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Invasive Aspergillosis in solid-organ transplant recipients:
Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Shahid Husain1 | Jose F. Camargo2 on behalf of the AST Infectious Diseases Community of Practice

1Division of Infectious Diseases, Multi-Organ Transplant Unit, University Health Network, University of Toronto, Toronto, Ontario, Canada
2Department of Medicine, Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami, Florida

Correspondence
Shahid Husain, Toronto General Hospital, Toronto, ON, Canada.
Email: shahid.husain@uhn.ca

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Abstract
These updated AST-IDCOP guidelines provide information on epidemiology, diagnosis, and management of Aspergillus after organ transplantation. Aspergillus is the most common invasive mold infection in solid-organ transplant (SOT) recipients, and it is the most common invasive fungal infection among lung transplant recipients. Time from transplant to diagnosis of invasive aspergillosis (IA) is variable, but most cases present within the first year post-transplant, with shortest time to onset among liver and heart transplant recipients. The overall 12-week mortality of IA in SOT exceeds 20%; prognosis is worse among those with central nervous system involvement or disseminated disease. Bronchoalveolar lavage galactomannan is preferred for the diagnosis of IA in lung and non-lung transplant recipients, in combination with other diagnostic modalities (eg, chest CT scan, culture). Voriconazole remains the drug of choice to treat IA, with isavuconazole and lipid formulations of amphotericin B regarded as alternative agents. The role of combination antifungals for primary therapy of IA remains controversial. Either universal prophylaxis or preemptive therapy is recommended in lung transplant recipients, whereas targeted prophylaxis is favored in liver and heart transplant recipients. In these guidelines, we also discuss newer antifungals and diagnostic tests, antifungal susceptibility testing, and special patient populations.

1 | ETIOLOGY

Aspergillus is a ubiquitous environmental fungus that causes potentially lethal infections in immunocompromised hosts.1,2 Inhalation is the most common route of entry of Aspergillus spores.1,2 A fumigatus is by far the most common species isolated (73%), and most cases (74%-78%) of invasive aspergillosis (IA) are limited to the lungs. Systemic antifungal agents

2 | EPIDEMIOLOGY AND RISK FACTORS

2.1 | All organ transplants

In a case-controlled study of the RESITRA (Spanish Network of Infection in Transplantation) cohort, which included patients from 16 transplant centers with a follow-up of 18 months, there were 156 cases of proven or probable IA diagnosed overall. Risk factors for the development of IA within 3 months post-transplant included
the following: use of vasoactive agents, prolonged intensive care unit (ICU) stay, post-transplantation renal failure requiring hemodialysis, cytomegalovirus (CMV) disease, or one episode of bacterial infection. Older age, renal failure, CMV disease, bacterial infection, chronic graft rejection, and immunosuppressive-related neoplasm were independent risk factors for IA 3 months post-transplantation6 (Table 1).

### 2.2 Liver transplant recipients

Most of the epidemiological data on IA in liver transplant recipients are from 1990s, where incidence rates range from 1% to 9.2%.7,10 However, two prospective studies noted an incidence rate of <1%.11,12 Among pediatric liver transplant recipients, the reported incidence of IA is 0.5%.13 Well-characterized risk factors for IA after liver transplantation include CMV infection, requirement of dialysis, and re-transplantation.14 In the European study, CMV infection conferred a sixfold increase in the risk of IA after 100 days post-transplant.15 Another study noted a MELD score (model for end-stage liver disease) greater than 30 was associated with increased risk of invasive fungal infection (IFI).16 Liver re-transplantation has been shown to confer a 30-fold higher risk while renal failure is associated with a 25-fold greater risk and as such, are the most significant risk factors for IA in liver recipients in the early period6,15,17,18. Other factors associated with IA in living donor liver transplant recipients include transplantation for fulminant hepatic failure, CMV infection, and prolonged ICU stay.19

Traditionally, IA had occurred earlier in liver transplant recipients, with time to presentation ranging up to 17 days.20,21 In more recent cohort studies, the median time to the onset of invasive mold infection or IA is now >100 days.5,12,14

Liver transplant recipients have the highest rate of disseminated disease with invasive mold infection (55%), which carries a mortality rate of 64%.5 Requirement of dialysis and CMV infection are independent predictors of mortality in solid-organ-transplant (SOT) recipients (including liver transplant recipients) with IA.22 Mortality rates remain high in patients who develop IA after liver re-transplantation (82%), particularly in those undergoing re-transplantation more than 30 days after primary transplantation (100%).22

### 2.3 Renal transplant recipients

IA has been reported in 0.7%-4% of renal transplant recipients.7,8,23-28 In a prospective study, the incidence of IA in kidney
transplant recipients was reported to be 0.3%. In a multinational case-control study, the overall mortality among early cases of IA was 61%, and 25% of living recipients experienced graft loss. Pre-transplant diagnosis of chronic obstructive pulmonary disease (COPD) (odds ratio [OR]: 9.96; \( P = 0.04 \)) and delayed graft function (OR: 3.4; \( P = 0.04 \)), bacterial bloodstream infection (OR: 18.8; \( P = 0.047 \)), and acute graft rejection (OR: 40.7; \( P = 0.003 \)) within the 3 months prior to the diagnosis of invasive pulmonary aspergillosis (IPA) were identified as independent risk factors for early IA (Table 1). Previous occurrence of post-transplant complications attributed to over-immunosuppression (eg, pneumonia, TB, CMV, PTLD) was identified as an independent risk factor for late IPA (OR: 19.3; 95% CI: 2.1-179; \( P = 0.009 \)). In previous studies, high doses (>3 g of methylprednisolone) or prolonged duration of corticosteroids, and graft failure requiring hemodialysis have been shown to be risk factors for IA after renal transplantation.

2.4 | Lung transplant recipients

The overall incidence of IA in lung transplant patients ranges from 4% to 23%. In a US multicenter study, the incidence rate of IFI was 8.4% per year. Of these, 63% were Aspergillus infections. Other studies have noted higher prevalence of Aspergillus infection in lung transplant recipients. In another global retrospective study of 900 lung transplant recipients, the rate of development of the first episode was 29.6 patients per 1,000 person-years. IA occurred at a median of 7.7 months post-transplantation. Among pediatric lung transplant patients, the reported incidence of IA is 5%. Risk factors that have traditionally conferred an increased risk of IA in lung transplant recipients are as follows: ischemia at the bronchial anastomosis or bronchus, receipt of a single-lung transplant, hypo-gammaglobulinemia, CMV infection, and pre-/post-transplant colonization of the airways with Aspergillus (Table 1).

Cystic fibrosis (CF) increases the risk of pre-transplant Aspergillus colonization. However, the risk of IA in lung transplant recipients with a diagnosis of CF has not yet been clearly documented. Respiratory viral infections have not been associated with IA.

In a multicenter study, risk factors for IA included the following: single-lung transplant (hazard ratio [HR]: 1.8, \( P = 0.02 \)), and post-transplant colonization with Aspergillus spp. within 1 year of transplantation (HR: 2.11, \( P = 0.003 \)). Pre-transplant Aspergillus spp. colonization, CMV infection and the presence of CF were not significant risk factors. In a study involving 93 CF patients, intraoperative positive Aspergillus culture from the bronchoalveolar lavage (BAL; OR: 4.4, \( P = 0.01 \)) and treatment for acute cellular rejection within 90 days after transplantation (OR: 3.5, \( P = 0.05 \)) were independent risk factors for IA. Pre-transplant colonization with Aspergillus did not contribute to risk. The lack of pre-transplant colonization as a significant risk factor for IA in various studies may be related to the widespread use of antifungal prophylaxis in CF patients undergoing transplantation.

The presence of obliterative bronchiolitis after transplantation as a risk factor for IA is not well determined.

2.5 | Heart transplant recipients

The incidence of IA in heart transplant recipient ranges from 1% to 14%. A prospective multicenter study from 15 transplant centers suggested that the cumulative incidence of IFI after heart transplantation was 3.4% per year, with Aspergillus accounting for 23%. Other studies have also reported the incidence from 0.53% to 4.8%. Among pediatric heart transplant patients, the reported incidence of IA is 0.3%. Risk factors for the development of IA include the following: isolation of Aspergillus fumigatus from BAL, re-operation, CMV disease, and post-transplant hemodialysis in the setting of outbreak, the existence of an episode of IA in any patient from the heart transplant program 2 months before or after heart transplantation, and airborne Aspergillus spores in the ICU.

Overall mortality in heart transplant recipients with IA at one year was 67% in one study from 2006. However, in recent years mortality has decreased to 38%.

3 | CLINICAL MANIFESTATIONS

The Transplant-Associated Infection Surveillance Network (TRANSNET) reported data on 227 patients with proven/probable IA, among 1063 SOT recipients between 2001 and 2006 with median time from transplant to IA diagnosis of 184 days. Among 246 cases of proven/probable IA in SOT recipients from the Prospective Antifungal Therapy (2004-2008 PATH Alliance) registry, the median time to diagnosis was 379 days. The time to onset was shorter among liver (109 days) and heart recipients (89 days); kidney (406 days), lung (486 days), and small bowel (516 days) recipients exhibited longer time to onset of infection. The Swiss Transplant Cohort Study (STCS: 2008-2014) reported shorter intervals between transplantation and IA among liver (18 days) and heart (11 days) recipients. Among pediatric SOT recipients, the median time from transplant to IA is 74 days (range: 19-129 days). The time to presentation in patients with donor-derived IA is variable. In a cluster of donor-derived Aspergillus infections, the kidney transplant recipients presented within 3 weeks, whereas the heart transplant recipient presented almost 6 months post-transplant. Donor-derived IA frequently originates at the graft site, might involve the vascular anastomosis, and almost invariably lead to early graft loss. Many reported cases of donor-derived Aspergillus have occurred in recipients from donors with history of immunosuppression, so clinical suspicion should be higher in...
that setting. Contaminated preservation fluid is another potential mode of transmission.58

Clinical manifestations of aspergillosis range from asymptomatic colonization to invasive presentations including sinusitis, tracheobronchitis, IPA, and empyema. In a majority of cases of IPA, the clinical symptoms are subtle with cough, pleuritic chest pain, or fever. Acute respiratory failure secondary to IPA is uncommon. Tracheobronchial aspergillosis (TBA) occurs almost exclusively in lung transplantation recipients affecting 4%-6% of patients,69,70 and it may lead to airway obstruction, bronchial ulcerations, and pseudomembrane formation. Bronchial anastomotic infection can lead to dehiscence,7 necessitating aggressive combined medical and surgical therapy.71

Sites of infection beyond the respiratory tract include the following: mediastinitis, the musculoskeletal system, thyroid, skin, rhinocerebral disease, ocular, organ specific, endocarditis, central nervous system (CNS), and disseminated disease forms,72 the latter ones associated with poor outcomes. Liver transplant recipients may be at particularly high risk for disseminated disease and CNS involvement.5,6 Disseminated disease (defined as extra-pulmonary disease, excluding sinus disease) occurred in 15% of the cases of the PATH Alliance®. The highest incidence of disseminated disease (55%) occurred in liver recipients.5 Urinary tract aspergillosis has been reported in association with transmission through the renal graft.65,66

The overall 12-week post-diagnosis survival among SOT patients with IA from the PATH Alliance® registry was 78%.6 Consistent with this, the overall 12-week mortality in the more contemporary Swiss cohort was 23%.55 The 12-month survival after infection for the 227 patients with IA from the TRANSNET was 59%.3 In the Swiss cohort, a diagnosis of IA was associated with lower 5-year survival compared to a control group of 210 SOT recipients without IA (mortality was 41% vs 14%, respectively; P < 0.001). Among IA cases from the TRANSNET, hepatic insufficiency (OR: 3.9, 95% CI: 1.3-12), malnutrition (OR: 2.3, 95% CI: 1.0-5.1), CNS disease (OR: 6.6, 95% CI: 1.4-30), and use of an amphotericin B (AmB) preparation as part of initial therapy (OR: 4.4, 95% CI: 2.1-9.1) were associated with increased risk of death.73 In the Swiss cohort,55 higher risk of death was reported among older patients (OR: 1.2, 95% CI: 1.0-1.5), patients with disseminated IA (OR: 36, 95% CI: 1.6-827) and, in the univariate analysis, among liver transplant recipients (OR: 32, 95% CI: 3.4-293).

4 DIAGNOSTIC STRATEGIES

The substantial delay in establishing an early diagnosis of IA remains a major impediment to its successful treatment. Cultures of respiratory tract secretions lack sensitivity, and Aspergillus isolates may only be detected in clinical samples in the later stages of the disease. Additionally, a positive culture with Aspergillus from respiratory tract samples is not always indicative of invasive disease. The significance of a positive culture from an airway sample also varies with the type of organ transplant. While isolation of Aspergillus spp. from the respiratory tract of liver transplant recipients has a high positive predictive value (PPV) for the subsequent development of IA (ranging from 41% to 72%), it is an infrequent event (~1.5%).7 However, in airway samples of lung transplant recipients, Aspergillus spp. can be detected in ~25%-30% of cases.14,41,74 While positive airway cultures have a low PPV for the diagnosis of IA in lung transplant recipients, they portend a higher risk for subsequent invasive infection.7,36 Isolation of Aspergillus spp. from an airway sample in lung transplant recipients warrants a bronchoscopic examination, in order to exclude the presence of tracheobronchitis, bronchial anastomotic infection (BAI), or invasive disease. Radiographic studies including computed tomography (CT) scan of chest may be non-revealing at this stage. In heart transplant recipients, the estimated PPV of culturing Aspergillus from respiratory tract samples for the diagnosis of IA is 60%-70%.58 In cases of A fumigatus, the PPV of recovering a fungal isolate for the diagnosis of IA was 78%-91%, whereas it was 0% for other fungal species.58 The isolation of A fumigatus from the sputum had a PPV of 50%-67% that increased to 88%-100% when the sample was a respiratory specimen other than the sputum, such as BAL or bronchial aspirate.58

4.1 Serum galactomannan

The utility of the serum galactomannan enzyme immunoassay (GM-EIA; Plateia Assay, Bio-Rad, Marnes-la-Coquette) test for early diagnosis of IA has been assessed in a limited number of studies in SOT recipients. In kidney transplant recipients, the reported sensitivity of serum GM was 58% in 27 cases of IA.75 Similarly, another multicenter study reported the positivity rate of 68% for serum GM.76 In liver transplant recipients using archived sera, the sensitivity of the test was 55.6% and the specificity was 93.9%.77 A prospective study in 154 liver transplant recipients documented a specificity of 98.5% for serum GM.78 In another prospective study, serum GM area under the curve was 0.77, showing good sensitivity but poor specificity.79

In lung transplant recipients, the serum GM test had a specificity of 95%, but a relatively low sensitivity (30%) for the diagnosis of IA.80 Although the test was able to detect the only case of disseminated IA, and 29% of the cases of pulmonary IA, it detected none of the cases of Aspergillus tracheobronchitis.80 A meta-analysis showed that the serum GM assay may have greater utility in hematopoietic stem cell transplant recipients than in SOT recipients, in whom the sensitivity and specificity of the test was 22% and 84%, respectively.81 In pediatric acute lymphocytic leukemia patients, screening with serum GM resulted in higher false positivity.82

4.2 BAL galactomannan

Sensitivity of the GM assay for the diagnosis of IA in SOT recipients may be improved by testing BAL fluid. Sensitivity of BAL GM ranged from 67% to 100% while the specificity for the diagnosis of IA has ranged from 89% to 93% in various studies in lung transplant recipients.83 Increasing the index cutoff value to 1.0 decreases the sensitivity and increases the specificity.84-87
False-positive GM tests have been documented 13% of liver recipients and 20% of lung transplant recipients. Liver transplant recipients with autoimmune liver disease, and those requiring dialysis, were significantly more likely to have false-positive serum GM tests, especially during early transplant period. The false-reactivity with the Aspergillus GM-EIA has been documented in 20% (14/70) of these patients. Most false-positive tests occurred in the early post-transplant period (ie, within 14 days of transplantation in 79% of the patients). Patients undergoing lung transplantation for CF and COPD were more likely to have positive tests in the early post-transplant period. Determination of pentraxin-3 levels (a biomarker of inflammation) in lung transplant recipients may aid in differentiating Aspergillus colonization from disease in lung transplant recipients with positive BAL GM. In lung transplant recipients, BAL GM was also noted to be positive with the isolation of other molds such as Fusarium, Paecilomyces and Penicillium spp. as well as other yeast, for example, Histoplasma and Chaetomium globosum and Cryptococcus. 

In pediatric patients with IA, sensitivity has ranged from 82% to 87% with specificity around 87%-93%, with OD index value of 0.59.

4.3 | (1-3)-β-D-Glucan

Beta-D-Glucan (BDG) is a non-specific marker of fungal infection found in cell wall of pathogenic fungi including molds, yeasts (eg, Candida), as well as Pneumocystis. However, it is notably absent in Mucorales, Cryptococcus and some Blastomycetes spp. The utility of (1-3)-β-D-Glucan for the diagnosis of IA has not been fully discerned. The two studies utilizing Fungitell® (Associates of Cape Cod, East Falmouth, MA) in liver transplant at the cutoff of 80 pg/mL reported the sensitivity and specificity of 58%-75% and 65%-83%, respectively. In lung transplant, recipient's sensitivity and specificity were noted to range from of 71% to 80% and 59% to 70%, respectively, for diagnosis of IFI.

4.4 | Aspergillus polymerase chain reaction (PCR)

PCR assays have been developed in order to amplify Aspergillus DNA. PCR is usually performed on serum and BAL samples; however, none of the tests have been cleared by the Food and Drug Administration (FDA). The overwhelming majority of the data have been derived from patients with hematological malignancies. A recent systemic review of EORTC/MSG criteria revealed that when incorporated, the sensitivities and specificities for diagnosing IA were 81.6% and 91.6% for GM-EIA, and 76.9% and 89.4% for BDG, respectively. Aspergillus PCR showed similar sensitivity and specificity (76.8%-88.0% and 75%-94.5%, respectively). It is, however, important to note that the detection of PCR in the respiratory sample is unable to differentiate between colonization and disease in cardiothoracic organ transplant recipients. It may also yield false-positive test results, due to the cross-reactivity with certain mold species (Penicillium) genetically homologous to Aspergillus. Moreover, PCR detects DNA from dead conidia or hyphae and thus might not be ideal for monitoring the efficacy of antifungal therapy.

It is difficult to interpret the data on sensitivity and specificity of the PCR test due to the non-standardization of samples used, extraction techniques, and primers used in the in studies. Overall, the pooled sensitivity of blood or serum PCR is 84% among studies with ≥1 positive results and 64% among studies with ≥2 positive results, with reported specificity of 95%.

Similar to GM-EIA, Aspergillus PCR performs better in BAL than in blood. In a systematic review of nine studies, sensitivity and specificity of Aspergillus PCR in BAL were 77% and 94%, respectively.

Recently, results have been reported from standardized PCR assays for Aspergillus spp.: the MycAssay Aspergillus, and the Viracor pan-Aspergillus PCR. The sensitivity and specificity of the MycAssay Aspergillus PCR (Myconostica Ltd., Manchester, UK) in the serum for diagnosis of IA, varied between 60% and 70% and 90% and 100%, respectively.

The MycAssay Aspergillus PCR in BAL samples yielded a sensitivity and specificity of 86% and 87%, respectively. However, there were only 3 heart transplant recipients who did not develop IA, and no lung transplant recipients were included in the study.

In a study of the performance of the Viracor pan-Aspergillus PCR (Lee’s Summit, USA) and the GM in 150 BAL samples among lung transplant recipients for the diagnosis of IA, the test had a sensitivity and specificity of 100 and 88%, respectively. Compared to the BAL GM (at a cutoff of 0.5), the Viracor pan-Aspergillus PCR was more sensitive (100% vs 93%) for detection of invasive disease; however, among lung transplant recipients with Aspergillus colonization, the BAL GM was more specific than the Viracor pan-Aspergillus PCR (92% vs 50%).

Pan-fungal PCR has not been specifically studied in pediatric SOT recipients. However, in children with hematological malignancy the sensitivity of (1-3)-β-D-Glucan was 88% with specificity of 59.5%. Similarly, pan-fungal PCR had sensitivity of 89% and specificity of 69.2%.

AsperGenius (Pathonostics, Maastricht, The Netherlands) is a newer multiplex real-time PCR Aspergillus detection assay that can also detect azole resistance in A fumigatus. It has been assessed in hematological malignancy with sensitivity and specificity of 79% and 100%, respectively. However, no data exist in SOT recipients.

4.5 | Newer tests

The “lateral flow device” is an immunochromatographic assay that uses JF5, a monoclonal antibody that binds to an extracellular glycoprotein secreted during active growth of Aspergillus. It has been studied in SOT recipients, in both serum and BAL fluid. In a recent meta-analysis, it displayed a better performance in BAL, where pooled sensitivity and specificity for the diagnosis of proven/probable IA were reported as 86% and 93%, respectively. Studies on the use of this device in lung transplant recipients are lacking.

Another method utilizes exhaled air for detection of volatile organic compounds (VOCs) derived from various metabolic pathways.
In a study of hematological malignancies with IPA, the reported detection of α-trans-bergamotene, β-trans-bergamotene, a β-vatirenene-like sesquiterpene, or a trans-geranylacetone had a sensitivity and specificity of 94% and 93%, respectively.55

Another study reported the result of lateral flow dipstick assay using galactofuranose-specific monoclonal antibody (mAb476) for the diagnosis of IA in seventeen SOT recipients. Sensitivity and specificity for diagnosis of proven/probable IA in the overall cohort were 80% and 92%, respectively. In the non-cancer group, sensitivity and specificity were 64% and 93%, respectively. The antibody was not detectable in lung transplant recipients with bronchial airway diseases.112

Several antibodies have been used in the diagnosis of IA. Antibody response takes an average of 11 days to develop after onset of illness and may be detectable in 29%-100% of patients during the course of acute IA infection.113 However, most of these studies have been done in patients with hematological malignancy and chronic pulmonary aspergillosis.114–116 These findings are promising but need to be validated in larger scale studies before it can be widely applied.

### 4.6 Radiological diagnosis

There are limited studies evaluating the radiological manifestations of IA in SOT recipients. However, several studies have been performed in hematological malignancy patients.117–120

Most common manifestations on CT scan include ground-glass opacification, peri-bronchial consolidation, macronodules, and mass-like consolidation. The “classic” halo sign and air-crescent signs are uncommon in SOT.121,122 Among patients from the Swiss cohort, radiographic findings for angio-invasive IA, defined as nodular and/or widely applied.

Consolidation or mass (72%) was the most common CT finding of IPA in a cohort of 46 adult SOT recipients with proven/probable IA, followed by large nodules (59%) and ground-glass opacity (50%). Although clinical improvement in response to antifungal therapy is usually seen within 3-5 days, radiological improvement in IA can take up to 4-6 weeks of proper antifungal therapy.123

Other modalities such as high-resolution CT, pulmonary angiography (CTPA), and positron emission tomography CT (PET/CT) using fluorodeoxyglucose (FDG) uptake have also been reported to diagnose IPA in patients with hematological malignancy with varying sensitivity and specificity.124–127 Their role in lung transplant recipients is not defined.

#### 4.6.1 Recommendations

- Serum GM is not recommended to diagnose IA in SOT recipients (Strong; moderate)
- BAL GM is the preferred sampling method for the diagnosis of IPA in SOT recipients (Strong; high quality)
- BAL GM index value cutoff of ≥1.0 is preferred for the diagnosis of IA in lung and non-lung transplant recipients, in combination with other fungal diagnostic modalities (eg, chest CT scan, culture) (Strong; moderate)
- Standardized BAL *Aspergillus* PCR can be used in combination with other fungal diagnostic modalities (eg, chest CT scan, BAL GM, culture) for the diagnosis of IA. (Strong; low)
- Serum or BAL β-D-Glucan is not recommended for early screening and diagnosis of IA in lung and liver transplant recipients (Strong; low)

### 5 Treatment

Prompt initiation of antifungal therapy is critical for achieving optimal outcomes in SOT recipients with IA. The three main classes of antifungal agents in clinical use for treatment of IA are the polyenes, the triazoles, and the echinocandins (Table 2). Voriconazole is the drug of choice to treat IA,71 with isavuconazole and lipid formulations of AmB regarded as alternative agents. This recommendation is endorsed by both the Infectious Diseases Society of America (IDSA),71 and the European Society for Clinical Microbiology and Infectious Diseases.128 In patients with liver insufficiency, liposomal AmB (L-AmB) is usually the first therapeutic option. Posaconazole is mainly used in treatment of cases of IA that are refractory or intolerant to other first-line antifungal agents.71,129 The echinocandins are typically used alone or in combination for salvage therapy.71

Voriconazole remains the drug of choice for treatment of IA based on randomized controlled trial (RCT) data (only 14 SOT recipients enrolled) where it was associated with improved survival (71% vs 58%) compared with AmB deoxycholate (D-AmB) as primary treatment for IA (HR: 0.59, 95% CI: 0.40–0.88).130 Subsequent studies further demonstrated the efficacy of voriconazole for the treatment of IA in SOT with response rates of 50%-100%.131–133 Voriconazole has excellent CNS and eye penetration, important for cases of disseminated disease. Mean hospital length of stay in SOT recipients with IA in the current era is 30 days, and initial voriconazole use was associated with decreased length of stay.134 Intravitreal voriconazole has also been used in a lung transplant patient with *Aspergillus* endophthalmitis,135 and it is now recommended by IDSA as adjuvant to systemic voriconazole in this setting.71

A major development in antifungal therapy in recent years is the advent of isavuconazole, approved in March 2015. In the SECURE RCT conducted in hematological patients, isavuconazole was non-inferior to voriconazole for the primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi, as determined using all-cause mortality through day 42 as the primary endpoint (19% vs 20%, respectively).136 Isavuconazole was better tolerated than voriconazole with fewer visual, skin, or subcutaneous tissue, and hepatobiliary disorders.136 Isavuconazole was safely used in a lung transplant recipient who developed QT prolongation while on voriconazole.137

Due to poor absorption, which can effect CNI levels as well, itraconazole is considered suboptimal therapy for IA in the current era, but it might be used in resource-limited settings. Although not approved by the FDA for the treatment of IA, posaconazole has been...
### TABLE 2  Antifungal therapy for IA in adult organ transplant recipients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing (adult)</th>
<th>TDM</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Primary therapy</strong></td>
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<tr>
<td>Voriconazole</td>
<td>6 mg/kg IV/PO&lt;sup&gt;a&lt;/sup&gt; every 12 h for 1 d, followed by 4 mg/kg IV/PO every 12 h</td>
<td>Target trough level for treatment is &gt;1 mg/L&lt;sup&gt;179,180,184&lt;/sup&gt;. A level of 1-5.5 mg/L is considered adequate for most patients. A higher target (eg, 2-6 mg/L) should be used if there is disease with a poor prognosis (eg, CNS infection, bulky disease, multifocal infection); infections with pathogen with elevated MICs (eg, an MIC of 2 mg/L)&lt;sup&gt;128&lt;/sup&gt;. Once steady-state levels have been reached, repeat sampling is warranted every 3-5 d&lt;sup&gt;184&lt;/sup&gt; in unstable patients and when there is uncertainty about voriconazole concentrations. Measurement of serum trough concentration within 5-7 d.</td>
<td>Due to accumulation of the IV vehicle (cyclodextrin), the manufacturer recommends the use of oral voriconazole in patients with CrCl &lt;50 mL/min. In clinical practice, however, IV voriconazole has been safely administered to patients with different degrees of renal failure&lt;sup&gt;209,210&lt;/sup&gt;. Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended.</td>
</tr>
<tr>
<td><strong>Alternative therapies</strong></td>
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<tr>
<td>Isavuconazole</td>
<td>372 mg (isavuconazole 200 mg) IV/PO&lt;sup&gt;a&lt;/sup&gt; every 8 h for 6 doses, followed by 372 mg (isavuconazole 200 mg) IV/PO once daily</td>
<td>Trough level in the range of 2-3 mg/L (mean concentration range from phase II/III clinical studies) after day 5 suggests adequate drug exposure&lt;sup&gt;128&lt;/sup&gt;. No apparent relationship between exposure and efficacy to support routine TDM for isavuconazole&lt;sup&gt;183&lt;/sup&gt;. Has 130-h half-life—long clearance after discontinuation.</td>
<td>Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended. Dose adjustment is not required in renal impairment. Linear pharmacokinetics with low interpatient variability&lt;sup&gt;136&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Liposomal amphotericin B (AmBisome&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>3-5 mg/kg/d IV</td>
<td>There is currently insufficient evidence to support the routine use of TDM</td>
<td>Monitoring of electrolytes, and renal and hepatic function is recommended. Higher dosages are not more effective. Better tolerated than Abelcet&lt;sup&gt;®&lt;/sup&gt;.</td>
</tr>
<tr>
<td>Amphotericin B Lipid Complex (Abelcet&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>5 mg/kg/d IV</td>
<td>There is currently insufficient evidence to support the routine use of TDM</td>
<td>Monitoring of electrolytes, and renal and hepatic function is recommended. Higher dosages are not more effective.</td>
</tr>
<tr>
<td><strong>Other therapies</strong></td>
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<tr>
<td>Anidulafungin</td>
<td>200 mg IV on day 1 and 100 mg IV daily thereafter</td>
<td>There is currently insufficient evidence to support the routine use of TDM</td>
<td>It has been evaluated only as salvage therapy. Its role as single-agent therapy is controversial. It does not require dosage adjustments in patients with renal or hepatic dysfunction. Monitoring of hepatic function is recommended. Dose adjustment is not required in renal impairment. Drug interactions are less clinically important.</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>70 mg IV on day 1 and 50 mg IV/d thereafter</td>
<td>There is currently insufficient evidence to support the routine use of TDM</td>
<td>It has been evaluated only as salvage therapy. Its role as single-agent therapy is controversial. Monitoring of hepatic function is recommended. Dose adjustment is not required in renal impairment. Drug interactions are less clinically important.</td>
</tr>
<tr>
<td>Micafungin</td>
<td>100-150 mg IV daily</td>
<td>There is currently insufficient evidence to support the routine use of TDM</td>
<td>Monitoring of hepatic function is recommended. Non-FDA-approved use (for treatment of IA). Dose adjustment is not required in renal impairment. Drug interactions are less clinically important.</td>
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</tbody>
</table>

(Continues)
TABLE 2 (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing (adult)</th>
<th>TDM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole</td>
<td>300 mg PO (delayed-release tablets)/IV twice daily on day 1 followed by 300 mg PO (delayed-release tablets)/IV once daily on day 2 and thereafter</td>
<td>Target trough level for treatment is &gt;1 mg/L(^{184}) (preferably &gt;1.25 mg/L)</td>
<td>Although the delayed-release tablet can be taken without food, a high-fat meal (~70 g fat) can increase its serum concentration by ~1.5-fold(^{295})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>When using suspension 200 mg PO every 8 h or 400 mg PO every 12 h</td>
<td>Dose adjustment is not required in renal impairment. Dose after HD in patients on RRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Measurement of serum trough concentration within 7 d of initiation of therapy or following dose adjustment(^{184})</td>
<td>Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended Non-FDA-approved use (for treatment of IA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 mg PO 3 times daily for the first 3 d of therapy, followed by 200-400 PO mg/d</td>
<td>Target trough level is &gt;0.5-1 mg/L(^{178}) (^{a})Hydroxy-itraconazole is an active metabolite with antifungal activity similar to itraconazole. Assays that measure total (itraconazole + hydroxy-itraconazole) concentration of itraconazole are preferred Measurement of serum trough concentration within 5-7 d</td>
<td>Itraconazole capsules are poorly orally bioavailable, and absorption is both food- and acid-dependent. In contrast, the oral solution has better bioavailability and there is no significant food or acid effect Use with caution in patients with renal impairment; some recommend decreasing dose by 50% in CrCl &lt;10 mL/min Use should be considered only in mild cases intolerant to other therapies</td>
</tr>
</tbody>
</table>

CNI, calcineurin inhibitor; CrCL, creatinine clearance; FDA, US Food and Drug Administration; h, hours; HD, hemodialysis; IA, invasive aspergillosis; IV, intravenous; kg, kilograms; mg, milligrams; mTOR, mammalian target of rapamycin; PO, by mouth; RRT, renal replacement therapy; TDM, therapeutic drug monitoring.

\(^{a}\)IV loading favored in patients with CNS infection, bulky disease, and multifocal infection.

\(^{b}\)Agents listed here can be considered when first-line antifungals are contraindicated, or for salvage therapy in patients who are intolerant to, or whose infections are refractory to standard therapy. Echinocandins are frequently used as second agent in patients receiving combination therapy.

used as salvage therapy,\(^{71,138}\) In November 2013, a new formulation of posaconazole with improved pharmacokinetic (PK) profile, the posaconazole delayed-release tablet, was approved by the FDA. More than 90% of patients on 300 mg daily of this formulation achieve therapeutic levels,\(^{139}\) In a cohort of 24 lung transplant recipients, posaconazole trough levels were three times higher with the posaconazole tablets compared to the suspension.\(^{140}\) Posaconazole delayed-release tablet formulation was successfully used in the treatment of Aspergillus brain abscess.\(^{141}\) An intravenous (IV) formulation of posaconazole was subsequently approved in March 2014.

All three echinocandins have been used anecdotally as salvage therapy as single agent\(^{142}\) and in combination with other drugs in SOT recipients.\(^{143,144}\) However, caspofungin is currently the only approved echinocandin by the FDA as salvage therapy for the treatment of IA. Growing evidence supports the efficacy of caspofungin not only for salvage but also for first-line therapy.\(^{145}\) Anidulafungin has potent in vitro activity against Aspergillus species, and a good safety profile was demonstrated in a cohort of 86 SOT (mostly liver and lung) recipients receiving anidulafungin for prevention or treatment of IFI.\(^{143}\) A unique attribute of anidulafungin is that it is eliminated by non-enzymatic degradation in the blood and does not require dosage adjustments in patients with renal or hepatic dysfunction.\(^{146}\) Although anidulafungin has been studied in combination therapy,\(^{147}\) it has not been evaluated in monotherapy as primary or salvage therapy for IA. In a study of 225 patients (including 13 SOT), favorable responses were observed in 50% and 41% of patients treated with micafungin monotherapy as primary or salvage therapy, respectively, and a third of those who received micafungin in combination with other agents.\(^{148}\) All three echinocandins exhibit a high degree of binding to plasma proteins and distribute minimally to cerebrospinal fluid, urine, and the eye.

Among the polyenes, the use of conventional D-AmB is no longer recommended due to toxicity; liposomal formulations are less nephrotoxic and are preferred. Although both lipid formulations are effective in the treatment of IA, L-AmB is better tolerated than amphotericin B complex (ABLC).\(^{149,150}\) Both D-AmB and lipid formulations can be administered as adjunctive therapy via the inhaled route achieving a high concentration in the small airways with minimal systemic side effects. For the treatment of invasive TBA, adjunctive inhaled AmB in the setting of anastomotic endobronchial ischemia or ischemic reperfusion injury due to airway ischemia associated with lung transplant is recommended.\(^{71}\)

5.1 Combination therapy

The combination of antifungal drugs for primary therapy of IA is not routinely recommended by IDSA, but it may be considered in salvage therapy, particularly in cases of......
situations. When used, the combination of echinocandins with a triazole or lipid AmB formulations are preferred, except in cases of CNS infections. Due to poor tissue penetration of echinocandins into the brain and CSF, a combination of voriconazole and L-AmB might be favored in these cases.

Although to date its use has not been convincingly proven to be more effective than monotherapy, combination antifungal therapy is a commonly reported practice in the clinical setting, ranging from 28% to 71%. Combination therapy is used as first-line treatment in 47% and as salvage therapy in 80% of the liver transplant centers in North America. Primary combination therapy was used in 28% of cases in the TRANSNET. More than half of IA patients in the Swiss cohort and 38% of patients in the PATH Alliance registry received combination antifungal therapy. In a cohort of 116 liver transplants (1985-2013), combination antifungal regimens were used in 51% of the cases and combination therapy performed better than monotherapy. In the International Pediatric Fungal Network cohort, 54% pediatric IA patients received combination therapy with 2 or more concurrent agents sometime within the 12 weeks after diagnosis.

A prospective, multicenter study in SOT recipients compared the outcomes of 40 patients who received voriconazole plus caspofungin as primary therapy for IA, with those of 47 patients from an earlier cohort who received a lipid formulation of AmB as primary therapy. Overall survival at 90 days was 68% in the cases and 51% in the control group. Combination therapy was independently associated with reduced mortality in patients with renal failure and in those with Aspergillus infection, even when adjusted for other factors predictive of mortality in the study population. Patients in the combination therapy arm were more likely to develop an increase in calcineurin-inhibitor (CNI) agent level or gastrointestinal intolerance.

In a retrospective study that assessed the efficacy of voriconazole in the treatment of 192 fungal CNS infections, there was evidence for improved survival in 24/37 (65%) patients who received voriconazole with other antifungal agents over those who did not 74/155 (48%, P = 0.02).

In a meta-analysis of studies published through May 2013 (including 8 studies in SOT) comparing the combination of triazoles or lipid AmB plus an echinocandin to non-echinocandin monotherapy for IA, dual antifungal therapy was associated with significantly improved 12-week survival at the end of treatment over monotherapy when given as salvage therapy for IA. The survival benefit of combination therapy for primary treatment of IA was less pronounced.

More recently, Marr et al performed the first large RCT to compare combination therapy with voriconazole plus anidulafungin vs voriconazole alone in 454 hematological patients. Combination therapy was administered for 2-4 weeks, followed by continuation of voriconazole. There was a trend toward decreased mortality at 6 weeks (P = 0.09) in the combination therapy group. The safety profile of combination therapy was similar to that of voriconazole monotherapy; however, there was a slightly higher frequency of hepatobiliary adverse events in patients who received the combination.

Combination therapy should be considered in selected circumstances as follows: when Aspergillus species is unknown (7% of cases in TRANSNET and >50% of cases in report by International Pediatric Fungal Network) until susceptibility testing results are available; when a loading voriconazole dose is not given or its metabolism is expected to be highly influenced by concomitant medications until therapeutic serum trough levels are documented; in patients with disseminated or CNS disease; and as salvage therapy in those who do not respond to monotherapy.

5.2 | Duration of therapy
The optimal duration of therapy for IA depends upon the response to therapy, and the patient’s underlying disease(s) or immune status. Treatment is usually continued for 12 weeks; however, the precise duration of therapy should be guided by clinical response rather than an arbitrary total dose or duration. A reasonable course would be to continue therapy until all clinical and radiographic abnormalities have resolved, and until fungal biomarkers and cultures (if they can be readily obtained) no longer yield evidence of Aspergillus.

5.3 | Antifungal susceptibility testing and antifungal resistance
Clinical breakpoints for itraconazole, voriconazole, and posaconazole against Aspergillus spp. have been suggested by The Clinical & Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Epidemiologic cutoff values (ECV) by CLSI or ECOFF by EUCAST (ie, the upper minimum inhibitory concentration (MIC) value describing the wild type distribution) have been reported for isavuconazole and echinocandins. Isavuconazole and voriconazole exhibit reduced efficacy against isolates with MICs >16 μg/mL, but there is no clearly defined relationship between in vitro susceptibility and clinical outcomes in cases where the MIC is <16 μg/mL.

Among 288 Aspergillus isolates prospectively collected as part of the TRANSNET, the vast majority had MIC values at or below the ECV for caspofungin, micafungin, and anidulafungin. The voriconazole ECOFF for A fumigatus is 1 mg/L, but 2 mg/L for A flavus, A niger, and A nidulans. The EUCAST has defined voriconazole breakpoints for A fumigatus in the following way: susceptibility <1 and resistance >2 mg/L. Isolates with a MIC of 2 mg/L are classified as “intermediate.” The MIC distributions of posaconazole against a variety of Aspergillus species have been published. Depending on the species, the ECOFF is 0.25-0.5 mg/L; the posaconazole ECOFF for A fumigatus is 0.25 mg/L. Isavuconazole MICs have a high degree of correlation with voriconazole MICs. Thus, in patients with treatment failure attributed to suspected or confirmed triazole resistance, it might be prudent to switch antifungal class. The clinical utility of in vitro synergy testing, if any, remains to be established.

A fumigatus stricto sensu can acquire resistance to azoles by mutations in the drug target particularly after prolongedazole exposure.
with high (>50%) mortality. A recent surveillance study of fungal infection in SOT recipients in the United States showed a low rate of triazole resistance (1/181) in *A. fumigatus* isolates. A large global survey reported 3.2% of clinical *A. fumigatus* isolates to be azole resistant; however, in some European countries resistance rates are even higher. Targeted antifungal prophylaxis did not lead to cyp51A resistance mutations in a small cohort of lung transplant recipients.

Multiple members of the *Aspergillus* family exhibit high MICs to azoles such as *A. lentulus* (voriconazole MIC typically ≥2 mg/L), and *A. calidoustus* (MIC to azoles typically ≥4 mg/L). Although considered uncommon in the clinical setting (likely due to under-diagnosis), over 10% of the isolates associated with IA in transplant recipients from TRANSNET were found to be cryptic species, including *A. lentulus* and *A. calidoustus*. A *calidoustus* (A ustus complex) was recently reported as an emerging pathogen in lung transplant recipients receiving triazole prophylaxis. Outcomes for *A. calidoustus* and *A ustus* infections have been poor. It should be noted that mixed infections due to ≥2 *Aspergillus* species occurred in 12% of cases in the TRANSNET (almost exclusively among patients with pulmonary IA).

Certain *Aspergillus* species such as *A. terreus* are typically resistant to the polyenes but susceptible to voriconazole; only 5%-6% of IA in SOT recipients is due to *A. terreus*. Other *Aspergillus* spp. that can exhibit elevated MIC to AmB include *A. flavus*, *A. lentulus*, *A. calidoustus*, *A. alliaceus*, and *A nidulans*.

In patients with documented infection who do not respond to initial monotherapy, especially those suspected to have an azole-resistant *Aspergillus* isolate, antifungal resistance testing should be considered to guide treatment, in addition to combination therapy.

### 5.4 Therapeutic drug monitoring

Consistent with other current guidelines, AST-IDCOP recommends monitoring of serum trough drug levels for azole antifungal agents and for potentially interacting drugs such as cyclosporine, tacrolimus, and sirolimus. Therapeutic drug monitoring (TDM) is highly recommended in patients receiving azole antifungals under the following clinical conditions: concerns about gastrointestinal absorption; clinical or laboratory manifestations of toxicity; uncertain compliance with oral therapy; initiation or discontinuation of interacting drugs; cystic fibrosis; critically ill patients such as those with multiorgan failure or unstable hemodynamics requiring vaso-pressors or ECMO; or after alteration in therapy to a second-line agent after the initial failure of therapy. Except for such clinical scenarios, there is little role for monitoring serum drug levels in patients receiving IV formulations where expected bioavailability is 100%.

Two meta-analyses demonstrated that therapeutic voriconazole serum concentrations (>1 mg/L) are predictive of clinical success. In patients with disseminated or CNS aspergillosis, trough levels >2 mg/L (or even >3 mg/L) should be considered. Studies have suggested that a trough level/MIC ratio (when the MIC is estimated using CLSI methodology) of 2.5 is associated with a near-maximal probability of response. Active dosage adjustment to keep serum concentrations <5.5 mg/L prevents voriconazole-related toxicity. In patients receiving posaconazole, levels >1.0 mg/L should be targeted for treatment of IA. In a clinical study in which posaconazole was used as salvage therapy, an average concentration of 1.25 mg/L was necessary to obtain the highest favorable outcome rates.

In a prospective, observational study of lung transplant recipients (n = 93) receiving voriconazole prophylaxis, the median initial and subsequent serum voriconazole trough levels (n = 331) were 1.91 and 1.46 mg/L, respectively. The age of the patient directly correlated with initial troughs (*P* = 0.005). Patients that were ≥60 years old and CF patients were significantly more likely to have higher and lower initial troughs, respectively.

For isavuconazole, in the IA trial patients (n = 66) achieved mean ± SD (range) day 14 trough plasma concentration of 3.35 ± 1.81 mg/L (0.81-9.95 mg/L), with assumed steady-state concentrations (≥day 21) trough of 3.91 mg/L. A post hoc analysis of the SECURE trial found no relationship between isavuconazole exposure and either efficacy (including overall mortality and clinical response at the end of therapy) or safety endpoints. Consequently, there is no current clinical evidence for recommending routine TDM for isavuconazole. Although concentrations of isavuconazole will begin to change immediately after the dose or dosing interval is amended, the time to a new steady state is approximately 4 weeks, which makes TDM for this agent impractical from a clinical standpoint.

### 5.5 Special populations

#### 5.5.1 Pediatric patients

Data are limited on the safety and efficacy of triazoles and echinocandins in children. Due to the higher weight-adjusted clearance of voriconazole that is observed in pediatric patients, children require higher doses of voriconazole than adults (Table 3). A dose of 8 mg/kg of voriconazole IV in children approaches that for 4 mg/kg in adults. TDM is highly recommended.

#### 5.5.2 Intestinal transplant recipients

Among SOT recipients, intestinal/multivisceral transplantation (IMVT) carries the highest risk for IFI. Fungal infections are major causes of morbidity and mortality in IMVT recipients. In addition to inhalation, conidial ingestion is a potential port of entry for mold infections in IMVT recipients. It is conceivable that the same risk factors from liver transplant recipients confer risk of IA in this population as many IMVT procedures include livers. All the small bowel transplant recipients with IA from the PATH Alliance registry (n = 4) died within 12 weeks of diagnosis. Dissemination to CNS in IMVT is common. Successful outcomes in IMVT...
recipient patients with disseminated IA have been reported with the use of combination antifungal therapy.213,214

5.5.3 | Cystic fibrosis

Colonization of the airway by A fumigatus is common in CF patients (41%-58% in some series) with the highest prevalence among those aged 16 years and older,195-197 and high rates of azole-resistance.198 CF patients have a number of characteristics that can influence the pharmacokinetics of azole antifungal agents, including the following: (a) younger age; (b) relatively lower body mass index; (c) altered gastrointestinal function; (d) changes in the volume of distribution; and (e) increased creatinine clearance. In patients with CF having undergone transplantation, increased doses are necessary to maintain therapeutic concentrations compared to healthy subjects.199,200 Lower-than-expected serum isavuconazole levels were reported in a CF double-lung transplant recipient treated with the recommended dose.201

5.5.4 | Critically ill patients

Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients have been recently published.202 The PK profile of antifungals in the setting of extracorporeal membrane oxygenation (ECMO) is difficult to predict due to multiorgan dysfunction, the large volume of exogenous blood required to prime the circuit, and drug extraction by the circuit.203 Micafungin is extracted by the ECMO circuit especially when a hemofilter for patients with renal failure is present,203 whereas case reports indicate this might not be true for adinulafungin.204 Sub-therapeutic drug exposure has also been reported in some,205,206 but not all,207 ECMO patients treated with caspofungin. Voriconazole pharmacokinetics are highly variable in critically ill patients requiring ECMO support.207,208 Thus, it is highly recommended to monitor azole plasma levels in critically ill and ECMO patients to ensure efficacy and avoid toxicity. When unable to document adequate blood azole or echinocandin concentrations in ECMO patients, L-AmB might be indicated.

5.5.5 | Renal failure

Although significant accumulation of cyclodextrin can occur in hemodialysis patients treated with IV voriconazole, clinical significant adverse reactions associated with the accumulation of cyclodextrin in this setting have not been reported.209-211 The use of IV voriconazole in critically ill patients with pretreatment impaired renal function was not associated with renal or liver damage nor with an increase in ICU mortality.212 In another study, IV voriconazole was associated with less acute renal toxicity than D-AmB-containing regimens for treatment of IFI210 in patients with baseline renal insufficiency. Thus, several clinical reports indicate that IV voriconazole can be safely administered to patients with renal dysfunction. The PK profile of echinocandins does not seem to be affected by renal replacement therapy in critically ill patients.213,214

5.5.6 | Influenza co-infection

Influenza-associated aspergillosis is now increased reported in critically ill patients.215-220 The majority of cases are due to the A (H1N1) strain.216,220 At least 8 cases of influenza-associated aspergillosis have been reported in transplant patients220 including 2 kidney217 and 2 liver recipients.221 The median time between influenza and IA diagnoses is 6 days (range: 0-32)218,220; in addition to H1N1 infection, risk factors may include steroids and viral-induced lymphopenia.217,220 In a report of 57 cases, two thirds of the patients required mechanical ventilation and 21% required ECMO.220 High mortality rates were noted (46%-61%),216,218,220 primarily from respiratory and/or multiorgan failure. Prompt diagnosis and early antifungal therapy are recommended.217,220

5.6 | Complications during therapy

Decreasing immunosuppression should be done with caution in SOT patients with IFI including IA.222 In a cohort of 68 lung transplant recipients with proven/probable IA followed for 12 months, 5 (7%) patients developed an immune reconstitution syndrome-like entity, and three of these patients with immune reconstitution syndrome (IRS) died (2 deaths due to chronic rejection). The risk of IRS correlated significantly with change in CNI therapy. The odds for developing IRS were 29.5 (P = 0.002) with discontinuation and 9.9 (P = 0.046) with ≥ 50% reduction in calcineurin-inhibitor agent.222 Other risk factors for IRS included heart-lung transplantation, T-cell depletion, and disseminated IA.

A well-known side effect of itraconazole, voriconazole, and posaconazole is QT interval prolongation, especially when given in combination with other QT-prolonging agents. Unlike other triazole antifungals, isavuconazole can shorten the QT interval in a concentration-dependent manner, and it is contraindicated in patients with familial short QT syndrome.217 In a case series of adult patients treated for IFI, 24/26 (92%) patients experienced shortening of QT interval while on isavuconazole therapy.224

Patients on long-term triazole therapy should be monitored for neurological symptoms. A 10% incidence of peripheral neuropathy after an average of 4 months (range: 1-18 months) of antifungal therapy was reported in a cohort of 222 patients receiving triazole therapy for chronic aspergillosis. Risk was highest for itraconazole (17%) compared to voriconazole (9%) and posaconazole (3%).225 If peripheral neuropathy is suspected, diagnosis should include nerve conduction studies, exclusion of other causes, and consideration of dose reduction or cessation of therapy.

Skin cancer is another well-established complication of voriconazole therapy.226,227 In a cohort that included 900 lung transplant recipients, exposure to voriconazole alone (adjusted hazard ratio [aHR]: 2.4, 95% CI: 1.3-4.4) and exposure to voriconazole and other azole(s) (aHR: 3.5, 95% CI: 1.1-11) were associated with squamous cell carcinoma (SCC).227 However, the association of voriconazole with an
increased risk in SCC in vulnerable lung transplant recipients should be weighed carefully with its benefits in preventing or treating IFI. There is no established association between posaconazole or isavuconazole and risk of malignancy, and these are potential alternatives for patients who require prolonged antifungal therapy.

Another adverse consequence of long-term voriconazole therapy is periostitis, which is characterized by bony pain and diffuse periosteal ossification resulting from accumulation of fluoride levels. This condition typically resolves after discontinuation of voriconazole. Since this phenomenon does not appear to be a class effect, substitution to posaconazole or isavuconazole can be considered.228

### 5.7 Drug interactions of antifungal agents with immunosuppressants

Drug interactions must be carefully considered when treating transplant recipients with IA. Drug-drug interactions between triazole antifungal agents and immunosuppressants have been reviewed elsewhere.229,230 The triazole agents are potent inhibitors of the CYP3A4 isoenzymes and have the potential to increase the levels of CNI agents and mTOR inhibitors such as sirolimus.208 A 50-60% reduction in the dose of CNIs may be necessary with the concurrent use of voriconazole.208 The use of sirolimus is contraindicated in patients receiving voriconazole. In some reports, however, the two agents have been safely co-administered with sirolimus dose reduction by 75%-90%.231,232 When concurrently used with voriconazole, liquid formulation of sirolimus can be used for more accurate dosing.

Co-administration with isavuconazole increased the area under the concentration-time curves of tacrolimus, sirolimus, and cyclosporine by 125%, 84%, and 29%, respectively.233 In a study that evaluated the interaction between isavuconazole and tacrolimus among 55 SOT recipients, a 1.3-fold decrease in tacrolimus daily dose was required to maintain desired tacrolimus levels.234 After initial dose

### TABLE 3 Antifungal agents for potential use in children with IA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing (children)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>Children 2 to &lt;12 y (regardless of weight), and 12-14 y (&lt;50 kg)</td>
<td>Voriconazole, while only FDA approved for children 12 y and older, is the mainstay of pediatric aspergillosis treatment in all ages</td>
</tr>
<tr>
<td></td>
<td>9 mg/kg IV every 12 h for 2 doses on day 1, followed by 8 mg/kg every 12 h</td>
<td>In children, there is still considerable pharmacokinetic variability, but (pseudo)-linear pharmacokinetics are observed166</td>
</tr>
<tr>
<td></td>
<td>Oral suspension: 9 mg/kg every 12 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12-14 y (&gt;50kg) and ≥15 y (regardless of weight)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mg/kg IV every 12 h for 2 doses; followed by 4 mg/kg every 12 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral: 200-300 mg every 12 h or 3-4 mg/kg every 12 h</td>
<td></td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>No pediatric information available</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>1.0-1.5 mg/kg; infuse as a single dose over 2 h</td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B (Ambisome®)</td>
<td>3-5 mg/kg/d IV</td>
<td>Acceptable front-line therapy Monitoring of electrolytes, renal and hepatic function is recommended</td>
</tr>
<tr>
<td>Amphotericin B Lipid Complex (Abelcet®)</td>
<td>5 mg/kg/d IV</td>
<td>Higher dosages are not more effective Monitoring of electrolytes, renal and hepatic function is recommended</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Loading dose of 70 mg/m², followed by 50 mg/m² daily thereafter, not to exceed 70 mg</td>
<td>Not for CNS disease FDA approved for children 3 mo and older</td>
</tr>
<tr>
<td>Micafungin</td>
<td>2-3 mg/kg/d</td>
<td>Not for CNS disease FDA approved for children 4 mo and older.</td>
</tr>
<tr>
<td></td>
<td>Higher doses might be needed in infants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients &gt;40 kg use the adult dose (100 mg)</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>Loading dose of 1.5-3 mg/kg once, followed by 0.75-1.5 mg/kg/d</td>
<td>Not FDA approved for children Limited pediatric data; not for CNS disease</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Pediatric dosing has not yet been fully defined. See adult dosage for children 13 y and older</td>
<td>FDA approved for children ≥13 y for the PO formulations, and ≥18 y for the IV formulation Limited pediatric data</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>5-10 mg/kg PO divided into two doses</td>
<td>Mild infections in selected older individuals</td>
</tr>
</tbody>
</table>

See Table 2 for additional information on each agent. Adapted from: Recommended doses of parental and oral antifungal Drugs, and Drugs for Invasive and Other Serious Fungal Infections.71,187,296
reduction, adjustments in CNI dosing in patients receiving triazoles should be guided by TDM.

5.8 | Adjunctive therapies

Surgical excision or debridement remains an integral part of the management of IA for both diagnostic and therapeutic purposes. Specifically, surgery is indicated for a persistent or life-threatening hemoptysis, for lesions in the proximity of great vessels or pericardium, for sinonasal infections, for single cavitary lung lesions which progress despite adequate treatment, and for lesions invading the pericardium, endocardium, bone, subcutaneous, or thoracic tissue. Surgical resection is also indicated for intracranial abscesses depending upon the location, accessibility of the lesion, and neurologic sequelae.

Enhancement of the host’s immune status with immunomodulatory agents is an attractive therapeutic adjunct in the management of IA. Neutropenia (<500 cells/µL) has been associated with increased 12-week attributable mortality in patients with IA. Colony-stimulating factors (G-CSF or GM-CSF) stimulate proliferation and maturation of myeloid precursor cells and also augment neutrophil (and macrophage) function. G-CSF use in SOT recipients appears to be safe; however, there are no studies that have evaluated its efficacy as adjunctive to antifungal therapy specifically in these patients. In vitro studies and case reports have also demonstrated a potential role of interferon-γ (IFN-γ) against Aspergillus. However, the use of interferon-γ (IFN-γ) in SOT recipients is of concern given the risk of potential graft rejection.

5.9 | Key recommendations (Treatment of IA)

- Early initiation of antifungal therapy in patients with strongly suspected IA is warranted while a diagnostic evaluation is conducted (Strong; high).
- Voriconazole is the drug of choice to treat all forms of IA (Strong; high).
- Isavuconazole and lipid formulations of AmB, preferably L-AmB, can be considered as alternative agents (Strong; moderate).
- Posaconazole can be considered for salvage therapy in patients who fail or do not tolerate first-line antifungals (Strong; low).
- Primary therapy with an echinocandin is not recommended (Strong; low). However, echinocandins can be considered when other antifungals are contraindicated (Weak; low).
- Combination therapy can be considered in select cases such as in patients with disseminated or CNS disease (Weak; low).
- Inhaled AmB (in conjunction with systemic antifungal therapy) may be used in the setting of tracheobronchial aspergillosis associated with anastomotic endobronchial ischemia, or ischemic reperfusion injury due to airway ischemia associated with lung transplant (Weak; low).
- Duration of treatment should be guided by clinical and radiological response; most cases will require a minimum of 12 weeks, if tolerated (Strong; moderate).
- Secondary prophylaxis should be considered in patients with history of IA who undergo augmentation of immunosuppression (eg, T-cell depletion, high-dose steroids) and during episodes of prolonged neutropenia (eg, <500 cells/µL longer than 7 days) (Weak; low).
- Routine antifungal susceptibility is not recommended, but it can be considered for patients suspected to have an azole-resistant isolate and those who are unresponsive to antifungal agents (Weak; low).
- Antifungal TDM is recommended for all patients receiving voriconazole-based therapy for IA (Strong; moderate).
- Dosing of antifungals should be adjusted in coordination with a transplant pharmacist in special populations including pediatrics, CF, and ECMO/critically ill patients (Strong; low).
- Dose of CNI/mTOR inhibitor should be reduced (and increased) in coordination with the respective organ transplant subspecialist and a transplant pharmacist in patients starting (and completing), triazole therapy, respectively; and CNI/mTOR inhibitor levels monitored closely (Strong; moderate).
- Baseline and follow-up electrocardiogram to assess QT interval (for patients receiving triazoles other than isavuconazole) and regular skin examination (for patients receiving voriconazole) are indicated in patients receiving chronic azole therapy (Strong; high).
- Surgery and reduction of immunosuppression are important adjunctive components of management in selected patients (Strong; low).
- Colony-stimulating factors may be considered in neutropenic patients with IA (Strong; low).

6 | PREVENTION

6.1 | General measures

All transplant recipients should avoid activities that increase the exposure to Aspergillus conidia such as gardening, mulching, and raking leaves in the fall. If this cannot be avoided, personal protective equipment including shoes/boots, long pants, long-sleeved shirts, and more importantly mask and gloves should be used when handling materials such as soil, moss, or manure. Transplant recipients should also avoid construction areas or excavation sites, and wear an N95 respirator at all times in such areas to prevent inhalation of dust. Hand wash is also highly recommended after exposure to soil or dust. It is important to note that although these actions are recommended, they have not been proven to prevent aspergillosis.

6.2 | Liver transplant

At present, universal prophylaxis against IA is not routinely recommended in liver transplant recipients. A more rational approach is to target prophylaxis specifically for high-risk liver transplant recipients. It is to be noted, however, that the clinical risk factors are
derived from small, single-center, retrospective cohort studies in the earlier era. An optimal approach to the prevention of IA in these patients therefore has not yet been defined.

It is difficult to assess the efficacy of the antifungal prophylaxis strategies against IA in liver transplant recipients, as most of the prophylaxis were directed specifically against the prevention of Candida infections. Several meta-analyses of antifungal prophylactic trials in liver transplant recipients have documented a beneficial effect in decreasing the overall rate of fungal infection/colonization. However, this has come at the cost of increasing the emergence of non-albicans Candida spp. infections, without an overall benefit in mortality rate.255,256

In a meta-analysis, the mortality attributable to fungal infection was significantly reduced with the use of prophylaxis, without any reduction in the rate of IFI due to IA.257

The strategy of targeted vs universal prophylaxis with voriconazole was studied in 382 high-risk liver transplant recipients. Targeted prophylaxis was safe and effective at preventing IFIs, and reduced the number of patients exposed to antifungals. No difference in the rate of IFI was noted between universal vs targeted prophylaxis groups. It is to be noted that only one case of IA was noted among 145 liver transplant recipients who receive targeted prophylaxis. The median duration of therapy was 11 days.258 In another study of 174 high-risk liver transplant recipients who received voriconazole prophylaxis, no cases of IA were noted after 90 days of follow-up.259

Two randomized trials have assessed the effect of echinocandin prophylaxis. The first was a double-blind RCT of anidulafungin vs fluconazole for antifungal prophylaxis, in 200 high-risk liver transplant patients. The overall incidence of IFI was similar for the anidulafungin (5.1%) and the fluconazole groups (8.0%; OR: 0.61, 95% CI: 0.19–1.94, P = 0.40). However, anidulafungin prophylaxis was associated with a trend to less Aspergillus colonization or infection (3% vs 9%, P = 0.08). Both drugs were well-tolerated. Graft rejection, fungal-free survival, and mortality were similar for both groups. Median duration of therapy was 21 days.260

Since anidulafungin does not undergo hepatic metabolism, it has theoretical advantage above other echinocandins. However, in a study of treatment of IFI among patients with severe abnormal liver function, 62% of patients experienced greater than two times elevation of liver enzymes.261

The second study to assess the effect of echinocandin prophylaxis was an open-label RCT of 344 high-risk liver transplant recipients. Administration of 100 mg of micafungin was compared to standard of care (caspofungin, amphotericin B, or fluconazole). Clinical success rate at the end of prophylaxis was 98.6% in the micafungin group, in comparison with 99.3% in the standard of care group. However, there were three breakthrough infections with Aspergillus noted in the micafungin group. The median duration of therapy was 21 days.262

In another propensity score analysis of 195 high-risk liver transplant recipients, caspofungin use resulted in significant reduction of IA (absolute risk reduction: 0.06; 95% CI: 0.001–0.11; P = 0.04).263

Targeted antifungal prophylaxis using the lipid formulations of amphotericin B, in doses ranging from 1 to 5 mg/kg/d has been shown to be effective in observational studies.264,265

Data for risk factors and prophylaxis for aspergillosis in pediatric liver transplant recipients are lacking, and the following recommendations in adult liver transplant recipients should be extrapolated to pediatrics with caution.

6.2.1 | Recommendations

- Targeted prophylaxis in patients with any of the following high-risk factors is recommended (Strong; moderate).
  - Re-transplantation (second or third liver transplant).
  - Renal replacement therapy (hemodialysis or continuous venovenous dialysis) at the time of or within 7 days of transplantation.
  - Reoperation involving thoracic or intra-abdominal cavity, for example, exploratory laparotomy or any intrathoracic surgery.
  - Anidulafungin, micafungin or caspofungin in standard dose, or voriconazole is recommended for the use of targeted prophylaxis against IA in liver transplant recipients (Strong; high)
  - Targeted prophylaxis with a lipid formulation of amphotericin B in dosages ranging 3–5 mg/kg may be considered (Weak; moderate)
  - Targeted prophylaxis should be continued for 14–21 days (Strong; high)
  - Screening with serum GM and β-D-Glucan is not recommended for preemptive therapy (Weak; low)

6.3 | Lung transplant recipients

Like it is the case for other organs, the optimal Aspergillus prevention strategy in lung transplant recipients remains to be defined. Current practices of antifungal prophylaxis in lung transplant recipients are derived from non-randomized clinical trials of small sample size, single-center non-comparative case series, or case-control studies.31,268,269 In a meta-analysis of universal vs no antifungal prophylaxis in lung transplant recipients, 19 of 235 (8.1%) and 28 of 196 (14.3%) developed IA in the universal prophylaxis and no prophylaxis arms, respectively (RR: 0.36, 95% CI: 0.05–2.62). No significant reduction in IA or Aspergillus colonization with universal anti-Aspergillus prophylaxis was noted.276 Another meta-analysis, involving universal and targeted antifungal prophylaxis strategies, showed reduction in the rate IA in lung transplant recipients.277 Several studies have used a risk stratification strategy for antifungal prophylaxis using itraconazole, voriconazole, and posaconazole, with varying reported efficacy rates.278,279

Two studies have specifically evaluated preemptive therapy in this setting. In one study involving more than 300 lung transplant recipients, culture-directed therapy was effective in preventing subsequent development of IA. However, half of the cases of IA occurred in patients without pre-transplantation or post-transplantation airway colonization with Aspergillus spp.281 In the second study, both BAL culture and BAL GM (index value cutoff used
in this study was 1.0) directed preemptive therapy were utilized in 519 lung transplant recipients; preemptive therapy was associated with significantly lower rates of IA at 1 year post-transplantation compared with no preemptive therapy (HR: 0.23, 95% CI: 0.09-0.58). Mortality rates among patients receiving preemptive therapy were similar to those who did not have any positive Aspergillus culture or BAL GM at 1 year.282 In a cohort of 62 lung transplant recipients, preemptive treatment with voriconazole was effective at preventing progression to invasive disease, with reported low incidence of IFIs (1.6% and 3.2% at 6 and 12 months after initiation of prophylaxis, respectively).280 The median (range) duration of prophylaxis was 85 (4-455) days.

Among the antifungal drugs, aerosolized amphotericin B allows the direct administration of the drug into the transplanted lung, avoiding systemic side effects and drug-drug interactions. Its use, however, is limited by tolerability. Common side effects include cough, bronchospasm and nausea. D-AmB and the lipid formulations have been shown to be safe and well tolerated.269,283 Aerosolized ABLC was associated with fewer side effects in one study,269 but in the meta-analysis, the side effect profile was not significantly different between inhaled ABLC/L-AmB and D-AmB.276 A major disadvantage of aerosolized amphotericin B is the fact that distribution in single-lung transplant recipients occurs preferentially in the allograft, with unreliable distribution in the native lung, which could remain as a source of infection.284 It is also important to note that use of aerosolized amphotericin B may fail to prevent systemic fungal infections such as candidemia and pleural candidiasis in lung transplant recipients.285 Triazoles including itraconazole and voriconazole have been shown to decrease the rate of IA in lung transplant recipients.

In one study using voriconazole prophylaxis, liver enzyme abnormalities developed in more than 40% of the patients.31 Itraconazole appears to be less hepatotoxic than voriconazole in lung transplant recipients receiving antifungal prophylaxis.286 Recently, posaconazole has also been evaluated in lung transplant recipients showing lower rates of hepatotoxicity than voriconazole.279,280 The data on the newer azole, isavuconazole, are minimal in lung transplant recipients.

Data for risk factors of Aspergillus infection in lung transplant and prophylactic strategies in pediatric patient population are lacking. Recommendations regarding prophylaxis in adult lung transplant recipients should be extrapolated to pediatrics with caution.

6.3.1 | Recommendations

These recommendations are intended for the first year following the lung transplant. No definite recommendation can be made for the later years following lung transplantation due to the lack of published data.

- In cases where a preemptive therapy strategy is employed, both BAL culture and BAL GM should be incorporated into the protocol (Strong; low).
- A BAL GM index value of 1.0 is preferred as a threshold for the initiation of preemptive therapy (Strong; low).
- It is recommended to initiate targeted antifungal prophylaxis if any one of the following risk factors is present in lung transplant recipients (Strong; moderate)
  - Pre-transplant Aspergillus colonization
  - Post-transplant Aspergillus colonization within a year of transplant
  - Single-lung transplant
  - Positive intraoperative Aspergillus culture in CF patient
- Targeted antifungal prophylaxis against IA may be considered if more than one of these risk factors are present in lung transplant recipients (Weak; low)
  - Early airway ischemia
  - Induction with alemtuzumab or anti-thymocyte globulin
  - Cytomegalovirus infection
  - Rejection and augmented immunosuppression (particularly the use of T cell-depleting monoclonal antibodies post-transplant)
  - Acquired hypogammaglobulinemia (IgG level <400 mg/dL)
- The use of serum GM for the screening of IA is not recommended in lung transplant recipients (Strong; moderate).
- In cases of universal and targeted antifungal prophylaxis, the recommended duration is 4-6 months. However, when using a preemptive strategy, the duration of antifungal therapy should be 3-4 months (Strong; moderate).

With regard to the choice of the drugs against Aspergillus in lung transplant recipients, the following recommendations are made:

- No data exist regarding the use of inhaled amphotericin (lipid or deoxycholate) in preemptive therapy (ie, positive Aspergillus culture or positive BAL GM), and they should be used with caution in this setting (Strong; low).
- Inhaled amphotericin B or lipid preparation of amphotericin B can be used for targeted prophylaxis post-operatively in patients with a risk of developing IA. Caution should be exercised in single-lung transplant recipients. The dosage of D-AmB may vary from 20 mg three times a day to 25 mg/d. The duration of prophylaxis should be guided by interval airway inspection, respiratory surveillance fungal cultures, and clinical risk factors (Weak; low).
- Nebulized ABLC can be used at a dose of 50 mg once every two days for two weeks, and then once per week for at least 13 weeks (Weak; low).
- Nebulized L-AmB can be administered as 25 mg three times/week for two months, followed by weekly administration for 6 months, and twice per month thereafter (Weak; low).
- Systemic antifungal agents active against Aspergillus such as voriconazole (6 mg/kg for two doses followed by 4 mg every 12 h), itraconazole (200 mg every 12 h), or posaconazole (300 mg/d delayed-release tablets) can be used for prophylaxis or preemptive therapy
• Liver enzymes should be monitored to assess the hepatic toxicity in patients receiving systemic antifungal prophylaxis with azoles (Strong; moderate).
• Voriconazole should be used with caution in patients with previous history of squamous cell carcinoma, or who are residing in geographical areas with higher incidence of cutaneous malignancy. Voriconazole use warrants photo-protective measures to be put in place, and enhanced skin surveillance (Strong; high).
• Alternatives to voriconazole may include posaconazole or isavuconazole (Weak; low).

6.4 | Heart Transplant Recipients
Data on the prophylactic strategies in heart transplant recipients have been primarily reported in single-center studies. Most of these studies have used targeted prophylaxis with the exception of one study, which used universal prophylaxis and screening along with a CT scan of the chest and serum GM.

No recommendations can be made for prophylaxis in heart transplant recipients in pediatric heart transplant recipients, owing to the lack of data.

6.4.1 | Recommendations

• Targeted prophylaxis with itraconazole or voriconazole at a dosage of 4 mg/kg every twice daily for 50-150 days, or echinocandins up to 120 days, is recommended in recipients with one or more of the following risk factors (Strong; low)
  o Isolation of Aspergillus species in respiratory tract cultures without radiological abnormality
  o Presence of airborne Aspergillus spores in the ICU
  o Re-operation (thoracic)
  o Presence of CMV disease
  o Post-transplant hemodialysis
  o Existence of an episode of IA in any patient within the heart transplant program, 2 months before or after heart transplant.

6.5 | Other solid-organ transplant recipients
There are insufficient data to routinely recommend anti-Aspergillus prophylaxis in other solid-organ transplant recipients.

7 | RESEARCH AND FUTURE AREAS OF INVESTIGATION
Although the field of IA in SOT has advanced significantly over the last few years, there are areas that require further investigation.

Rezafungin (CD101-IV) is a novel echinocandin with distinctive pharmacokinetic properties that allow once-weekly dosing, and has potent in vitro activity and in vivo efficacy against a broad range of Aspergillus species. E1210/APX001 is a broad-spectrum antifungal with a novel mechanism of action—inhibition of fungal glycosyl-phosphatidylinositol biosynthesis—and reported efficacy in animal models of IA. Ibrexafungerp (SCY-078) is another investigational antifungal agent, first representative of a novel class of structurally distinct glucan synthase inhibitors, triterpenoids. Clinical trials with these new agents are ongoing.

The development of ECVs/breakpoints for isavuconazole against Aspergillus will aid in the interpretation of isavuconazole MICs. A recent survey of US infectious diseases physicians found that 21% of respondents lacked access to antifungal susceptibility testing. Thus, access to antifungal susceptibility testing should be improved.

Although a number of potential genetic and immune correlates of protection in IA have been identified, the clinical utility of these biomarkers remains largely unexplored. In a recent study, the levels of pentraxin-3 (PTX-3) in BAL samples were significantly higher among lung transplant patients with IA.

The role of combination antifungals for primary therapy of IA remains controversial, and further research in this area is needed. Finally, pharmacokinetics studies are necessary to determine the optimal dosing of antifungals in patients on ECMO/cardiovascular support and special populations such as children and patients with CF.

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CONFLICT OF INTEREST
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ORCID
Shahid Husain: https://orcid.org/0000-0002-9216-5229
Jose F. Camargo: https://orcid.org/0000-0001-9584-5011

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Husain and Camargo


