan assays with IgG superior to IgM and a sensitivity/specificity of the combined assay of around 83 and 86%, respectively [49••, 50–52]. On the other hand, βDG is a cell wall constituent of *Candida* species and several fungi and has been approved by the FDA to aid in the diagnosis of IFIs. It has a sensitivity of 70% and a specificity of 87%. False-positive results from the use of albumin or immunoglobulin, antibiotics derived from fungi, gram positive and negative bacteremia, hemodialysis, and mucositis and with the use of glucan-containing material such as gauze [2, 21, 49••, 53–58]. The use of βDG allows identification of IC earlier than blood cultures, allowing earlier initiation of antifungal therapy. Likewise, the use of *Candida* PCR assays allowed earlier diagnosis and initiation of therapy for IC [49••, 59, 60]. The sensitivity and specificity of *Candida* PCR for IC can be variable [21, 49••]. T2MR is a fully automated technology that uses PCR and T magnetic resonance to amplify and detect *Candida* DNA allowing rapid, accurate, and species-specific diagnosis [61••].

Candida speciation is important for choosing antifungal therapy due to the difference in antifungal susceptibilities and in predicting clinical outcomes. The germ tube test

specifically identifies *C. albicans* and *C. dubliniensis*. However, chromogenic isolation media may better detect yeasts with less cost [21, 62]. The peptide nucleic acid fluorescent in situ hybridization assay (PNA-FISH) can recognize the five most common *Candida* species in positive blood cultures (*C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, and *C. tropicalis*). Most recently, the matrix-assisted laser desorption ionization-time of flight mass spectrometry assay (MALDI-TOF) has been used to identify strains of bacteria and yeasts. Hospital epidemiology can help to identify common local species, and testing for antifungal susceptibilities and azole resistance is recommended for *C. glabrata* and when treatment fails [19••, 63–67].

Prophylaxis and Prevention of *Candida* Infection

In order to prevent IFIs in SOT recipients, it is important to identify patients most likely to have the risk of developing an infection. The use, choice, and duration of antifungal agents remain controversial awaiting further studies [5, 19••, 21]. There is currently insufficient data to recommend the use of universal antifungal prophylaxis to prevent IFIs in all SOT recipients [5, 67, 68]. Instead, a more targeted approach in SOT recipients with predisposing conditions is preferred [19••]. To be effective, a prophylactic agent should be safe to the allograft, with minimal side effects, low or no interaction profile, and affordable. Duration of prophylaxis should be at least for 14 days post-transplantation and can be given until resolution of risk factors. Fluconazole 100–400 mg/day or (3–6 mg/kg daily) is the first line for antifungal prophylaxis and is commonly used in recipients of intra-abdominal organ transplantation. Antifungal prophylaxis is not routinely used to prevent *Candida* species infections in renal, heart, and lung transplantation. Patients who cannot tolerate fluconazole due to gastrointestinal side effects or drug interactions may require switching to other antifungal agents [21]. Also, liposomal amphotericin B (AmB) (1–2 mg/kg daily) is to be considered in SOT recipients at risk for *Aspergillus* species or other molds, or in centers where non-*albicans Candida* are frequently seen.

Recently, a multicenter study showed that anidulafungin or caspofungin given for 21 days were efficacious and well tolerated [19••, 69••, 70]. Echinocandins are active against non-*albicans Candida* and do not interact significantly with tacrolimus nor cause renal toxicity. These factors may allow them to gain more use in the future. Of note, SOT recipients who received antifungal prophylaxis developed more infections with non-*albicans Candida* infections. Breakthrough candidemia (particularly with non-*albicans Candida*) may develop during systemic antifungal prophylaxis and is associated with a high mortality rate [27•, 71–74].

Treatment (Preemptive, Early/Empirical, Definite, and Step-Down)

There is currently no recommendation to start preemptive treatment for IFIs in SOT recipients. Similarly, in non-neutropenic patients, the use of empirical antifungal therapy is not well established. Critically ill patients with otherwise unknown etiology of fever despite broad-spectrum antibiotics, with *Candida* colonization, suggestive clinical imaging and/or risk factors of IC, and detection of fungal markers should be considered for empirical treatment [5]. Antifungal therapy given early may lead to better outcomes in critically ill patients, but its use has to be weighed against its cost, toxicities, and risk of resistance [5]. Echinocandins should be used when patients develop hemodynamic instability, in patients who received azoles in the past, and in patients colonized with *Candida* species with azole resistance [5]. However, if other IFIs are on the differential, the safer choice would be liposomal amphotericin B or an azole, because echinocandins have a limited spectrum of activity (basically *Candida* and *Aspergillus*). The use of liposomal AmB is limited due to the risk of toxicity [5, 21].

Recommendations for treatment of IC in SOT recipients are not different from non-neutropenic patients and are based on different large randomized studies that included a small percentage of SOT recipients. Azoles are potent inhibitors of hepatic cytochrome P-450 CYP3A4 and increase the levels of sirolimus, everolimus, and calcineurin inhibitors (CNIs), thus, careful monitoring of drug levels is critical to reduce doses of CNIs after starting azoles [5, 19••, 75, 76].

Repeated blood cultures should be done every 48–72 h until clearance of candidemia [5]. It is strongly recommended to do a dilated funduscopic exam and to remove central venous catheters as soon as possible [41]. Asymptomatic candiduria is frequently seen in SOT recipients especially in the kidney and pancreas, and treatment is not recommended unless urological procedures are indicated. Cystitis should be treated with fluconazole for 2 weeks, while patients with fluconazole-resistant *Candida* species should receive liposomal AmB or oral flucytosine for 2 weeks. For patients with pyelonephritis, fluconazole for susceptible *Candida* species or AmB with flucytosine or flucytosine alone are frequently used. Neither liposomal AmB nor echinocandins achieve satisfactory urinary levels. Removal of urinary catheters is strongly recommended [19••, 21, 77].

Anastomotic tracheobronchitis in lung transplant recipients should be based on positive cultures, direct visual examination, and histopathological confirmation and should be treated with inhaled or systemic lipid formulations of AmB. Otherwise, when *Candida* is recovered from sputum, treatment is rarely necessary [19••, 21, 78–80].

Conclusions

Particularly after transplantation of abdominal organs, IC remains an important cause of morbidity and mortality. Diagnosis of IC can be made by recovering *Candida* species from a sterile body site by blood cultures or by other non-culture-based rapid diagnostic methods. Testing for antifungal susceptibilities should be done with non-*albicans Candida* and in treatment failure. Identifying patients with the highest risk of infection is the key in deciding appropriate antifungal prophylaxis in SOT recipients. Empirical treatment should be considered in critically ill patients and may improve their outcome but has to be weighed against its cost, toxicities, and risk of resistance.

Compliance with Ethical Standards

Conflict of Interest Ahmed Al Hammadi declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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