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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Fungal Infections in Intestinal Transplantation

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Abstract

Purpose of Review Invasive fungal infections (IFIs) remain a cause of morbidity and mortality among solid organ transplant recipients. This review focuses of summarizing key clinical and diagnostics findings of yeast, mold, and endemic fungal infections in intestinal transplant recipients and recent advances in therapies.

Recent Findings There is limited data on IFIs in intestinal transplant recipients and the majority of infections are due to *Candida*. Several novel antifungal agents are in development as well as nanotechnology to combat antifungal resistance and emerging pathogens.

Summary Limited data regarding IFIs in intestinal transplant exist and further multi-center collaborative studies are needed to describe scope of IFIs in intestinal transplant recipients to improve the outcomes of this disease.

Keywords Invasive fungal infection · Intestinal transplant · *Aspergillus* · Mucormycosis · Candidiasis · Endemic fungal infections

Introduction

Invasive fungal infections (IFIs) remain an important cause of morbidity and mortality among solid organ transplant (SOT) recipients [1]. The incidence, pathogen, and clinical course are influenced by the type of allograft, degree of immunosuppression, and institutional antimicrobial prophylaxis strategies. Data from Transplant-Associated Infection Surveillance Network (TRANSNET) show that invasive candidiasis is the most common cause of IFI among SOT recipients (53%), followed by invasive aspergillosis (19%), non-*Aspergillus* molds (8%), cryptococcosis (8%), endemic fungi (5%), and zygomycosis (2%) [2]. *Candida* infections are the most common IFIs in SOT recipients, except lung transplant where invasive aspergillosis is the most common [1, 3]. The epidemiology of IFIs in SOT recipients has changed over the last two decades, with non-albicans *Candida* spp., *Fusarium* spp., and Zygomycetes being increasingly recognized [2, 4–6]. Intestinal transplantation carries a substantial risk for infection due to high needs of immunosuppression. Abu-Elmagd et al. showed that after rejection, infection was the second most common cause of graft failure among intestinal transplant recipients [7]. They report that 31% of patients developed a fatal lung infection (64.7% aspergillosis, 17.6% *Scedosporium* infection, and 17.6% *Candida* infection). In this review, we aim to review the available data on fungal infections in intestinal transplantation and describe new therapies available and in development for IFIs.

Candida

Candida spp. are responsible for the majority of invasive fungal infections in the intestinal transplant recipients [8–10]. In data from TRANSNET, the proportion of *Candida* infections in small bowel allografts was the highest [2]. The true incidence of *Candida* infections may be underestimated since these infections are sometimes underrecognized and underdiagnosed. Invasive *Candida* infections are mostly considered nosocomial in nature, for example, intra-abdominal infections related to surgical procedures, while

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candidemia is related to venous access [10]. In the first weeks after transplantation, intraabdominal fungal infections tend to be more common than fungemia, most likely due to *Candida* colonization of the gastrointestinal tract, bowel ischemia during recovery, and possible contamination of the surgical procedure [8, 10]. Candidemia is associated with multiple courses of antibiotics that alter the gastrointestinal microbiota, presence of a central venous catheter, or total parenteral nutrition [8]. Several risk factors for invasive candidiasis in solid organ transplantation have been described, some unique to abdominal allograft transplantation: older age, diabetes, repeated courses of broad spectrum antibiotics, colonization with *Candida*, prolonged neutropenia, central venous catheters, need for total parenteral nutrition, repeated surgical interventions, renal replacement therapy, complicated intraoperative or postoperative courses, anastomotic leakage, re-transplantation, higher degree of immunosuppression, need for mechanical ventilation, and cytomegalovirus disease [9–11]. In intestinal transplant recipients, non-albicans *Candida* spp. are more frequently isolated than *C. albicans*, *C. glabrata* being the most common isolated species followed by *C. albicans*, reflecting widespread use of antifungal prophylaxis after transplantation [2, 12, 13]. Recent TRANSNET data shows that female gender, black race, azole, and methylprednisolone use are risk factors associated with invasive *C. glabrata* infections, while younger age and echinocandin use were associated with *C. parapsilosis* infections [12].

Candida auris is an emerging fungal pathogen causing mainly nosocomial infections, especially in hospitalized patients. *C. auris* is difficult to eradicate from the environment due to resistance of standard disinfectants [14]. *C. auris* causes severe infections in patients with risk factors including prior exposure to antibiotics and/or antifungal agents, diabetes, recent abdominal or vascular surgery, chronic kidney disease, central venous or urinary catheters, and immunosuppression [14].

Candida can cause a wide spectrum of infection ranging from gastrointestinal manifestations, urinary tract infections to more invasive infections including fungemia or endocarditis. Oral candidiasis is commonly seen in clinical practice; many patients are asymptomatic or complain of loss of taste or odynophagia. Patients with esophagitis sometimes have thrush; patient can be asymptomatic or complain of dysphagia, odynophagia, acid reflux, or chest pain. *Candida* colitis has been rarely reported in the past, including a case of fatal colitis due to *C. glabrata* after intestinal transplantation [15]. In an autopsy case series among immunocompromised patients, colonic involvement was found in 20% of the cases of gastrointestinal candidiasis [15–17]. Patients with *Candida* urinary tract infections usually had or have indwelling catheters and recent antibiotic treatment; most common symptoms are dysuria, urinary frequency and urgency, suprapubic pain, and hematuria. Patients with candidemia can be asymptomatic, or present with minimal symptoms (fever) or septic shock. It is important to perform ophthalmologic examination inpatients with candidemia since they can have chorioretinitis or vitritis.

Isolation of *Candida* spp. from a sterile site is considered the gold standard for the diagnosis of invasive infections, but it is limited by the low sensitivity (~50%) of the blood cultures [10]. The 1,3-β-D-glucan assay is a surrogate marker of *Candida* infections, it is not specific for *Candida* infections, and it can be positive in invasive aspergillosis and *Pneumocystis jirovecii* pneumonia [10]. The main 1,3-β-D-glucan detection assays available have different cut-off values: 60 pg/mL for Fungitell (Associates of Cape Code, Inc., East Falmouth, MA, USA); 11 pg/mL for Wako (Wako Pure Chemical Industries, Ltd., Tokyo, Japan); 20 pg/mL for Fungitec-G test (Seikagaku, Kogyo, Tokyo, Japan); the pooled sensitivity and specificity of these three tests were reported to be 78 and 81%, respectively [18]. False positive 1,3-β-glucan assays have been reported in patients with severe mucositis, administration of immunoglobulins, albumin, amoxicillin-clavulanate or piperacillin-tazobactam, use of cellulose membranes for hemodialysis, leukoreduction for platelet infusion, or surgical gauze containing glucan [10, 19, 20]. The DNA-based diagnostic methods are more reliable to early detect positive yeast culture; they are accurate, reproducible, and available in few hours after a positive blood culture [21]. The sensitivity and specificity for PCR testing was 80% and 70%, higher than 56 and 73% for 1,3-β-D-glucan assay BDG (cutoff at 80 pmol/mL); PCR test was more sensitive than 1,3-β-D-glucan assay and blood cultures for diagnosing deep-seated candidiasis (89 vs. 53%; $p=0.004$; 88 vs. 17%; $p=0.003$) [22]. T2 *Candida* assay (T2 Biosystems) combines magnetic resonance and nanotechnology to identify whole blood *Candida* cells, providing fast identification (hours) for *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* [10]. The sensitivity and specificity of T2 *Candida* assay were reported to be 89–91% and 99% [23, 24].

Adequate source control (i.e., line removal, abscess drainage) is paramount in the management of invasive candidiasis. Usually, antifungal susceptibility can be predicted based on the species isolated and local epidemiology patters which can guide empiric therapy. In choosing an antifungal agent, the severity of illness, renal function (i.e., when choosing amphotericin and for fluconazole dose adjustments), QTc interval, drug-drug interactions (i.e., azoles with tacrolimus), site of infection for drug penetration, and previous antifungal exposure (especially the past 3 months) should be also taken in consideration. In general, *C. krusei* is resistant to fluconazole, *C. parapsilosis* is less susceptible to echinocandins, and *C. glabrata* can have reduced susceptibility to fluconazole or can be dose-dependent susceptible [10]. For

candidemia, invasive candidiasis, and critically ill patients, an echinocandin (anidulafungin 200 mg loading dose then 100 mg/day; caspofungin 70 mg loading dose then 50 mg/day; micafungin 100 mg/day) should be chosen as first line of therapy; alternative treatment should be fluconazole 12 mg/kg loading dose followed by 6 mg/kg/day [10]. For esophageal candidiasis, treatment should be started with fluconazole 200–400 mg/day or itraconazole solution 200 mg/day or voriconazole 3 mg/kg q12h for refractory infection; echinocandins are alternative therapy [10]. For *Candida* urinary tract infections, urine concentration of the drug should be considered; the treatment of choice is fluconazole, with amphotericin B as alternative [10]. For any endovascular infections, including implantable cardiac device infection, lipid formulation of amphotericin B should be preferred with high-dose echinocandins (anidulafungin 200 mg/day, caspofungin 150 mg/day, micafungin 150 mg/day) as alternatives [10]. Echinocandins are usually used as the first-line treatment for *C. auris*, but resistance to echinocandins has been reported [14]. In vitro combinations of echinocandins or amphotericin B with flucytosine were reported to be the most active [25]. New antifungal agents in clinical development such as ibrexafungerp may provide effective treatment options. Several nanoparticle-based antifungal therapies (silver, bismuth-based, trimetallic, nitric oxide nanoparticles) are in development against *C. auris* [26].

Candida infections have a negative impact on morbidity and mortality. From TRANSNET data, that includes all allografts, the mortality for non-albicans *Candida* infections (31.4%) was statistically and significantly higher than for *C. albicans* (22.6%); mortality associated with *C. parapsilosis* (35.2%) and *C. tropicalis* (44%) infections was also very high [12]. *C. auris* infections are associated with higher mortality rates (up to 78%), mainly due to underlying comorbidities of the patients and multidrug resistance of this species (resistance > 99% to fluconazole, ~ 60% to amphotericin B, and > 80% to voriconazole) [14]. In a study that included only intestinal transplant recipients, we demonstrated that fungal infections did not have any significant impact on long-term survival, with the exception of *C. glabrata* infections [8]. In our study, the choice of empiric or subsequent antifungal therapy, the length of antifungal therapy, the removal of central access, and recurrence of fungal infection infections did not adversely impact survival [8].

To decrease the risk of invasive candidiasis in transplant recipients' prophylaxis is recommended. Intestinal transplant recipients are at high risk for candidiasis if they are colonized with *Candida*; if underwent choledocho-jejunostomy anastomosis, re-transplantation, or early reintervention after transplantation; if they develop graft dysfunction, rejection, or renal failure; or if they receive more than 40 units of blood products [10, 27]. The recent AST guidelines recommend prophylaxis for a minimum of 4 weeks until the anastomosis has completely healed, and rejection is not present [10]. However, in my opinion, a more tailored approach is warranted, taking into consideration individual-risk factors (for *Candida* and other molds) should be taken in selection the antifungal agent and the duration of prophylaxis; such prolonged antifungal exposure would lead to emergence of resistance, and may negatively impact infections that develop after 1 month. Bowel decontamination to reduce invasive candidiasis does not seem to positively impact early infections after transplantation [10], mainly because early infections are driven by the surgical procedures (i.e., bowel perforation, anastomosis leak) and late infections are due to the presence of central venous catheters or new procedures.

Cryptococcosis

Cryptococcosis is the third most common IFI in solid organ transplant recipients, but it has been rarely reported in intestinal transplant recipients [2]. Most of the epidemiological and clinical data regarding cryptococcosis in small bowl transplantation is extrapolated from other allografts. Most infections in transplant recipients are caused by *C. neoformans*, with *C. gattii* complex identified mainly in the Pacific Northwest region in the USA and Canada [10]. *Cryptococcus* either reactivates after transplantation from a latent infection, or it is acquired as primary infection [10]. Cryptococcal infections are diagnosed usually 16–21 months after transplantation [1, 28]. Donor-derived infections are rare but can have devastating complications. Donor-derived infections should be suspected when cryptococcal infections are diagnosed early (< 30 days) after transplantation, especially if more than one recipient from the same donor is infected. It is described that older age, diabetes, the use of T-cell-depleting antibodies (antithymocyte globulin, alemtuzumab), and corticosteroids increases the risk of cryptococcal infection in transplant recipients.

The clinical presentation is usually insidious, subacute, or chronic. Patients with pulmonary infections can be asymptomatic or present with nonspecific symptoms consistent with pneumonia (fever, chills, cough, malaise, night sweats, chest pain, shortness of breath). Skin involvement presents as cellulitis, nodular, or ulcerative lesions and is usually associated with central nervous system disease. Patients with meningitis or meningoencephalitis present with headache, lethargy, malaise, personality changes, memory loss, confusion, and sometimes fever [28]. Most cases of cryptococcosis in transplant recipients have central nervous system involvement (up to 75%), up to 39% have pulmonary involvement, and about one-third have with fungemia [2, 29, 30].

Serum cryptococcal antigen is a rapid diagnostic tool, but it may be negative with low disease burden or only pulmonary disease [31]. Once the diagnosis of cryptococcosis

is made, the extent of the disease needs to be evaluated to determine the antifungal regimen and the duration of therapy. All patients with positive *Cryptococcus* antigen in the blood or fungemia should undergo lumbar puncture to assess for central nervous system involvement. Brain imaging should be done prior to lumbar puncture to assess for hydrocephalus and cryptococcomas. Since up to 70% of patients with central nervous system involvement have elevated intracranial pressure, it is important to assess the opening pressure when performing the lumbar puncture and to decrease the intracranial pressure by 25–50% if it is high [28]. *Cryptococcus* can also be detected in the bronchoalveolar specimens or from tissue biopsy specimens (lung, liver, prostate, skin, kidney) using Gomori methenamine silver, periodic acid-Schiff, or mucicarmine staining. If the organism is grown from CSF, urine, and blood cultures, the spp. can be identified, and susceptibility testing can be performed, especially in patients who develop infection on azole prophylaxis, who are infected with *C. gattii* or fail primary therapy [28]. Chest imaging might show pulmonary infiltrates or nodules and it is useful to follow the imaging for response to treatment.

Gradual decrease in immunosuppression should be done in combination with antifungal therapy. The preferred treatment for central nervous system infection, disseminated disease, and moderate-to-severe pulmonary disease consists of liposomal amphotericin B (3–4 mg/kg/day) or amphotericin B lipid complex (5 mg/kg/day) plus 5-flucytosine (100 mg/kg/day) [28]. The overall mortality is about 14%, but it increases up to 50% in patients with central nervous system involvement [29].

Aspergillosis, Mucormycosis, and Other Mold Infections

Aspergillosis

Aspergillosis represents a minority of fungal infections in intestinal transplant recipients [2, 32, 33]. PATH Alliance registry reported on 280 SOT recipients with invasive aspergillosis; among these, 13 (4.6%) occurred in intestinal transplant recipients with *Aspergillus fumigatus* being the most common species isolated [34]. The most important risk factors for invasive aspergillosis infections are the net state of immunosuppression related to induction therapy with T-cell-depleting antibodies, CMV infection, neutropenia, renal failure, prolonged ICU stay, and re-transplantation [27, 32–34]. The lung is the most common site of infection but with angioinvasion and the possibility of dissemination any organ system can be involved, especially the central nervous system [35]. Fungal infective endocarditis is a rare entity in solid organ transplant recipients but carries a high mortality, with *Aspergillus* spp. being a leading pathogen [36].

Diagnostic criteria and definitions (possible, probable, proven IFI) have been developed to try to simplify a complex diagnosis which requires host, clinical, and mycological elements [37]. Imaging findings vary; the classic findings are a pulmonary nodule with the halo sign (central consolidation with surrounding ground glass opacities due to local hemorrhage from angioinvasion). Other presentations including peri-bronchial infiltrates, mass-like lesions, and bronchopneumonia cab also be observed [32, 38]. Serum galactomannan has acceptable specificity (84%) but low sensitivity (22%) in solid organ transplant recipients and the test performs better in hematologic malignancy and stem cell transplant recipients [39]. Using a cut-off index value of more than 1 in BAL specimens improved the sensitivity of galactomannan to 67% and specificity to 98% [40]. The utility of the 1,3-β-D-glucan assay in SOT has not been fully defined [32]. Isolation of *Aspergillus* from a BAL specimen does not equate to invasive disease but does indicate a risk for development of invasive aspergillosis [32, 38]. Isolation from a sterile site such as blood, CNS, tissue, or histopathological evidence of hyphal invasion with or without angioinvasion establishes the definitive diagnosis [37]. *Aspergillus* spp. PCR can be performed on blood, BAL, and CSF and a meta-analysis demonstrated a sensitivity of 84% and specificity of 76% to detect invasive aspergillosis [41]. Most centers have incorporated PCR testing in conjunction with serologic testing as standard while histopathologic diagnosis remains the gold standard. A lateral flow device, which has been studied in SOT recipients, is under development that detects a protein that is produced by growing *Aspergillus* species and has similar performance characteristics to galactomannan and PCR [42].

Voriconazole is the drug of choice to treat any form of *Aspergillus* disease, with amphotericin B, posaconazole, isavuconazole, and micafungin as alternative agents; surgical debridement may be necessary as an adjunct in certain clinical syndromes [43]. Both posaconazole and isavuconazole have been shown to be as effective as voriconazole in the treatment of invasive aspergillosis but because of greater clinical experience and more data, voriconazole remains first line. Voriconazole has penetration to the CNS and eye which is an important consideration in disseminated disease. Combination therapy using triazole plus echinocandin or triazole plus lipid AmB formulations is not routinely recommended but is common clinical practice [44, 45]. Combination therapy is often considered as a salvage therapy, in those with more severe disease and as bridging until voriconazole levels become therapeutic. There is no evidence to recommend antifungal prophylaxis for *Aspergillus* in intestinal transplantation recipients.

Several newer antifungal drugs are in development to help overcome toxicity issues, drug-drug interactions, and drug resistance. Azole-resistant *Aspergillus* (*A. lentulus*, *A. calidoustus*) have emerged as potential pathogens with poor outcomes, one study of stem cell transplant recipients and SOT recipients reporting an overall mortality of 66% and attributable mortality of 30% [46]. Novel echinocandins, rezafungin and ibrexafungerp; fosmanogepix, a novel glycosylphosphatidylinositol inhibitor; and olorofim, a novel orotomide resulting in inhibition of fungal pyrimidine synthesis plus many others in development will hopefully play a role in treating resistant infections [47].

Nanomaterials (metallic and polymer-based nanoparticles) are drug delivery systems that have been developed as an adjunct to antifungal medications to help to overcome anti-fungal resistance and treat IFIs. They have less adverse effects, improve antifungal solubility, and do not generate resistance and have intrinsic antifungal activity. Several polymeric nanoparticles have been explored as carries for liposomal AmB and have shown better drug delivery to the site of infection [26, 48]. This remains an area in development.

Mucormycosis

Mucormycosis is a rare infectious complication in immunocompromised hosts and carries a mortality of 40–50% [49]. Risk factors for zygomycosis in SOT recipients include retransplant, diabetes mellitus, renal failure, prior voriconazole, or caspofungin use [50]. Cases are observed within 3–6 months post-transplant [51]. Most common clinical presentations include pulmonary involvement, rhino-cerebral, and skin but disseminated disease can also be seen. Diagnosis is histopathologic demonstrating aseptate hyphal elements in the tissue specimen. Cultures can be negative despite demonstration of hyphal elements on tissue staining [51]. Fungal serologic markers have no role in mucormycosis diagnosis. Prompt initiation of empiric antifungal therapy is imperative as well as surgical debridement of affected areas, still mortality remains high [51]. There are no reports of mucormycosis among intestinal transplant recipients in TRANSNET consortium or PATH Alliance registry [2, 34].

Other Molds

Fusarium, *Scedosporium*, and *Lomentospora* are non-*Aspergillus* molds that are being increasingly recognized in the SOT recipients. TRANSNET data reports 8.5% of total IFIs as other or unspecified mold, though no cases reported in intestinal transplant recipients [2]. Risk factors for disease include neutropenia, T-cell depletion, and previous IFI [51]. Pulmonary disease, disseminated disease, and skin involvement are common clinical manifestations and blood cultures may also be positive [51]. Demonstration of septate hyphal elements (similar to *Aspergillus*) on histopathological examination remains mainstay of diagnosis. Treatment depends on the site of infection, but generally surgical debridement is necessary for source control in localized disease with adjunctive antifungals of which voriconazole is first line [51]. Mortality remains very high.

Endemic Fungal Infections

Endemic fungal infections are not a common infection in solid organ transplant recipients, with < 5% incidence [52, 53]. The infections that are diagnosed very early after transplantation, usually weeks after transplantation, are donor derived infections, mainly histoplasmosis or coccidioidomycosis [52]. Histoplasmosis should be in the differential diagnosis when granulomas or organ lesions are found at the time of harvesting. Routine donor testing is not recommended for histoplasmosis, but it is recommended for donors from endemic areas for coccidioidomycosis. The donors should be screened with serology, complement fixation, and immunodiffusion for coccidioidomycosis [54, 55].

Histoplasmosis

Histoplasmosis is the most common endemic mycosis in the USA. Histoplasmosis in transplant recipients is a reactivation of a prior infection in the setting of immunosuppression or new infection after inhalation of the mold from the environment (i.e., dust from construction, farming, bat exposure in caves, chicken coops) [55]. However, very few cases have been reported in pediatric transplant recipients. Clinical manifestations depend on the size of the inoculum and the state of immunosuppression and range from self-limited illness, pulmonary involvement to disseminated disease [55]. The most common form of presentation is progressive disseminated infection frequently associated with thrombotic microangiopathy, hemophagocytic lymphohistiocytosis, and adrenal dysfunction [55–59].

In clinical practice, urine, blood, BAL, or CSF *Histoplasma* antigen is the most commonly used diagnostic method. Urine *Histoplasma* antigen has 73% sensitivity in patients with isolated pulmonary histoplasmosis and 97% in those with disseminated disease [53, 55, 60, 61]. Serum *Histoplasma* antigen has a sensitivity of 59% for isolated pulmonary infection and 89% for disseminated infection [55, 56]. The sensitivity increases when combining urine and serum antigen testing [55]. Sensitivity of the BAL antigen is 93% with a 99% negative predictive value for pulmonary histoplasmosis [55, 60]. *Histoplasma* antigen test has cross-reactivity with *Blastomyces*, *Coccidioides* spp., *Paracoccidioides brasiliensis*, *Talaromyces marneffei*, and *Sporothrix schenckii* [55, 56, 60]. Serum (1,3)-β-D-glucan assay does

not have any role in diagnosing histoplasmosis or any other endemic mycosis. Histopathologic examination of liver, lung, skin, lymph nodes, or bone marrow biopsy can demonstrate the presence of granulomas; hematoxylin and eosin stains or Wright-Giemsa stains can visualize *Histoplasma* in blood or bone marrow samples, while GMS or PAS stains can be used for the biopsy from other tissues [55, 62].

The preferred treatment for mild to moderate infection is itraconazole at 200 mg twice daily for at least 12 months. For moderately severe and for severe infections, the initial therapy should always be amphotericin or an amphotericin formulation for the patient is clinically stable, followed by therapy with itraconazole (200 mg twice daily) for minimum 12 months. For severe infections, a reduction in immunosuppression is recommended [55]. The role of voriconazole, posaconazole, and isavuconazole in the treatment of histoplasmosis is not well defined, but there is data showing treatment success with these agents. Mortality was reported to be 15% in TRANSNET [52].

Coccidioidomycosis

Coccidioidomycosis, also known Valley fever, is caused by even a small inoculum of *Coccidioides immitis* and *Coccidioides posadasii* [55]. The incidence of coccidioidomycosis has been reported up to 6.9% in endemic regions, with most of the infections diagnosed within the first year after transplant. The infections diagnosed within the first month after transplantation are associated with high mortality and should raise the suspicion for donor-derived infection [52, 55].

The clinical presentation can range from asymptomatic to mild, self-limited disease (including pneumonia), to disseminated disease (severe pneumonia, cavitary lung lesions, ARDS, meningoencephalitis, liver, spleen, kidney, skin, joints involvement) [55, 63]. Eosinophilia is common (up to 50% of patients), and while it is not diagnostic its presence might raise suspicion for coccidioidomycosis [55]. *Coccidioides* grows faster (5–7 days) in culture than other endemic mycoses. Histopathology can identify the characteristic spherule containing endospores, aiding in rapid diagnosis. The sensitivity of enzyme immunoassays, immunodiffusion-based assays, and complement-fixing anti-coccidioidal antibodies in immunocompromised patients is low (21–56%), but it improves when with serial testing and combination of serologic testing [55, 64]. *Coccidioides* PCR testing is increasing in availability and has high sensitivity and specificity in respiratory and CSF specimens [55].

For mild-to-moderate pulmonary coccidioidomycosis, treatment with fluconazole 400 mg/day is recommended. For severe or rapidly progressive acute pulmonary disease or disseminated coccidioidomycosis, an amphotericin formulation is recommended as induction therapy, followed by fluconazole for a total of 6–12 months of treatment. For meningeal coccidioidomycosis, fluconazole (400–1200 mg/day) is recommended in conjunction with serial lumbar punctures. Lifelong azole suppression is indicated since the risk of recurrent infection is substantial and higher than with the other endemic mycoses [55, 63]. There is less experience with voriconazole, posaconazole, and isavuconazole in the treatment of coccidioidomycosis.

Blastomycosis

Blastomycosis is caused by 2 distinct species: *B. dermatitidis* and *Blastomyces gilchristii* [63]. Blastomycosis is an extremely uncommon infection in transplant recipients, with time to infection ranging from 1 week to 20 years post-transplant [55]. Blastomyces donor-derived infection has not been documented [52]. The infections can be asymptomatic; of the symptomatic cases, most common clinical presentation is pneumonia with or without extra-pulmonary manifestations (skin, lytic osteoarticular lesions, prostatitis, epididymitis, reticuloendothelial system involvement, meningitis, and brain abscesses) [55, 63]. Compared with other endemic mycoses, *Blastomyces* causes more severe pulmonary disease, and it is associated with a higher mortality [2, 63].

Rapid diagnosis of blastomycosis is based on yeast visualization in bronchoalveolar lavage fluid and tissue [55, 63]. In respiratory specimens, KOH or calcofluor white wet preparation can rapidly detect *Blastomyces* [55]. Histopathology can demonstrate micro-abscesses and noncaseating granulomas, with positive PAS or methenamine silver stain for the yeast forms. Gold standard for diagnosis of blastomycosis is made by culture of the respiratory and tissue specimens, but the growth is slow (2–4 weeks) [55]. The utility of serum, urine, BAL fluid, and CSF *Blastomyces* antigen is limited by the sensitivity (62–83%) and high cross-reactivity with other endemic fungi [55, 65].

For severe pulmonary or disseminated infections, amphotericin formulations are the first-line therapy. For infections of the central nervous system, amphotericin formulations should be administered for 4–6 weeks, in comparison to 1–2 weeks for severe pulmonary infections [55]. Itraconazole is the preferred step-down drug for pulmonary infections while voriconazole is preferred for central nervous system infections, given the limited penetration of itraconazole (< 1%) [55, 66]. In mild localized infections, oral itraconazole may be given as initial therapy with close clinical monitoring [55]. As with other endemic fungal infections, voriconazole, posaconazole, and isavuconazole are emerging treatments for blastomycosis.

Conclusion

The data on invasive fungal infections in intestinal transplant recipients is limited to single-center experiences, case reports, and case series. Furthermore, these patients are excluded from participation in clinical trials. Knowledge of IFIs in other solid organ allografts is extrapolated and helps guide management of IFIs in intestinal transplant recipients. This remains an area where more research is needed to further understand the host factors specific to intestinal transplant recipients and how the fungal factors interplay with the host. The promising development of nanotechnology as a new drug delivery system could serve as a potential alternative to prevent toxicity and development of fungal resistance and novel antifungal agents in the pipeline provide some promise for the treatment of these challenging infections.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national institutional guidelines).

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