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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Epidemiology of Invasive Fungal Infections in Solid Organ Transplant Recipients: an Indian Perspective

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Abstract

Purpose of Review This review summarizes the available Indian data on epidemiology of invasive fungal infections (IFI) in recipients of solid organ transplants (SOT). The epidemiology is further compared with studies from other parts of the world for each SOT type.

Recent Findings The available studies on Indian epidemiology of IFI in SOT are scarce, though the number of SOTs performed in India have increased tremendously in recent years. The limited data from India present a distinct spectrum of infection in transplant recipients with high incidence of mucormycosis. During COVID-19 outbreak, IFI rate increased and renal transplant recipients acquired mucormycosis earlier than previous studies.

Summary Maximum data on IFI was available from renal transplant recipients, wherein mucormycosis was the predominant IFI in Indian patients in contrast to invasive candidiasis in majority countries. The other IFIs had varied spectrum. With the increasing number of SOTs being performed and the already persisting high burden of IFI in India, there is an urgent need of larger prospective studies on epidemiology of IFI in transplant recipients.

Keywords Invasive candidiasis · Mucormycosis · Epidemiology · Solid organ transplant

Introduction

With the advancement of medical science, the numbers of solid organ transplants (SOT) have increased [1]. In this progress, infection is the major challenge to have better outcome of SOT recipients. Among the different infections, invasive fungal infections (IFI) contribute to significant morbidity and mortality of SOT recipients [2•]. Epidemiology of IFI in SOT remains a moving target. In addition to incorporating newer immunosuppressive regimens, novel prophylactic strategies, and variation in induction regimens, the advancements in diagnostic modalities and follow-up of patients also contribute to the dynamics of IFI in SOT [3, 4]. Most of the available data on epidemiology of IFI in SOT is derived from multi/mono-centric transplant centers which, usually caters to a particular organ transplant or from experiences of a single transplant center describing a single case or series. IFIs are rampant in India, and their epidemiology is ever-evolving [5]. Extensive reviews on IFIs in SOTs are available from developed countries [2•, 6–8, 9••, 10–18, 19•, 20, 21]. Such reviews are limited in developing countries though SOT cases have tremendously increased in recent years [1]. The current review summarizes epidemiology of IFI cases in SOT recipients with particular reference to the Indian scenario. Data on diagnosis and treatment are not included. Though there are dedicated studies on the overall epidemiology of IFI among Indian patients, including those in intensive care settings [22–25], data on IFI in SOT recipients in India is limited and sketchy.

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Overview of Epidemiology of IFI in SOT

The development of IFI in SOT is primarily governed by the balance between the host characteristics including immune status, and exposure to the prevalent fungi in the environment [26, 27]. The host factors like prior colonization with the fungal agent, a breach in mucosal barriers, co-morbid conditions like diabetes, malnutrition, cirrhosis, etc. all contribute towards increased predisposition towards IFI post-SOT [18]. Environmental exposure to common molds like *Aspergillus* or endemic fungi leading to the chronic carriage of fungi during the pre-transplantation stage act as reservoirs of infection which can cause IFI once the patient goes into immunosuppression post-transplant [11]. Another major determinant is the use and impact of antifungal prophylaxis therapy, which determines the type of IFI and its time of onset. For instance, invasive candidiasis (IC), the most common form of IFI in SOT, accounting for 50–60% of IFIs [9••], appears weeks to months after a lung or liver transplant, but usually appears after two years of renal transplant [8]. Invasive Aspergillosis (IA), the second most common type of IFI in SOT accounting for 20–25% of all IFIs [9••], appears within six months of liver transplant but much later in heart, lung, or renal transplant [8]. Though the appearance of IA is expected sooner post-lung transplant, owing to inhalation/colonization of *Aspergillus* via respiratory tract, the use of specific prophylactic antifungal regimen influences the time of onset of this IFI [4]. Patients posted for liver transplant are also at increased risk of IFI before and after the transplant due to decompensated cirrhosis and immune dysfunction [28]. The timing of IFI post-SOT varies with the type of SOT[29]; however, it has geographical variations determined by environmental exposure and the antifungal prophylaxis used in different healthcare settings.

There are several sources by which a patient can develop IFI post-SOT. The most important being the patient's flora or colonization [11]. *Candida* species frequently colonize human's gastrointestinal, respiratory, and genital systems and skin. The gut and the skin serve as the most important endogenous sources of *Candida*, leading to IC at the opportune moment of a breach in skin/mucosa integrity and immunosuppression [18]. Another important source is the reactivation of a dormant or subclinical infection following immunosuppressive therapy [2•]. IA following a lung transplant would have been a perfect example of reactivation of a quiescent infection; however, this is usually taken care of by the anti-mold prophylactic therapy given to these patients. Reactivation, however, continues to be a major mechanism for other IFI like cryptococcosis, histoplasmosis, and coccidioidomycosis.[8, 9••] A pre-transplant carriage of these agents, especially in the respiratory tract, can act as a continuous source of potentially pathogenic fungi leading to invasive disease post-transplant. Continuous/heavy environmental exposure, by place of residence in case of endemic mycoses or occupational/recreational exposure to fungal spores at construction sites, garden and agricultural fields, caves, etc., can also act as an important source of IFI in SOT patients [4, 7]. The hospital environment, containing fungal pathogens, can also be a convenient source for SOT patients. Fungal pathogens, including Mucorales, have been isolated at high number from the environment of Indian hospitals [30••], and so have *Aspergillus* spp.[24]; they could be potential sources of infection in post-SOT recipients. Finally, the donor organ can be the source of IFI in SOT [31]. The transplanted organ could be a fungal pathogen reservoir, especially of endemic mycoses like *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, and other fungi like *Scedosporium apiospermum*.[7, 32]

The Transplant-associated Infection Surveillance Network (TRANSNET), a global repository of data on transplant patients till 2010, suggested that the risk of IFI in SOT varied with the organ type, being highest in the small bowel (11.6%), followed by lung (8.6%), liver (4.7%), heart (4%), pancreas (3.4%), and kidney (1.3%) [9••]. This data has been undergoing continuous flux. However, It would not be prudent, to extrapolate this data to the Indian context. The reasons may be that organ transplant in India, though established for organs like the kidney and liver, is in a relatively nascent/developing stage for other organs like the heart, pancreas, and small bowel [1]. Further, even if a decent number of SOTs are being conducted in India, there is a dearth of reported literature on IFI following SOT. Indian studies have reported IFI mostly following renal transplants and few reports on lung, liver, and heart transplants. Therefore, the Indian data on IFI in SOT is skewed towards these organs and has significant diversions from the global trend. The possible reluctancy to report IFI in private-sector hospitals where high number of transplantations are performed compared to public-sector hospitals has lead to limited data from India. Renal transplantation is performed in large number in public-sector hospitals as well, and majority data have come from those hospitals. The overall comparison of spectrum of agents causing IFIs in different transplant groups is depicted in Fig. 1.

IFI in SOT: India vs. the World

Renal Transplant

Despite only a handful of Indian studies reporting IFI in Renal transplant (RT), stark differences are evident between

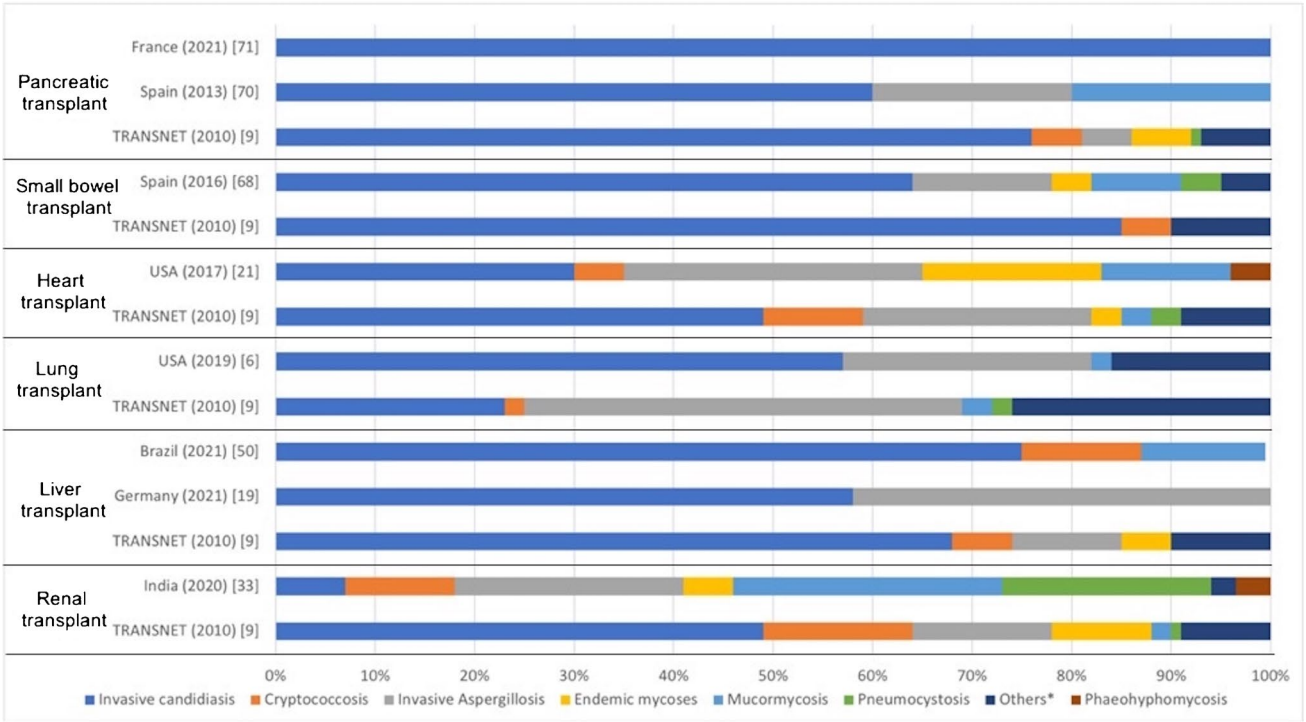

Fig. 1 The reported spectrum of invasive fungal infections from different parts of the world in specific solid organ transplants

the Indian and global epidemiology. RT is the standard of care management for end-stage renal failure. The TRANSNET global prospective study on > 8000 RT recipients over five years observed that 332 (4%) patients developed IFI [9••]. IC was the most common IFI detected in 164 (49%) patients, followed by cryptococcosis in 49 (15%), IA in 47 (14%), endemic mycoses in 33 (10%), mucormycosis in 8(2%), pneumocystosis in 5 (1%), and other unclassified fungi in remaining patients (Fig. 1) [9••]. In contrast to this global data, a single-center experience from a tertiary care hospital in North India revealed that out of the 550 RT done between 2014 and 2017, IFI occurred in 56 (10.2%) RT recipients [33••]. The most common IFI was mucormycosis (27%), closely followed by IA (23%) and pneumocystosis (21%) [33••]. Cryptococcosis constituted 11% of IFI, and invasive candidiasis was limited to 7% cases, histoplasmosis in 3 (5%) and phaeohyphomycosis in 2 (3.5%). Interestingly, twenty (36%) patients had dual IFI in north Indian study [33••], suggesting a possible environmental source for multiple pathogens simultaneously [24, 30••]. Mucormycosis was observed to involve the lung in the form of cavity and consolidation in 11 out of 15 cases, and two cases developed mucormycosis in the renal graft itself, one was rhino-cerebral mucormycosis, and one was disseminated form [33••]. The higher incidence of mucormycosis could be attributed to post-transplant diabetes mellitus, as observed in the study in 32% of cases [33••]. Meshram et al., from western India, also reported that diabetes mellitus was significantly associated with post-RT mucormycosis.[34] The patients of RT also witnessed the brunt of mucormycosis-associated morbidity and mortality during the COVID-19 waves in India [35]. In a multicentric evaluation of 1382 RT recipients, COVID-19-associated mucormycosis (CAM) was observed in 61 (4.4%) cases over seven months [35]. The mortality rate of CAM was 26.2%, while pulmonary mucormycosis was 100% fatal [35]. Further, on comparing the first and second wave of covid-19 in India, it was observed that the rate of fungal culture positivity in RT patients and mortality was significantly higher during the second wave than in the first wave [36], consistent with the outbreak of mucormycosis during the second wave of covid-19 in India.

The mean time-to-diagnosis observed in TRANSNET was eight months for IC, 15 months for IA, 26 months for mucormycosis, and 28 months for endemic fungal infections [9••], and the mean time-to-diagnosis was 25 months (ranging from 1 to 96 months) in a north Indian study [33••]. However, during the COVID-19 pandemic in India, the RT recipients acquire mucormycosis within 7–14 days post-COVID 19 infection [34].

A case series from south India, consisting of six cases of IFI in RT recipients, reported mucormycosis in two, IA in two and one case each of disseminated histoplasmosis and cutaneous phaeohyphomycosis.[37] Another study by Shekar et al. from south India reported different

epidemiology of IFI in RT patients. They reported 67 (9.2%) IFI among 735 RT done over 20 years. The most common IFI was IC (66%), followed by mucormycosis (16%), IA (6%), cryptococcosis (4%), and histoplasmosis (3%) [38]. IC, mucormycosis, and IA usually presented within three months of RT, while cryptococcosis developed up to 15 months and histoplasmosis up to seven years post RT [38]. The one-year survival rate was 0% for histoplasmosis, 25% for IA, and 33% for cryptococcosis, 55% for mucormycosis and 68% for IC [38]. A study from western India by Patel et al. on 1900 RT from 2010 to 2015 reported IFI in 30 (1.5%) cases. IC was the most common IFI following RT in this study observed in 16 (53%) cases, followed by IA in 13 (43%), and one case of mucormycosis.[39] The mortality was 25% for IC, 30% for IA, and 100% for mucormycosis. Among the surviving patients, 25% IC patients and 15% IA patients developed graft rejection [39].

The Indian epidemiology in RT patients varies from the rest of the world with regarding endemic mycoses also. While Histoplasmosis has been reported both from north India and south India from RT recipients [33••, 37], globally, other endemic mycoses are predominant depending on the endemicity. Two of the nine cases reported of sporotrichosis following RT in the world literature have been reported from India [40]. One case of talaromycosis has been reported from an Indian RT recipient, while 13 more are reported from China and Taiwan [41]. A case of disseminated blastomycosis post-RT has been reported from Toronto, USA,[42]; however, neither blastomycosis nor coccidioidomycosis or paracoccidioidomycosis has been reported from SOT patients of India.

Rare cases involving other IFIs are also reported from India. A 50-year-old post-RT woman developed a brain abscess involving *Scedosporium apiospermum*.[43] Realizing the high burden of fungal infections in India, transplant centers have incorporated fungal screening strategies before planning a patient for transplant[44] to avoid post-transplant IFI. An asymptomatic aspergilloma diagnosed during the pre-operative period was resected surgically before RT. The patient was maintained on an optimum balance between immunosuppressive therapy and antifungal prophylaxis [45]. Similarly, pulmonary mucormycosis which has nearly 100% mortality in RT patients, was managed with surgical resection and antifungals in the perioperative period; this along with decreased immunosuppression post-RT lead to a favorable outcome of RT in ten Indian patients [46]. Infection with *Pneumocystis jirovecii*, though uncommon due to universal usage of cotrimoxazole in post-transplant period, was noticed as organizing pneumonia towards the end of prophylaxis therapy in an Indian patient of RT on triple immunosuppression [47].

Liver Transplant

IFIs are reported to occur in 4 to 40% of all liver transplant recipients, with mortality ranging from 25 to 67% [10]. The epidemiology of IFI in liver transplants in India is limited to a few case reports, though number of liver transplants has increased in recent years. Sabhapandit et al. reported a case of rhino-orbital mucormycosis post-liver transplant in a 42-year-old patient from Hyderabad who succumbed to infection [48]. Jadaun et al. have also reported a similar case of rhino-orbital mucormycosis along with Covid-19 infection in a liver transplant recipient who also succumbed to illness four days after transplant [49]. These Indian reports are only rare infections and fall short in describing the true epidemiology of IFI in liver transplant recipients.

The TRANSNET study of 2010 reported that out of 4468 liver transplants, 378 (8.4%) developed IFI, and the most common IFI was IC (68%), followed remotely by IA (11%), cryptococcosis (6%), and endemic mycosis (5%).[9••] A recent German study also reported 33 (5.6%) cases of IFI in 579 liver transplants over five years, with 58% being IC and 42% being IA. The mortality was 37% for IC and 50% for IA.[19•] A Brazilian study reported eight (1.1%) episodes of IFI in 673 liver transplants, six of which were IC.[50•]

IC is the most common IFI reported in liver transplants globally, constituting 70–90% of all IFIs [9••, 10, 13]. *Candida albicans* is the most commonly involved species; however, non-albicans species have increased during recent years. A Spanish cohort compared IC in SOTs (between 2010–2011 and 2016–2018) and reported an increased incidence of *C. glabrata* from 19 to 30%, with a concomitant decrease in *C. albicans* [51]. In recent times, IC by C. *auris* has also been reported as an outbreak among liver transplant recipients [52], posing a potential threat to prophylactic therapy and infection control practices in transplant settings. Though older age, parenteral nutrition, prolonged neutropenia, broad-spectrum antibiotics and *Candida* colonization are important risk factors for IC following any SOT [11], those specific to liver transplant include choledochojejunostomy, repeat laparotomy and anastomotic leakage [10, 53].

IA can occur in 1 to 9% of post-liver transplant recipients [14, 54]. Though environmental spores are important source of infection, host factors like prolonged surgery, cytomegalovirus infections, re-transplantation, and massive intraoperative transfusion also contribute to IA in liver transplant recipients [55].

Other mold infections and endemic mycoses are relatively rare in liver transplant recipients owing to less immunosuppression. However, with newer antifungal agents targeting IC, mold infections by *Scedosporium* species, mucormycosis, and localized *Fusarium* infections have been reported in liver transplant recipients. The rate of mucormycosis is estimated to vary from 0.4 to 1.6% in liver transplant recipients

[10], and nearly 25% of non-*Aspergillus* mold infections in liver transplant recipients are due to *Scedosporium* species [56]. Cryptococcal infection in liver transplants has also been reported [57].

Lung Transplant

Lung transplant, in the form of a single lung, double lung, heart–lung, or lobar lung, is a potentially life-saving alternative to chronic lung diseases. Ever since the first successful lung transplant in 1983 [58], the number of lung transplants occurring each year has increased. In the year 2019, in USA alone, a total of 2714 lung transplants was performed, with a 7.3% increase from 2018 [59]. The first successful lung transplant in India was conducted in 1999[58], and 266 transplants were performed in 2021 [1]. Data on IFIs following lung transplant is derived from a few global studies. However, there is no reported data on IFIs following lung transplant in India.

Among different SOT, recipients of lung transplants are at increased risk of developing IFI [2•]. The risk may be attributed to the graft that is directly exposed to the environmental sources of fungi, the intense immunosuppressive regimens and compromised upper respiratory tract's defenses of the host [2•]. IFI has been reported to occur in 3 to 19% of lung transplant recipients within the first year of transplant [6, 9••, 15, 59]. Lung transplants outcome remain inferior to other SOTs; the median survival at 1-year and 5-year is 78% and 51%, respectively [6, 9••, 15, 59]. While the rejection and graft failure rates are comparable to other SOTs due to better immunosuppressive regimens, these advancements come at the cost of increased opportunistic infections like IFIs. IFIs are implicated in increasing all-cause mortality by three times in lung transplant recipients [15]. IFIs are also responsible for increased lengths of hospital stay and healthcare costs in lung transplant recipients as compared to other SOTs [59].

The TRANSNET study reported IFIs in 248 (20.7%) of 1195 lung transplant recipients [9••]. The most common IFI was IA (44%) followed by IC (23%) and other molds (23%), mucormycosis (3%), unspecified yeasts (3%), cryptococcosis (2%), and pneumocystosis (2%) [9••]. Similar rates have been reported by a few other centers as well [60, 61]. Among the IA cases, *Aspergillus fumigatus* is most commonly implicated, seen in 2 to 30% of all IFIs in lung transplant recipients [59, 62]. Recent studies have shown the emergence of non-*Aspergillus* molds as an important cause of IFI in lung transplant recipients, like *Scedosporium apiospermum*, *Fusarium* spp., *Paecilomyces* spp., *Talaromyces* spp., etc. [16] Unlike other SOTs, non-*Aspergillus* mold infections are seen more in lung transplant recipients and are associated with higher mortality [9••]. An essential determinant of this mortality is the ability of these non-*Aspergillus* molds to develop resistance to antifungal agents used in the prevention, thus limiting therapeutic options [15]. A retrospective analysis of breakthrough IFIs in SOT recipients and other immunocompromised populations revealed that patients on voriconazole or posaconazole prophylaxis significantly tended towards non-*Aspergillus fumigatus* mold infections like intrinsically azole-resistant *Scopulariopsis*, and those with high azole MICs like *Aspergillus ustus* complex [16, 63]. Since the persisting azole resistance patterns drive these breakthrough IFIs in the concerned healthcare settings, the rates of IFIs by these agents vary with the local epidemiology. For example, while azole-resistant *A. fumigatus* is an important cause of IFI in Europe, it is relatively uncommon in the USA [59]. The precise data on the Indian scenario is lacking, however, considering that India too reported azole-resistant *Aspergillus* spp. and other molds [24, 64], and that these agents are prevalent in the Indian hospital environments [30••, 65], they pose a continuous threat to all lung transplant recipients in India.

Heart Transplant

The first heart transplant in the world was performed in 1963, and in India in 1994 [66]. Heart transplant is slowly catching up in India, the hub of heart transplant in South East Asia. Fifty-four heart transplants were conducted in India in 2014, which increased to 187 in 2019, though still representing only 2% of global cases [1]. During the Covid pandemic, the number of heart transplants performed in India reduced to 151 in 2021 [1]. Considering the relatively scanty cases of heart transplants in India in comparison to global figures, it is expected that the data on post-operative complications would be lacking in India. Current literature on IFIs in heart transplants in India is limited to a single center report, wherein fungal pneumonia was observed in three out of 25 patients who underwent a successful heart transplant [44]. The infections were identified during induction therapy, and patients were successfully treated with liposomal amphotericin B ($n=2$) and oral posaconazole ($n=1$); though the implicated fungal species was not identified [44].

Global IFI data in heart transplant recipients is also scarce. A single-center study from the USA, spanning over 11 years from 2005 to 2016, reported IFI in 23 (9%) patients out of 256 heart transplant recipients. There were seven cases each of IC and IA, three of mucormycosis, two each of histoplasmosis and blastomycosis, and one each of cryptococcosis and phaeohyphomycosis.[21] The IFIs occurred at 23 months post-heart transplant and were associated with 17.4% attributable mortality. Further, recipients with IFI had significantly higher 1-year mortality than those without IFI (30 vs. 7%) [21].

Isolated cases of endemic mycosis following heart transplant have been reported. Tambini et al. reported a lung lesion by *Sporothrix cyanescens* in an Italian patient [63], and Alamri et al. reported disseminated histoplasmosis in a Saudi Arabian patient [64] following a heart transplant.

Small Bowel Transplant

Small bowel transplant (SBT) constitutes a tiny percentage of SOT; while there were > 2 lakh renal transplants in the world in 2019, only 146 SBT were performed globally in the same year [1]. The Global Observatory on donations and transplants of organs report that out of 158 SBTs performed in the last two years, seven were in India [1].

Among all SOTs, the SBT carries the highest risk of infection in the recipient [11]. This is because, by definition, the transplant is performed on a highly contaminated site with inevitable risk factors like damage to mucosal barriers and dependency on parenteral nutrition [3]. It was in 2014 that India's first successful SBT was performed on a 27-year-old man by noting all parameters to pinpoint the evidence of infection in the post-transplant period [67]. The authors acknowledge that there have been several unreported unsuccessful attempts at SBT in India wherein infection/sepsis was the most important cause of mortality [67].

Data on IFI following SBT is, however, available from a few other global centers. IFIs are observed at a higher frequency in SBT than any other SOT, occurring in nearly 23% to 59% of recipients [3, 17]. Nearly 80–100% of these IFIs are IC, causing intra-abdominal abscesses, leakage, and recurrent candidemia.[68] A single center evaluation showed that *C. albicans* was the predominant species causing IC in 37–46% of patients of SBT, followed by *C. glabrata* (25%) and *C. parapsilosis* (13%) [17].

A decade-long retrospective multicentric evaluation on Spanish patients undergoing SBT reported 22 episodes of IFI in 18 patients [69]. There were 14 episodes of IC, three of IA, two of mucormycosis and one each of *Cladosporium* spp., pneumocystosis, and histoplasmosis. IFI were significantly higher in adults than pediatric recipients of SBT (23 vs. 6%) [69]. The study also highlighted that post-transplant renal replacement therapy and a lymphocyte-depleting agent as induction therapy were independent risk factors for IFI in SBT; 71% mortality was attributed to infections following SBT in that study [69]. Another survey on pediatric SBT from the USA reported 56 episodes of IC and four episodes of IA among 98 recipients [17]. Intra-abdominal candidiasis appeared much earlier than candidemia (9 vs. 160 days), and the all-cause mortality was comparable between patients with and without IFI [17].

Pancreatic Transplant

The magnitude of pancreatic transplant (PT), in isolation or as a kidney-pancreatic transplant (KPT), is low in India. In 2020, India performed nearly 26 PT + KPT transplants, contributing to 1.3% of > 2000 such transplants worldwide [1]. The first pancreatic transplant in India was performed in 2014 at a tertiary care hospital in north India. A recent study from the same center reported that despite no shortage of donors, even after eight years, the low number of PT was attributed to adverse donor factors [70]. They reported that nearly 43% of the donated pancreases were rejected for transplant due to prevailing age limit criteria, 25% due to donor sepsis, 14% due to ischemic hepatitis, and 10% due to hemodynamic instability [70]. They further suggested that expanding the age limit and better donor management could improve the harvesting of the pancreas for potential transplants [70]. With such impediments in PT, it is not surprising that there is no Indian data on IFI following PT.

Nonetheless, few authors from outside India have documented their experience of IFI in PT, which could serve as a guiding light for India and the rest of the world. A single-center Spanish study retrospectively analyzed their patients of PKT over 13 years and reported 40 episodes of fungal infections in 32 patients. However, only five were IFI [71]. There were three cases of IC and one case each of IA and mucormycosis. The authors also reported that fungal infections were independent risk factors for severe pancreatic graft dysfunction [71]. A French cohort analyzing 15 patients of KPT over 11 years reported IFI in seven (47%) cases, all being IC [72]. There were four cases of *C. albicans* and one each of *C. glabrata*, *C. dubliniensis*, and *C. krusei*. All these seven patients required surgical revision within 20 days of transplant owing to thrombosis of pancreatic graft. The outcome was dismal, with six patients requiring graft removal and one succumbing to IFI within the first year of KPT [72].

Conclusions

To conclude, IFIs are important cause of morbidity and mortality in SOT recipients. The Indian data on the epidemiology of IFI among SOT recipients is meagre and needs to be strengthened. The limited data show different spectrum of fungal pathogen with higher prevalence of mucormycosis in SOTs with variation in the time of onset of infection. The present review emphasizes the need of setting up surveillance networks reporting IFIs in SOT recipients. An in-depth understanding of the regional epidemiology of IFIs following different SOTs in India would improve the post-operative outcome of recipients.

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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