Yeast Infections in Solid Organ Transplantation

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KEYWORDS

- Yeast infections in organ transplants • Invasive candidiasis after organ transplant
- Cryptococcosis after organ transplant
- Emerging fungal pathogens in organ transplant

KEY POINTS

- Invasive candidiasis (IC) remains the most common invasive fungal infection following solid-organ transplant (SOT) but risk factors have evolved over the past several years. Current challenges include drug resistant non-albicans and emerging novel species such as Candida auris. Preventive antifungal use in SOT needs to be re-examined in light of these current challenges.
- Cryptococcus gattii is an emerging pathogen in SOT and should be considered in cases of cryptococcosis with history of travel or residence in the Pacific NW of USA and Canada. Infections due to C. gattii might be associated with reduced in-vitro susceptibility to antifungals.
- Diagnosis of cryptococcus associated IRIS remains a clinical entity. Reduction in calcineurin inhibitors is associated with significantly increased risk of IRIS in SOT recipients with cryptococcosis. Data on optimal treatment is lacking and guidance is based on expert opinion.

INTRODUCTION

Invasive fungal infections (IFIs) remain a major cause of morbidity and mortality among solid organ transplant (SOT) recipients. Over time, better understanding has been gained of the pathophysiology and risk factors for these infections and significant changes in epidemiology and management approach have been observed. Although IFIs have remained a commonly encountered challenge among SOT, information on epidemiology of these infections has been limited mostly to single-center and retrospective studies. Transplant-Associated Infection Surveillance Network (TRANSNET), a consortium of 23 United States transplant centers, provided the first prospective multicenter database on IFIs in SOT.[1] Based on 5-year surveillance data contributed by 15 transplant centers under the TRANSNET consortium, 1208 IFIs were identified among 1063 organ transplant recipients. The 1-year cumulative incidence of first IFI after SOT were 11.6%, 8.6%, 4.7%, 4.0%, 3.4%, and 1.3% for small bowel (SBT),

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lung (LTX), liver (LT), heart (HT), pancreas (PTX), and kidney transplant (KT) recipients. The most common IFIs were invasive candidiasis (IC) at 53%, invasive aspergillosis (IA) at 19%, cryptococcosis (8%), non-*Aspergillus* molds (8%), endemic fungi (5%), and zygomycosis (2%).[1] This is a review of IC and cryptococcosis in SOT focusing on key aspects with significant change in the recent past.

INFECTIONS DUE TO *CANDIDA* SPECIES IN SOLID ORGAN TRANSPLANTATION

Infections due to *Candida* species remain the most common type of IFI across all types of SOT, with the exception of LTX, where IA is more common.[1] In the TRANSNET database, the 12-month cumulative incidence of IC was 1.9%—highest in SBT, followed by PTX, LT, KT, HT, and LTX.[1,2] A subsequent analysis of the TRANSNET database looked at IC specifically and included proved and probable cases, as defined by the European Organization for Research and Treatment of Cancer/Mycosis Study Group criteria.[3,4] The most common sites of IC were bloodstream and intra-abdominal; and the median time to onset was 80 days post-SOT (interquartile range 14–545 days). Consistent with clinical observation and prior studies, IC was seen most frequently in abdominal transplant recipients (LT: 41.1%, KT: 35.3%, kidney-pancreas: 9.1%, and LTX: 8.7%). The most commonly encountered species were *Candida* albicans (46.3%), *C glabrata* (24.4%), *C parapsilosis* (8.1%), *C tropicalis* (3.9%), and *C krusei* (3.1%).[3]

Risk Factors for Invasive Candidiasis in Solid Organ Transplant Recipients

Risk factors for IC after SOT have been best described in LT recipients.[5–10] These risk factors have evolved significantly over the past 2 decades, hence are worthy of discussion in this review. The initial risk factor analysis provided by Collins and colleagues[5] showed that operative variables, such as length of transplant operation, retransplantation, and abdominal and intrathoracic reoperations, were independent predictors of IFIs post-LT. The impact of these operative variables, however, seems reduced based on data from more recent studies.[6,8,10] One of the earlier studies that revealed this was by Husain and colleagues.[6] Contrary to previous data, variables, including operative time and blood transfusion, were not found independent predictors of the risk of IFIs. Rather, the investigators found that post-transplant variables, including antibiotic prophylaxis for spontaneous bacterial peritonitis (odds ratio [OR] 8.3; $P = .002$), post-transplant dialysis (OR 7.6; $P = .0009$), and retransplantation (OR 16.4; $P = .0018$), were independent predictors of IC.[6] This evolution of risk factors is believed to reflect the changes in transplantation practices over the years. This correlation was demonstrated in a study by Singh and colleagues,[10] where, over a 10-year time period, significant decrease in the operation time, intraoperative transfusion requirements, cold-ischemia time, and rate of biopsy-proved rejection was observed. Over the same period, the investigators observed a decrease in the incidence of IC without an increase in medical risk factors for IC, such as CMV infection, hence proving the relationship to operative variables.[10]

Evolution in risk factors for IFI and paucity of data on risk assessment in the current era lead to study of Model for End-stage Liver Disease Score (MELD) as a predictor for IFIs.[7–9] MELD is a practical validated measure of the severity of hepatic failure and it is well-known that patients with higher MELD scores are at higher risk of complications, including infections. This was seen in a study by Saliba and colleagues,[9] who showed that MELD score of 20 to 30 or greater than or equal to 30 was associated with a 2-fold to 4.3-fold increase in relative risk of IFIs. In the same study, similar to earlier studies, other independent predictors for IFIs were choledochojejunostomy anastomosis,[11]

bacterial infection,[12] and CMV infection.[5,11,13] Another study by Raghuram and colleagues[8] identified MELD score of greater than 25 as a risk factor for IFI (OR 2.4; 95% CI, 1.2–4.9; $P = .02$) in univariate analysis; however, it was not identified as an independent predictor in multivariate analysis. In this study, the only independent risk factor for IFI in multivariate analysis was pretransplant fungal colonization (OR 7.8; 95% CI, 3.9–16.2; $P<.001$),[8] which is similar to findings from earlier studies where pretransplant and early post-transplant colonization were identified as a risk factor for post-LT IFIs.[5,11,13]

Risk factors for IC specific to nonliver SOT are less well understood. A brief overview is provided of risk factors for IC described for nonliver abdominal and thoracic transplants. In addition to LT, IC occurs most frequently in SBT, PTX, and multivisceral transplant (MVT) recipients.[1,3] Florescu and colleagues[14] provided an overview of IC in pediatric SBT recipients and reported that fungal infection occurred in 25% of the SBT recipients and *C albicans* was the most commonly seen infection. The investigators noted that patients who developed fungal infection (predominantly represented by IC) were older in age compared with those who did not develop fungal infections (mean age 61 months vs 29.8 months, difference +31.2; $P = .04$). Although this finding is not fully explained in this cohort, the investigators correctly postulate that it may be of significance because older recipients undergo a longer time on intestinal rehabilitation therapy in comparison to those who are transplanted at a younger age.[14] The other noteworthy finding in this study is that IC manifests more commonly as an intra-abdominal/surgical site infection earlier on after transplant whereas fungemia occurs later (>6 months post-transplant) in 80% of the patients. This description of timeline of IC by site of infection after SBT/MVT is a unique finding and informative of the continued risk for IC after SBT/MVT beyond the early postoperative period.[14] The continued risk of IC post-transplant is also described by van Hal and colleagues,[15] who lend the concept of late-onset candidemia based on findings from their multicenter cohort where 54% of IC was seen greater than 6 months post-transplant. They note that majority of late-onset IC episodes occurred in KT recipients with multiple risk factors for IC including prolonged inpatient stay, indwelling catheters and broad-spectrum antibiotic therapy. This finding highlights the significance of general risk factors for IC in the SOT population, in addition to those specific to transplantation.[15] Many groups have described risk factors for infection after PTX. The impact of the type of pancreatic drainage (bladder vs enteric) on risk of infection remains controversial and most studies have examined the risk of infection in general.[16–19] One study that looked at the impact of type of pancreatic drainage specifically on intra-abdominal fungal infections found that enteric drainage carried greater risk versus bladder drainage (21% vs 10%); however, the same finding has not been seen in other studies.[16] In a more recent publication by Herrero-Martinez and colleagues,[18] the investigators looked at a large retrospective cohort of pancreas-kidney transplant recipients. They found 40 episodes of fungal infection in 32 patients (mostly due to *Candida* species) and identified independent risk of IFI in recipients with pretransplant evidence of peripheral arterial disease, longer cold ischemia time, and high transfusion requirements. This study also highlighted the morbidity associated with these infections and found IFIs an independent risk factor for severe pancreatic dysfunction (OR 8.4; 95% CI, 1.9–37.0; $P = .005$).[18]

According to the TRANSNET data, IC is the most common IFI in following HT and second most common in LTX recipients.[1] Risk factors contributing to occurrence of IC after thoracic transplantation, however, remain poorly understood. In HT, most studies have examined the risk of IFI in general (IC, IA, and others) and have identified delayed chest closure,[20] induction with lymphocyte depleting agents,[20,21] renal replacement

therapy,[21,22] and extracorporeal membrane oxygenation as risk factors.[22] Another study that looked at epidemiology and risk factors for nosocomial bloodstream infections in SOT found that HT recipients were more likely to have IC than other SOT and the source seemed to be central venous lines.[23] As for LTX and combined HT-LTX recipients, although epidemiology and infection trends have been described, information on risk factors for development of IC is lacking and most research in HT, has focused on IA. Although *Candida* species are widely considered nonpulmonary pathogens, in the LTX population, respiratory disease in the form of airway anastomotic site infection leading to dehiscence,[24,25] candida empyema,[26] and disruption of large vessel anastomosis in HT-LTX has been described.[27] The risk of airway anastomotic site candidiasis seems higher in patients with partial dehiscence, necrosis, and airway stents,[24,26] and infection has been attributed not only to recipient but also to donor tracheal colonization with candida.[26,27] Based on these clinical observations, it is common practice to give systemic and inhaled antifungal prophylaxis in the early post-LTX period aimed at targeting *Aspergillus* and *Candida* species,[28,29] and although recent data are supportive of the efficacy of universal antifungal prophylaxis after LTX for prevention to IA, data specific to IC prevention were not examined.[29]

Shift in Spectrum of Candida Infections and Emergence of Novel Species

Epidemiologic data have shown a shift in the spectrum of candida infections over the past 2 decades with an increase in the number of nonalbicans species.[30,31] This shift in spectrum seems to coincide with a general increase in the use of fluconazole.[32] In the realm of SOT, Husain and colleagues[6] published one of the earliest reports highlighting this issue. Since then, there have been several publications bringing attention to the emergence of nonalbicans species and challenges in the management of these infections due to antifungal resistance.[8,33] The clinical impact of this shift was clearly shown in the TRANSNET data with higher mortality among those who had IC due to nonalbicans species than those with *C albicans* infection (80/255: 31.4% vs 67/296: 22.6%; $P = .02$).[3]

Analysis of the TRANSNET data by Lockhart and colleagues[33] revealed that most cases of IC in SOT were still due to *C albicans* with *C glabrata* and *C parapsilosis* the second and third most common species, respectively. Overall, 16% of the isolates in the cohort were fluconazole resistant and this was mostly due to *C glabrata* and *C krusei*. Although *C albicans* and other candida species were mostly fluconazole susceptible, this study conclusively showed the impact of fluconazole prophylaxis on the geometric mean minimum inhibitory concentration (MIC), which was significantly higher in the fluconazole prophylaxis group for all species (4.8676 μg/mL vs 1.020 μg/mL; $P<.001$).[33] Furthermore, on multivariate analysis, the investigators identified fluconazole use in the past 3 months prior to IFI onset as an independent risk factor for fluconazole nonsusceptibility (adjusted OR 2.65; 95% CI, 1.17–5.99).[33] Another study that highlights the emergence of nonalbicans species as significant pathogens in the SOT setting is by Raghuram and colleagues.[8] The investigators reported an IFI rate of 12% despite antifungal prophylaxis and a large percentage of IFIs due to *C parapsilosis*, approximately half of which were fluconazole resistant although typically fluconazole susceptible as a species. These data caution the impact of widespread antifungal prophylaxis on emergence of drug resistance species and also put into question the efficacy of current prophylactic strategies in current era of transplantation.

In addition to the observed change in the spectrum of known candida species, there are reports of global emergence of novel species, such as *C auris*.[34] *C auris* is an emerging pathogen that was first reported from Japan,[35] but since then there have been several reports of health care–associated infections from several countries. The Centers for Disease Control and Infection (CDC) issued an alert regarding the

global emergence of this pathogen in 2016, requesting that laboratories and health care facilities report *C auris* infection to the CDC.[36] The significance of this global emerging pathogen is multifold. The first challenge lies in diagnosis of *C auris*, which with commercially available diagnostics is often misidentified as *C haemulonii*. Since this issue was identified, health care practitioners and laboratories have been requested to send isolates that are identified as *C haemulonii* or are unable to be speciated to the CDC for further identification.[35] The second challenge lies in the treatment of *C auris* because in many cases it tends to be multidrug resistant and in some cases, pan-resistance to all available antifungal agents has been seen. In the cases reported in United States, however, most isolates have had lower MIC to echinocandins,[34] making these a potentially effective agent for treatment of these infections. Clinical and Laboratory Standards Institute (CLSI) guidelines, however, for drug susceptibility for this species have not yet been developed. Third, it is clear that *C auris* causes health care–associated outbreaks and there is evidence to suggest that there is nosocomial transmission to patients based on whole-genome sequencing of patient isolates from the same hospital, demonstration of skin and other body site colonization weeks to months after infection, and the presence of *C auris* in environmental samples from the hospital room of a patient with infection.[34] These findings have huge implications on patient care in all settings and, to prevent the emergence of a nosocomial outbreak, health care providers and hospitals must follow recommendations of the CDC on infection prevention and communicate patient history and recommended precautions to other facilities in case of interinstitutional transfer.

C auris infections in the United Sates have been most commonly identified in the blood stream and tend to occur in patients with immunocompromised states. Other sites of infection reported in the United States include urine and ear.[34] The initial report of *C auris* as a novel species came from a patient in Japan with ear infection, hence giving this organism its name.[35] More recently, there was report of donor-derived *C auris* infection in an LTX recipient in Boston, Massachusetts.[37] As anticipated based on recent reports, the identification of the isolate (from recipients bronchoalveolar lavage) proved challenging and it was misidentified as *C haemulonii*. On further testing at the local department of health and at the CDC, the isolate was confirmed *C auris*. Hospital respiratory cultures from the organ donor revealed *C haemulonii* but these were reportedly not tested further for species identification. Whole-genome sequencing of the recipient isolate, however, did show close link to *C auris* isolates from Illinois, which is where the organ donor was from, making donor-derived transmission of infection highly likely. As pointed out in this case report by Azar and colleagues,[37] cases such as this warrant review of current policies and procedures for infection assessment of organ donors. In current practice, isolation of candida in donor specimens other than in the blood are often believed colonizers and are not routinely identified to the species level. This raises the possibility of missed diagnosis and transmission of a potentially drug-resistant pathogen through transplantation. Until better diagnostic methodologies are made available, however, the issue of misidentification of *C auris* remains a real possibility and it is of utmost importance that transplant practitioners remain aware of these issues and seek guidance from transplant infectious diseases experts, local health department, and the CDC in evaluation of isolates that have characteristics suggestive of *C auris*.

Antifungal Prophylaxis in Solid Organ Transplantation

As with risk factors, antifungal prophylaxis for IC in SOT is best described in LT recipients. Several studies have established the role of antifungal prophylaxis for prevention of IFIs after LT.[38–41] As discussed previously, over the past 2 decades there has been

an evolution in the traditional risk factors for IC and the spectrum of candida species causing infection. This evolution in fungal species and risk factors plus the implication of universal antifungal prophylaxis in the rise of nonalbicans species led to re-examination of prophylactic strategies. Current American Society of Transplantation (AST) guidelines recommend using a targeted approach with use of antifungal prophylaxis in high-risk LT, SBT, and PTX, with choice of prophylactic antifungal agent to be targeted to risk factors for IC versus IA, and considering use of a mold-active agent in patients at high risk for IA.[2,42] Withholding antifungal prophylaxis in low-risk LT recipients has been studied and shown safe.[43] Despite these data, recent multicenter survey revealed that there remains wide variation in the antifungal prophylactic strategies among institutions, and use of universal prophylaxis remains significant, with fluconazole remaining the most commonly used prophylactic agent.[44] Studies that have examined echinocandin (anidulafungin and micafungin) versus fluconazole and amphotericin B have not found a statistically significant difference in outcomes.[38,40,41] In addition to systemic antifungals, topical agents are used for prophylaxis after SOT. A randomized controlled study comparing clotrimazole troche with placebo troche in patients with malignancy and KT showed a lower incidence of oral candidiasis in the clotrimazole group.[45] In subsequent years, studies looked at nystatin suspension in comparison with clotrimazole troche in KT[46] and LT patients[47] and found that both were equally effective in preventing oral candidiasis. The use of topical agents for fungal prophylaxis is a common clinical practice after SOT and although data suggest efficacy in prevention of oral mucosal candidiasis, the impact on IC (if any) is unknown and currently there are no international consensus guidelines on the role of these as prophylactic agents.

Use of antifungal prophylaxis after thoracic transplantation is targeted primarily at prevention of IA and has been shown in several studies efficacious in reducing the incidence of IFIs.[22,48–50] Because risk factors for IC remain poorly understood in this setting, no standardized guidelines exist and prophylactic regimens remain institution-specific.[48]

It is important to recognize the impact of widespread fluconazole prophylaxis on the observed shift in spectrum of *Candida* species and emergence of antifungal drug resistance, which has been highlighted by many experts in the field.[51,52] The use of targeted antifungal prophylaxis and avoidance of universal prophylaxis (as recommended in the current AST guidelines),[2] therefore, is of utmost importance to curtail the risk of further antifungal drug resistance. Furthermore, transplant practitioners must review institutional protocols on infection prophylaxis at regular intervals to update their policies in accordance with the latest information on host risk factors and species trends. Individual institutions must take into account local spectrum of fungal species and drug susceptibility profiles and tailor protocol to better target the risk to their patients.[51,52]

INFECTIONS DUE TO *CRYPTOCOCCUS* SPECIES IN SOLID ORGAN TRANSPLANTATION

Cryptococcus is the third most common etiology and accounts for 7% to 8% of IFIs after SOT.[1,53] According to multicenter epidemiologic data (TRANSNET and Prospective Antifungal Therapy Alliance registry), cryptococcal infection is seen most commonly in KT recipients followed by LT and HT.[1,53] It is typically a late-occurring infection (median time to onset: 464–805.5 days; range 4–4826)[1,53,54] that seems to have an earlier onset after LTX, LT, and HT compared with KT.[54,55] Very early-onset cryptococcosis ($\leq$30 days post-transplant) is well documented, with an incidence of 5% to 10% and has been reported most commonly in LT and LTX recipients.[54,56] Risk factors for development of cryptococcosis after SOT are not as well defined as

IC and IA. Cryptococcosis in SOT is primarily considered the result of reactivation of latent or old infection in the setting of iatrogenic immunosuppression. This was shown nicely in a study by Saha and colleagues,[57] where 52% of recipients who developed cryptococcosis post-transplant had serologic evidence of prior infection pretransplant. Furthermore, those who were seropositive developed cryptococcosis earlier post-transplant than those without (5.6 $\pm$ 3.4 months vs 40.6 $\pm$ 63.8 months, respectively; $P = .0011$). Cryptococcal serologic testing could prove a useful tool in gauging risk of reactivation cryptococcosis in the post-transplant setting and although available through select commercial laboratories anecdotally does not seem commonly used by most transplant centers. Other mechanisms of pathogenesis include donor-derived infection[56] and primary infection due to environmental exposures, both of which are well documented.[58–60]

Variables Influencing Clinical Manifestations and Mortality—Type of Transplant and Immunosuppression

Cryptococcosis is associated with significant morbidity and mortality in SOT recipients. The reported mortality rate in the literature ranges from 14% in some series to as high as 42%.[55,61] Disseminated cryptococcosis with fungemia and central nervous system (CNS) infection is seen in 55% to 68% of cases[55,61] and is associated with higher risk of mortality compared with localized pulmonary or cutaneous infection. Other than disseminated infection, renal failure in SOT recipients carries an independent significantly higher risk of mortality due to cryptococcosis (OR 16.4; 95% CI, 1.9–143; $P = .004$)[55] (hazard ratio [HR] 2.99; 95% CI, 1.12–7.98; $P = .028$).[61]

The clinical manifestations of cryptococcosis in SOT recipients (localized vs disseminated infection) and associated mortality are significantly impacted by the type of immunosuppressive regimen. A study by Husain and colleagues[55] showed that patients receiving tacrolimus-based regimens are at significantly lower risk of CNS infection (78% vs 11%; $P = .001$) and are more likely to have localized forms of disease (66% vs 21%; $P = .006$) in comparison with patients receiving non–tacrolimus-based regimens. Singh and colleagues[61] further showed that use of a calcineurin inhibitor (CNI)-based regimen is independently associated with lower mortality (adjusted HR 0.21; $P = .008$). The protective effect of CNI is attributed to inhibition of binding between cryptococcal protein CB1 and calcineurin.[62] Among CNIs, tacrolimus, which has better penetration of the blood-brain barrier, has been shown associated with lower risk of CNS cryptococcosis in comparison with cyclosporine (11% vs 67%; $P = .04$).[55] The same study showed the impact of immunosuppressive type on mortality, which was lowest among those who received tacrolimus versus cyclosporine versus azathioprine with mycophenolate mofetil (7.9% vs 20% vs 40%; $P = .004$).[61] Type of transplant also has an impact on clinical manifestations and mortality in cryptococcosis. It is well established that patients with liver cirrhosis are at higher risk of cryptococcosis.[63–65] The unique risk of cryptococcosis in patients with liver cirrhosis has been attributed to intrinsic immune defects, including impaired chemotaxis and hepatic iron overload.[66,67] After transplantation, the LT recipients remain at significantly higher risk of disseminated cryptococcosis, a risk that is independent of the type of immunosuppression (adjusted HR 6.65; $P = .048$).[61] LT recipients are also at higher risk of early-onset cryptococcosis ($\leq$12 months of transplant) in comparison with non-LT transplants.[55]

Cryptococcus gattii—An Emerging Pathogen in the United States

Pathogenic cryptococci are divided into 4 capsular serotypes (A, B, C, and D). *Cryptococcus gattii* comprises serotypes B and C. *C gattii* has been known as a pathogen

in the tropical and subtropical areas of the world for many years but is now also recognized as an emerging pathogen in the Pacific Northwest (PNW) of Canada and the United States.[68,69] Molecular subtyping categorizes *Cryptococcus gattii* into 4 genotypes: VGI to VGIV. Genotype VGII is further subdivided into VGIIa, VGIIb, and VGIIc. *Cryptococcus gattii* VGII has been identified as the most common molecular type in the PNW outbreak.[70] Cases of animal and human infection due to *Cryptococcus gattii* were first recognized in the PNW on Vancouver Island, British Columbia, in 2000. In 2004, the first case of human infection was identified in the United States in Oregon, followed by 13 more cases from 2005 to 2007.[68,69,71] Since 2008, there has been an ongoing joint collaborative effort for active surveillance of *Cryptococcus gattii* infection between British Columbia and the United States, which has contributed significantly to knowledge about this infection.[68,71]

Since recognition of the PNW outbreak, several studies have described clinical manifestations with an attempt to identify key differences between *Cryptococcus gattii* and *Cryptococcus neoformans*.[69,72–75] Key characteristics of *Cryptococcus gattii* infections identified in the PNW outbreak include infection in the immunocompromised host in up to half of the cases (38%–55%),[75,76] tendency to present as a mass lesion (cryptococcoma) more commonly than *Cryptococcus neoformans,*[72,74,75,77] and reduced in vitro susceptibility to antifungal agents.[73,78,79] A comprehensive review of clinical features of all the cases identified in the United States from 2004 to 2011 is provided by Harris and colleagues.[75] Most of these infections (83/96) occurred in persons with a history of travel or residence in the PNW and majority (78/83) were identified as molecular subtype VGII (outbreak strain).[75] Patients with infection not acquired in the PNW were found to have other molecular subtypes (nonoutbreak strain). The study revealed that persons with the infections due to the outbreak strain in comparison with the nonoutbreak stain are more likely to present with respiratory symptoms (38/51 vs 4/11; $P = .03$) and are less likely to present with CNS symptoms (15/41 and 9/10; $P = .008$). The outbreak strain seemed to cause infection more frequently in those with preexisting conditions compared with nonoutbreak strains (47/55 vs 4/13; $P<.0001$); and use of oral steroids in the past year was independently associated with increased risk of mortality (OR 7.1; 95% CI, 1.01–49.3; $P = .048$).[75] Overall, 91% of patients requiring hospitalization and infections were associated with a case fatality ratio of 33%.[75]

Data specific to SOT were published in 2015 by Forrest and colleagues,[73] who reviewed the cases of *Cryptococcus gattii* reported in Oregon with focus on clinical features and outcome in the transplant host. In this series, 11 of 62 patients were SOT recipients. The median post-transplant time to infection was 17.8 months (1 month to 15 years). Six of 11 patients were reported to have disseminated infection, including fungemia and CNS disease.[73] Findings that were seen more commonly among SOT recipients in comparison with non-SOT included radiographic abnormalities on lung imaging (90% vs 5%; $P<.001$) and leptomeningeal enhancement on brain imaging (70% vs 7%; $P = .002$). Cryptococcoma presenting as brain and lung masses were seen more commonly among the non-SOT patients.[73] The median CSF cryptococcal antigen titer was lower among the SOT than the non-SOT cases (1:8 vs 1:1012; $P<.034$), although the difference between serum cryptococcal antigen titer was not statistically different.[73] As reported previously, MIC to fluconazole was elevated for most isolates ranging from 2 μg/mL to 32 μg/mL. Overall, there were 8 deaths in the SOT-group compared with none in the non-SOT group; 90-day mortality among SOT patients was 36%, which as Forrest and colleagues[73] concluded, is significantly higher that the reported mortality for cryptococcosis in SOT (14%).

In a review of current literature on *Cryptococcus gattii*, available data on epidemiology of this outbreak are limited by the fact that most clinical microbiology

laboratories do not perform routine subtyping of isolates to species level. Therefore, the reported incidence is likely an underestimation due to misdiagnosis of clinical isolates as *Cryptococcus neoformans*. Also, although there seems reduced susceptibility to antifungal agents on in vitro testing, the clinical significance of this finding is not known because testing methodology is not standardized between laboratories and currently there are no CLSI breakpoints for interpretation.[69,71] Nevertheless, there is a possibility of antifungal resistance especially to fluconazole in the management of *Cryptococcus gattii* cases. Another fact that has come to light through recent studies is that *Cryptococcus gattii*, which was initially believed a pathogen solely of the immunocompetent host, in reality causes disease across a wider spectrum of hosts, including those with HIV and SOT.[73] Although HIV is an uncommon risk factor for *Cryptococcus gattii* (in comparison with *Cryptococcus neoformans*), it is by no means insignificant. As in the review by Harris and colleagues,[75] HIV was present as a risk factor in 5% of the overall cohort with *Cryptococcus gattii* infection and 55% had some form of immunocompromise. Similarly, 38% of the cases in the BC cohort were reported to have some form of immunocompromise.[77]

Cryptococcus-Associated Immune Reconstitution Syndrome

Immune reconstitution syndrome (IRIS) in SOT recipients has been most well described with cryptococcosis. In prospective studies of cryptococcosis in SOT recipients, IRIS was observed in 4.8% to 14% of the patients occurring at a median of 5.5 weeks from time of initiation of antifungal therapy.[80–82] Patients on tacrolimus, mycophenolate mofetil, and prednisone seem at higher risk of IRIS than those who are on other immunosuppressive regimens (4/4 vs 21/83; $P = .007$).[82] Shortly after the initial reports of IRIS in SOT recipients with cryptococcosis, the impact of IRIS on allograft function was realized.[81] In this study of 54 KT recipients with cryptococcosis, a higher incidence of graft loss due to chronic allograft rejection was seen among those with IRIS versus those who did not have IRIS (66% vs 5.9%; $P = .012$,[81] and 15.4% vs 2.6%; $P = .07$).[80]

The critical role of host $CD4^+$ helper T cells (T_H) in the cell-mediated immune response against cryptococcosis is well established.[83] T_H1 response is proinflammatory whereas T_H2 response is characterized as anti-inflammatory. Cryptococcus acts as a mitogen and a potent stimulator of T cells.[84,85] Furthermore, cryptococcus preferentially stimulates T_H2, which suppresses inflammation, weakens host defenses, and aids disease progression.[86–90] Immunosuppressive agents like tacrolimus have the same effect as cryptococcosis with a predominant T_H2 cytokine response.[87,91–93] After initiation of antifungal therapy and withdrawal of immunosuppression, the T_H1-T_H2 ratio is reversed, which leads to a predominant T_H1-based proinflammatory cytokine response. These immunologic changes promote inflammation, which forms the basis of IRIS and allograft loss associated with it.[81,82,87]

IRIS remains a clinical entity because there are no established biomarkers for diagnosis. Heightened awareness among transplant practitioners, therefore, is necessary for timely recognition and management. There are no studies to guide treatment and most of the published data describes clinical experience with management of IRIS in HIV/AIDS patients. Based on existing data and clinical experience, transplant infectious diseases experts have recommended treatment of IRIS with a prolonged steroid taper over 6 weeks to 8 weeks.[94] It is also recommended that in SOT recipients on treatment of cryptococcosis, withdrawal of immunosuppression be gradual and spaced out in relation to time of initiation of antifungal therapy to reduce the risk of IRIS.[94] In regard to this, data on CNIs are noteworthy. Discontinuation of CNI has been identified as an independent risk factor for IRIS in SOT recipients with

cryptococcosis with an associated 5-fold increase in the risk of IRIS (adjusted OR 5.11; $P = .02$).[80] This observation is strengthened by in vitro data on antifungal properties of CNI, including inhibition of binding between cryptococcal protein CB1 and calcineurin,[62] and the presence of synergism with antifungals against cryptococcal isolates.[95] In addition to the impact of CNI discontinuation on IRIS, data have shown that SOT recipients with CNS cryptococcosis carry a higher risk of IRIS.[80] In patients with HIV/AIDS, paucity of inflammation in the CSF at the time of cryptococcal meningitis diagnosis has been associated with higher risk of IRIS but whether this is true for non-HIV patients is not clear.[96] γ-Interferon has been used for treatment of cryptococcal IRIS but data are limited to a few case reports of its use in management in HIV/AIDS, SOT recipients, and patients with other cell-mediated immune deficiencies.[97–99] Until there are more definitive data on this area, the risk of allograft rejection with γ-interferon must be weighed against the benefits of such therapy in each case.

SUMMARY

IC remains the most common IFI in SOT recipients. The risk factors for IC have evolved over the past several years with reduced impact of operative variables; which is in correlation with advancement in transplantation practices. Infection due to candida species is more common in thoracic transplant recipients than commonly perceived, and risk factors for IC in this population remain poorly understood. Impact of widespread universal fluconazole prophylaxis on emergence of resistant species must be better recognized and institutions should use targeted antifungal prophylaxis for high risk patients. Emergence of drug-resistant (potentially pan-resistant) novel species like *C auris* is alarming. Health care practitioners need to be aware of the predilection of *C auris* toward immunosuppressed hosts, such as SOT recipients; tendency to cause infection in the nosocomial setting; and associated diagnostic and therapeutic challenges. Transplant institutions should contact their local health department for help with species confirmation and drug-susceptibility testing in suspected cases. Cryptococcus remains a pathogen associated with significant morbidity and mortality in SOT recipients. Disseminated infection and renal failure are associated with increased mortality whereas CNI-based regimens are associated with localized infection and reduced mortality. *Cryptococcus gattii* is an emerging pathogen in SOT recipients, which should be considered in cases of cryptococcosis with travel to or residence in the PNW of Canada and the United States. Infection due to *Cryptococcus gattii* might be associated with reduced susceptibility to antifungal agents although the true significance of this finding is at this time unclear. Cryptococcosis-associated IRIS remains a clinical entity and heightened awareness is necessary for timely diagnosis and management. Discontinuation of CNI is associated with significant increase in risk of IRIS, and data on optimal treatment are lacking and guidance is based only on expert opinion.

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