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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Epidemiology of Invasive Fungal Infections in Solid Organ Transplant Recipients: a North American Perspective

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Abstract

Purpose of the Review Invasive fungal infections (IFI) produce significant morbidity and mortality in solid organ transplant recipients, although their overall incidence is poorly defined. This review aims to provide insight into recent developments in the epidemiology of IFI in these patients.

Recent Findings Invasive candidiasis is the most common IFI encountered particularly those with intraabdominal transplants. In contrast, invasive aspergillosis is commonly seen in lung transplants. Voriconazole therapy has certainly increased the survival in invasive aspergillosis. The risk of disseminated cryptococcosis occurs more commonly in liver transplant than other organ transplants. Histoplasmosis usually arises from reactivation in the recipient but may also be donor derived. A higher rate of dissemination occurs in solid organ transplants with coccidioidomycosis. Of interest, climate change may enhance the risk of emerging fungal infection in transplant recipients.

Summary A better understanding of the incidence and risk factors for IFI is necessary. Future strategies based on such knowledge will assist in reducing IFI.

Keywords Epidemiology · Invasive fungal infections · Organ transplants

Introduction

Invasive fungal infections (IFI) are often unrecognized and therefore underestimated in solid organ transplantation. Thus, the exact overall incidence of IFI in solid organ transplant (SOT) recipients has not been well delineated. However, the burden of illness associated with IFI in these patients is considerable. Certainly, SOT recipients are at increased risk due to the immunosuppression used to prevent rejection of the transplanted organ, the surgical transplant procedure itself, colonizing fungi that may be part of the recipient's resident flora or acquired from the environment, as well as those organisms that are acquired from the donor. This increased risk of IFI in SOT recipients has recently been manifested by an increased incidence of 2.6 in the 1-year cumulative probability during the era of 2012-2016 compared to 1.8 during the periods of 2002-2006 and 2007-2011, respectively [1].

Previously, investigators in the United States (US) as part of the Prospective Antifungal Therapy Alliance reported the results of the epidemiology of proven and probable IFIs among SOT recipients from 17 transplant centers from March 2004 to September 2007 focusing on proven and probable IFIs [2]. IFIs were caused by *Candida* species (59.0%), *Aspergillus* species (24.8%), *Cryptococcus* species (7.0%), and other molds (5.8%) [2]. The invasive candidiasis cases primarily arose in liver, heart and lung patients in the first hundred days post-transplant primarily, while > 50% of the invasive aspergillosis cases were noted more than 1 year after transplant in lung transplant recipients. Similarly, Pappas and colleagues in the Transplant-Associated Infection Surveillance Network (TRANSNET) involving 23 transplant centers identified a total of 1208 IFIs in 1063 SOT recipients from March 2001 to March 2006 [3]. The most common IFIs were invasive candidiasis (53%), invasive aspergillosis (19%), cryptococcosis (8%), non-*Aspergillus* molds (8%), endemic fungi (5%), and zygomycosis (2%). However, the investigators also calculated

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the cumulative incidence of the observed IFIs by following a cohort of SOT recipients (16,808 patients) during the study period to arrive at a cumulative annual incidence rate for 729 IFIs among 633 patients: invasive candidiasis (1.95%), invasive aspergillosis (0.65%), and cryptococcosis, mold infections other than aspergillosis or zygomycosis, and endemic mycoses, all having similar incidence rates (~0.2%). Once more, this study underscored that invasive candidiasis cases were focused in gastrointestinal transplants (small bowel, pancreas, and liver transplants), with invasive aspergillosis and other mold IFIs being noted most commonly in lung transplant recipients. More updated information on the epidemiology and risk factors of IFIs in SOT recipients is needed as immunosuppressive regimens have evolved and antifungal prophylactic measures have been modified (see Table 1).

Invasive Candidiasis in SOT

Candida species are normal commensals of the SOT recipient's resident flora and as such, may be found throughout the gastrointestinal tract, on the skin, and in the vagina [4]. Because of its unique environmental niche, these organisms may cause infection in their native host as well as occasionally being acquired from the environment or from the donor organ. In the TRANSNET database, *Candida* spp. accounted for 23% of the fungal infections [3, 5], but the incidence of invasive candidiasis varied among the surveillance transplant centers. As mentioned above, invasive candidiasis predominates in gastrointestinal transplants. It most commonly presents clinically as candidemia that may be intravascular access catheter-related or arising endogenously from the gastrointestinal tract [6]. In contrast, the deep-seated form of invasive candidiasis arises from hematogenous seeding or contiguous spread. In patients with intra-abdominal solid organ transplantation, i.e., liver, pancreas with kidney and small bowel transplantation, the deep-seated form of invasive candidiasis may supersede candidemia in frequency. After liver transplantation, organ/space surgical site infections accounted for 70.2% of the 49 surgical site infections (SSIs) observed in 250 liver transplant recipients (rate of 17.2%), and *Candida* spp. were the third most common pathogen following *Enterobacteriaceae* and *Enterococcus* species producing such infections [7]. Both duct-to-duct anastomosis and dialysis were predictors of SSIs in these patients. Similarly, *Candida* spp. were the third most common pathogens implicated in producing surgical SSIs among pancreas and kidney transplant recipients, where 72.2% of the SSIs were organ/space in origin. Thus, it is well recognized that *Candida* spp. are important pathogens leading to deep-seated IFIs after intra-abdominal organ transplantation [8•].

C. albicans remains the most common *Candida spp.* isolated in SOT recipients accounting for 50% of the isolates [2] followed by *C. glabrata* (30%), *C. parapsilosis* (9%), and *C. krusei* and *C. tropicalis* each producing about 5% respectively [2, 9].

Specifically, in liver transplant recipients, the development of invasive candidiasis is partially predicated on whether antifungal prophylaxis is used at the time of transplantation, whether it be universal prophylaxis or targeted prophylaxis for high risk groups (risk factors include at least 2 of the following: retransplantation, creatinine level 12.0 mg/dL, choledochojejunostomy, intraoperative use of 140 units of blood products, prolonged intraoperative time (11 h), and fungal colonization detected at least 2 days before and 3 days after transplantation) [10]. Most invasive candidiasis infections occur at a median time of diagnosis of 103 days from the time of transplant [3]. However, fluconazole prophylaxis may predispose patients to the emergence of *Candida* spp. resistant to fluconazole (*C. glabrata* and *C. krusei*) and is associated with drug interactions with immunosuppressive medication.

In pancreas transplant recipients, the development of postoperative invasive candidiasis may be more frequent than previously believed [10]. In a retrospective review of 450 pancreatic transplant recipients from 2000 to 2015, organ/space SSIs were documented in 54.6% of the 108 SSIs with *Candida* spp. being the third most common pathogen [8•].

Small bowel transplant recipients are also predisposed to invasive candidiasis. The following are the predisposing risk factors for invasive candidiasis in small bowel transplantation: acute rejection and poor initial allograft function, hemodialysis, laparotomy after transplantation, anastomotic problems, and over-immunosuppression [11]. As a result, universal fluconazole prophylaxis is employed.

Donor-derived transmission of *Candida* may occur at the time of the operative procedure in renal transplantation manifested by renal parenchymal, renal vascular, or wound site involvement [12]. Although, candidemia still produces a significant proportion of the invasive candidiasis observed, but recent data on the incidence of invasive candidiasis in renal transplant recipients are lacking.

Candidemia is the most common presentation of invasive candidiasis in heart transplant recipients usually occurring within 3 months of transplantation, although invasive candidiasis may develop after re-exploration post-heart transplant [11, 13, 14].

Both candidemia and invasive candidiasis may occur after lung transplantation with the former being more common in these recipients. Recently, Marinelli and colleagues described the occurrence of 31 episodes of candidemia in 3.5% of 712 lung transplant recipients from 2016 to 2019 at a single center [15••]. Of these 61.2% (19) of the episodes of candidemia developed within 30 days of transplantation with a mortality of 31.2%. Of note, 11 of these 19 early episodes of candidemia were vascular catheter-related. The

Table 1 Invasive fungal infections in solid organ transplant recipients

Type of IFI	SOT recipient	Comments and risk factors
Invasive candidiasis	Liver transplant	Depends on whether antifungal prophylaxis used (universal vs. targeted) Third most common cause of liver transplant SSIs. Invasive candidiasis supersedes candidemia
	Pancreas transplant	Third most common cause of SSIs
	Small bowel transplant	Anastomotic problems, poor initial allograft function, hemodialysis, laparotomy after transplantation, over-immunosuppression
	Lung transplant	Candidemia secondary to other sites of infection such as empyema, pericardial infection, or osteomyelitis Risk factors: extracorporeal membrane oxygenation immediately post-transplant and renal replacement therapy
Invasive aspergillosis	Lung transplant	Most common IFI Risk factors — cystic fibrosis, older donor age, longer ischemia time, receipt of a single lung transplant, and CMV infection
	Liver transplant	Early IA associated with re-transplantation, renal failure with hemodialysis, fulminant hepatic failure, and reoperation involving the intra-abdominal and thoracic cavities Late IA associated with rejection (corticosteroid use) and hemodialysis
	Heart transplant	Risk factors — *Aspergillus* colonization of the respiratory tract, re-operation, post-transplant hemodialysis, rejection, CMV disease, admission to the ICU with mechanical ventilation, and extracorporeal membrane oxygenation and known contamination of the ICU with *Aspergillus conidia*
	Renal transplant	Risk factors — graft loss and post-transplant hemodialysis, pre-transplant chronic obstructive pulmonary disease, and prolonged high dose corticosteroid therapy
Cryptococcosis	Liver transplant	Third most common IFI Risks factors — reoperation, Roux-en-Y biliary anastomosis and massive intraoperative transfusion Higher risk of dissemination Early onset of cryptococcosis less 12 months
	Lung transplant	Early onset of cryptococcosis less 12 months
	Heart transplant	Late onset cryptococcosis Renal replacement therapy in heart transplantation
	Kidney transplant	Risk factor of mortality — renal failure in kidney recipients
Histoplasmosis	SOT	Endemic in the Mississippi and Ohio River valleys Pulmonary is the most common localization Risks factors for mortality: older age and severe disease Risk of relapse — less 2 years post-initial diagnosis
Blastomycosis	SOT	Endemic in the Mississippi and Ohio River valleys and in Canadian provinces surrounding the Great Lakes, and St Lawrence Seaway Median time of onset — 6 months until 5 years Pulmonary infection in 80% of cases, and 20% develop a disseminated disease in cutaneous, osteoarticular, genitourinary, or CNS sites Mortality of 30%
Coccidioidomycosis	SOT	Endemic in Southwestern US and Central and South America High rate of mortality — 58%. Most cases occurred within 1 month after transplantation Disseminated disease, up to 75% and mortality up to 72%
Mucorales	SOT	Lungs common site of infection Risks factors — diabetes mellitus and prior use of voriconazole Lung and liver transplant recipients highest incidence
Scedosporium	Lung transplant	Risks factors — previous colonization and prior antifungal therapy Rate of death at 6 months 55%
Fusarium	SOT	Skin and soft tissue the most common infections followed by pneumonia Affects mostly lung and kidney transplant recipients
Dark molds	SOT	Occur after first year of transplantation and affect mainly lung transplant recipient (53.3%) Most common sites of infection are pulmonary, cutaneous, and sinus *Alternaria* — most frequent (32%), followed by *Exophiala* (10.7%)

The following table is original

key risk factors for candidemia in the lung transplant recipients were as follows: pre-transplant hospitalization, requirement for extracorporeal membrane oxygenation immediately post-transplant, and renal replacement therapy. In addition, 5 cases of early candidemia were secondary to other infections that complicated the surgical transplant procedure (empyema 3, pericardial infection 2, and sternal osteomyelitis 1). These latter infections represent invasive candidiasis that occur secondary to the lung transplant procedure. At present, it remains unclear if *Candida* colonization of the recipient or donor at the time of transplantation requires therapeutic intervention to prevent subsequent invasive candidiasis sequelae in the recipient.

Invasive Aspergillosis in SOT

Aspergillus conidia are ubiquitous in the environment. As a result, acquisition of this organism ensues predominantly via inhalation into the respiratory tract or the sinuses. *Aspergillus fumigatus* is the most common pathogen implicated in these infections. Infections due to *A. flavus*, *A. niger*, *A. calidoustus*, and *A. terreus* are less common [10]. In addition, the organism may be acquired by the recipient through donor-derived transmission.

Invasive aspergillosis (IA) is the most commonly encountered in lung transplant recipients. Risk factors for this invasive disease include: cystic fibrosis, older donor age, longer ischemia time, receipt of a single lung transplant, and CMV infection [16–18]. In addition, the development of IA is associated with higher mortality. Indeed, cystic fibrosis patients with positive intraoperative cultures for *Aspergillus* spp. have a greater propensity of developing IA post-transplant [19]. Such infections occurred at a median time of 42 days following transplantation and were also correlated with treatment for acute cellular rejection within 90 days of the transplant. As mentioned, colonization prior to transplantation as seen in cystic fibrosis patients is a major predisposing factor for IA. However, the lung is an open window to the environment and *Aspergillus* being ubiquitous in the environment is easily acquired. Furthermore, on occasion this organism may be acquired from the donor lungs. Although some centers employed universal prophylaxis to prevent IA, IA due to *A. fumigatus* may develop in lung transplant recipients even when azole prophylaxis directed against this pathogen is employed [20].

Although IA most commonly occurs in lung transplant recipients as stated above, liver transplant recipients may be affected by this IFI in the early post-transplant period (within 3 months), as well as later. The predisposing risk factors for early IA are as follows: re-transplantation, renal failure with hemodialysis, fulminant hepatic failure, and reoperation involving the intra-abdominal and thoracic cavities [11]. Late IA (occurring > 3 months post-transplant) is associated with the receipt of more than 6 g of prednisone by the 3rd month after transplantation typically related to rejection, renal failure with hemodialysis, and leukopenia (< 500/mm^3) [11]. A recent literature review of proven and probable cases of IA in liver transplant recipients from 1985 to 2013 culled a total of 116 cases [21]. The most common cause of IA was *A. fumigatus* (73%), followed by *A. flavus* (14%) and *A. terreus* (8%). In the era of voriconazole use, there was increased survival. In addition, noteworthy is the fact that liver transplants have a predisposition for disseminated disease when affected by invasive mold infection with a significant mortality rate of 64% [22].

Heart transplant recipients are also subject to IA. The incidence in these patients has varied from 3.5 to 26.7% [23••]. A variety of risk factors predispose these recipients to IA: *Aspergillus* colonization of the respiratory tract, reoperation, post-transplant hemodialysis, rejection, CMV disease, admission to the ICU with mechanical ventilation, and extracorporeal membrane oxygenation and known contamination of the ICU with *Aspergillus conidia* [11, 23••]. Of concern, is the relative high mortality rates associated with IA that may reach 40% in heart transplant recipients [23••, 24]. The organ most often infected by IA are the lungs but the occurrence of late aspergillosis (beyond 3 months after transplant) was associated with disseminated disease particularly involving the central nervous system in a retrospective review of 479 heart transplant recipients [24].

Renal transplant recipients with graft loss and post-transplant hemodialysis, pre-transplant chronic obstructive pulmonary disease and prolonged high dose corticosteroid therapy are also at greater risk for IA [11, 23••]. The incidence of IA in these patients ranges from 1.2 to 4% with overall mortality ranging from 4 to 25% [23••]. However, a recent report of trends in IA from France documented a lower incidence in renal transplant recipients of 0.3% [25]. Of interest, even with the advent of voriconazole therapy, the prognosis for IA in renal transplant recipients is guarded with a 1-year survival of only 81% [26]. The onset of late IA has been attributed to over-immunosuppression [11].

Cryptococcosis

The TRANSNET database identified cryptococcal infections as the third most common IFI in SOT recipients and accounting for 7–8% of the IFIs [3]. Interestingly, 20–60% of the cryptococcal IFIs seen in HIV negative individuals occur in SOT recipients.

The disease usually arises from reactivation of latent infection. Saha and colleagues demonstrated that 52% of transplant recipients who developed cryptococcosis were seropositive prior to transplantation attesting to the

reactivation of latent infection [27]. Rarely, donor-derived cryptococcosis has been reported. Indeed, the presence of central nervous system symptoms within 30 days after transplantation should trigger suspicion for this infection [28••]. In contrast, primary infection may be caused by inhalation of spores or yeast cells due to environmental exposures from soil or decaying material [29].

Cryptococcosis occurred a median time of 1.6 years post-transplant, according to Husain et al. [30]. Thirty percent of cases are restricted to the lungs [31], but disseminated infection may occur in up to 68% with central nervous system (CNS), skin, and osteoarticular involvement [30].

Patients receiving tacrolimus-based regimens have a lower risk of CNS infection [30] and were associated with a lower mortality [31]. The mortality rate varies from 14 to 42% in some series [30, 31]. Recently, a large retrospective cohort of patients with cryptococcosis after SOT showed that older age, diabetes, liver disease and lung transplant conferred an increased risk of death [31].

Cryptococcus neoformans serotype 1 is the main the cause of cryptococcal infection [33]. However, *C. gattii* is now recognized as an emerging pathogen in the Pacific Northwest since the first case was reported from Vancouver Island in 1999 [34]. About 40% of the *C. gattii* cases were immunocompromised such as SOT or HIV patients. Most of these cases occurred in persons with a history of travel to the Pacific Northwest. Forrest et al. described *C. gattii* in the SOT population [35]. The median time from transplantation was 17.8 months. There was an elevated fluconazole MIC with a high concomitant mortality (72% died), and 45% of the deaths were attributable to the *C. gattii* diagnosis.

Drug resistance is described with all three antifungals in use (fluconazole, amphotericin B, and flucytosine) against *Cryptococcus* which contributes to mortality. This is particularly pertinent to the treatment of *C. gattii* where strains may have elevated MICs to fluconazole.

In liver transplant recipients, cryptococcosis is the third most common IFI after invasive candidiasis and aspergillosis. Reoperation, Roux-en-Y biliary anastomosis and massive intraoperative transfusion are independent risk factors for this infection [36•]. The risk of cryptococcal dissemination is higher in liver transplant recipients (OR 6.65 95%, CI 1.01–43.64, $p = 0.048$) [30].

Similar to liver transplants, lung transplant recipients can display very early onset cryptococcosis at less than 12 months. However, lung transplant patients have a low rate of disseminated infection [37].

It would appear that in kidney as well as heart transplant recipients, late onset cryptococcosis may be manifested at 23 months and 35 months, respectively. Renal failure was associated with high level of mortality in kidney recipients. Renal replacement therapy in heart transplantation was an independent risk factor of IFI [38•].

Endemic Fungal Infections

Histoplasma, *Blastomyces*, and *Coccidioides* spp. are dimorphic fungi that also cause IFI in SOT recipients. The infections produced by these fungi are categorized as the endemic mycoses and account for < 5% of the IFIs in SOT recipients [39].

Histoplasmosis

Histoplasmosis, caused by *Histoplasma capsulatum*, is endemic in the Mississippi and Ohio River valleys as well as areas around the Great Lakes. Its incidence is estimated to be less 1% [40]. Primary infection is acquired via inhalation and may be precipitated by exposure to disrupted soil around construction sites and farming. However, rare cases of donor-derived infection have been reported [41]. Infection appears to occur bimodally with 40% seen in the first 6 months after transplantation and 34% between 2- and 11-years post-transplantation [42]. The infection is most prevalent in renal, liver, and lung transplant recipients [42, 43].

Pulmonary involvement is the most common localization in 79% of SOT cases, and dissemination was present in 77% of cases [43]. The mortality rate as noted by Assi and colleagues was about 10% with 72% of deaths within the first month post-transplantation. In the multivariate analysis, older age and severe disease were independent risk factors for mortality [43]. Six percent of the patient cohort developed relapses, less 2 years after the initial diagnosis.

Blastomycosis

Blastomyces dermatitidis, the etiological agent of blastomycosis, is endemic in the Mississippi and Ohio River valleys, the Canadian provinces, and US states surrounding the Great Lakes, and St. Lawrence River valley. Activities that disrupt the soil in these regions lead to aerosolization of conidia with subsequent inhalation [39]. Blastomycosis in SOT recipients stems from primary infection or reactivation of latent disease [44]. Donor-derived infection has not been described. Nine cases of blastomycosis were described in the TRANSNET database between 2001 and 2006 [3]. The median time of onset was 6 months to 5 years after transplantation. Pulmonary infection is the main manifestation of disease in 80% of cases. and 20% develop a disseminated disease to cutaneous,

osteoarticular, genitourinary, or CNS sites [39]. McBride's study shows than immunocompromised patients develop more severe disease. However, there is not more dissemination [45•]. Overall mortality was 30% [46].

Coccidioidomycosis

This IFI is caused by inhalation of *Coccidioides* arthroconidia from disruptions of the soil in endemic areas such as in the Southwestern US and Central and South America [47]. Although primary and reactivated infections are most common, donor-derived transmission of infection has been described with a high mortality rate of 58%. Most of the cases have occurred within 1 month after transplantation [48]. In contrast, in liver transplants 60% of cases occurred in the first 6 months and 70% during the first year of transplantation [49]. Blair and colleagues determined that SOT recipients display higher rates of disseminated disease (up to 75%) and a mortality of up to 72% [50, 51]. Due to the paucity of data regarding the incidence of endemic mycoses cases, clinicians should be encouraged to report all such cases.

Emerging Fungal Infections

Emerging fungal infections represent 7–10% of IFI in SOT recipients [3]. The route of exposure is presumably due to direct contact or inhalation from environmental sources such as soil and water.

The emerging fungi include:

- Mucorales species of *Rhizopus, Mucor*, *Absidia*
- *Scedosporium* spp. — *S. apiospermum*, *Lomentospora prolificans* (formerly called *S. prolificans*) and *S. auranticum*
- *Fusarium* spp. — *F. solani* and *F. oxysporum*
- Dematiaceous fungi — *Alternaria* spp., *Bipolaris* spp., *Cladosporium* spp., *Exophiala* spp., *Ochroconis* spp., and *Rhinocladiella* spp.

Host risk factors for these IFI include: prolonged and profound immunosuppression, breaks in skin integrity and chronic respiratory disease [52]. The presence of these fungi does not necessarily indicate infection. Distinguishing colonization from invasive infection with these organisms can be challenging. Pulmonary colonization after lung transplantation does not necessarily lead to invasive infection, and thus antifungal therapy may be unnecessary [53].

Mucormycosis accounts for 2% of fungal infections in SOT. Lung and liver transplant recipients have the highest incidence of mucormycosis. The lungs are the common site of infection, although the nose and sinuses may become involved with further extension to the orbits or brain. The risk for mucormycosis may be augmented by the presence of diabetes mellitus and prior use of voriconazole. Infections occur at a median time of 6 months after transplant. However, in liver transplant recipients the infection may occur earlier within the first month after transplantation [54].

Scedosporium spp. represents 1% of all fungal infections in SOT recipients [3, 55]. Exposure may occur after donor contact with contaminated water such as near drowning or soil. Risk factors are previous colonization, particularly the lungs of lung transplant recipients, and prior antifungal therapy. This IFI has occurred mostly in the first year after lung transplantation associated with cystic fibrosis with a higher rate of mortality. Cases have been described with each type of SOT. Infection most often is manifested by pneumonia but also mediastinitis and fungemia. The mortality rate at 6 months was 55% [56].

Fusarium spp. account for 0.6% of IFI in SOT recipients [3]. The portal of entry is the skin or respiratory tract. In a recent review, skin and skin structure areas were the most common infection sites in 42%, followed by pneumonia (35%) and intra-abdominal infection (17%). Cases were reported with each type of SOT recipients but are most frequent in lung and kidney transplant recipients [57].

IFI due to dematiaceous fungi is called phaeohyphomycosis and represents 2.6% of all IFI in SOT patients. The TRANSNET database accumulated 30 cases between 2001 and 2006, among the 30 participating transplant centers. Most cases occurred after the first year of transplantation and affected mainly lung transplant recipients (53.3%) [3]. Most infections were localized to the lungs, skin, and sinuses. Only 2 cases with CNS involvement were described between 1988 and 2009 in Shieffelin's review of 27 cases of phaeohyphomycosis [58]. Disseminated infection was noted in 55% of cases. *Alternaria* was the most frequent genus (32%), followed by *Exophiala* (10.7%) [57].

Prospective studies are necessary to gain further insights into the epidemiology and treatment of these emerging fungal infections. In addition, the role of climate change in the emergence of these IFI by producing natural disasters (floods, tornados, tsunamis, etc.) warrants exploration, while the development of new ecological niches may increase the exposure to these fungal organisms and the onset of IFI [58].

Conclusions

IFI remain a major cause of morbidity leading to graft loss and mortality in SOT recipients. To avoid these infections, a better understanding of their incidence and risk factors is necessary. Further data are needed to shed light on these issues. In addition, the right balance between

immunosuppression used to prevent rejection in SOT recipients must be counterbalanced by potentially reducing the risk of IFI in these patients caused by these immunosuppressive agents. Future strategies should focus on risk reduction in SOT recipients based on an understanding of the epidemiology and risk factors for developing these infections.

Declarations

Conflict of Interest The authors declare no competing interests.

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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