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Special Article

Aspergillosis in Solid Organ Transplantation

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Abbreviations: BAL, bronchoalveolar lavage; CMV, cytomegalovirus; EORTC/MSG, European Organization for Research and Treatment of Cancer and Mycosis Study Group; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; IA, invasive aspergillosis; IgG, immunoglobulin G; PCR, polymerase chain reaction; SOT, solid organ transplant.

Introduction

Invasive aspergillosis (IA) occurs in 1–15% of the solid organ transplant (SOT) recipients. Mortality rate in transplant recipients with IA historically has ranged from 65% to 92% (1–4). However, currently reported mortality rate in IA among SOT recipients is 22% (5). An estimated 9.3–16.9% of all deaths in transplant recipients in the first year have been considered attributable to IA (6). Although the outcomes have improved in the current era, IA remains a significant posttransplant complication in SOT recipients. The review herein discusses the epidemiologic characteristics, risk factors, diagnostic laboratory assays and the approach to antifungal prophylaxis and treatment of IA in SOT recipients.

Epidemiology and Risk Factors

The net state of immunosuppression including the intensity of immunosuppressive regimen is a major determinant of the development of IA in SOT recipients, regardless of the type of transplant. However, the incidence of IA differs and there are unique risk factors for *Aspergillus* infections for various types of organ transplant recipients as discussed herein (Table 1). IA is typically acquired by inhalation of the conidia. Less frequently local infections may result in surgical wound infections. Invasive disease may manifest as localized (pulmonary or extrapulmonary disease) or disseminated aspergillosis. In lung transplant recipients, airway disease can manifest as tracheobronchitis or bronchial anastomotic infections.

Liver transplant recipients

IA occurs in 1–9.2% of the liver transplant recipients (1,4,6–9). A number of well characterized risk factors have been described for IA after liver transplantation. Retransplantation and renal failure are amongst the most significant risk factors for IA in these patients (4,10–12). Retransplantation confers 30-fold higher risk and renal dysfunction, particularly the requirement of any form of renal replacement therapy, e.g. hemodialysis or continuous venovenous hemofiltration is associated with a 15- to 25-fold greater risk of IA in liver transplant recipients (3,11). Most Invasive fungal infections in these high-risk patients occur within the first month posttransplant; the median time to onset of IA after renal replacement therapy and retransplantation was 13 and 28 days, respectively in one study (9,13). Other factors associated with IA in liver transplant recipients include transplantation for fulminant hepatic failure, cytomegalovirus (CMV) infection and prolonged intensive unit care stay (7–9,14–16; Table 2).

Historically IA in liver transplant recipients has occurred in the early posttransplant period; the median time to onset after transplantation was 17 days in one study (2) and 16 days in another (17). More recently, however, *Aspergillus* infections have been shown to occur in the late posttransplant period, i.e. more than 90 days after transplantation. In a study that compared a cohort of patients with IA from 1998 to 2002 with those from 1990 to 1995, median onset to IA was 60 days posttransplant; 55% of the infections in the later compared with 23% in the earlier cohort occurred after 90 days of transplantation (3). Improved outcome in the early postoperative period due to technical surgical advances, and delayed onset of posttransplant risk factors such as CMV infection, allograft dysfunction due to recurrent hepatitis C virus hepatitis are proposed to have led to delayed occurrence of IA in liver transplant recipients in the current era (3). CMV and hepatitis C virus infection are

Table 1: Risk factors for invasive aspergillosis in organ transplant recipients

Liver transplant recipients
– Retransplantation
– Renal failure, particularly requiring renal replacement therapy
– Transplantation for fulminant hepatic failure
– Reoperation
Lung transplant recipients
– Single lung transplant
– Early airway ischemia
– Cytomegalovirus infection
– Rejection and augmented immunosuppression
– Pretransplant *Aspergillus* colonization
– Posttransplant *Aspergillus* colonization within a year of transplant
– Acquired hypogammaglobulinemia (IgG < 400 mg/dL)
Heart transplant recipients
– Isolation of *Aspergillus* species in respiratory tract cultures
– Reoperation
– CMV disease
– Posttransplant hemodialysis
– Existence of an episode of invasive aspergillosis in the program 2 months before or after heart transplant
Kidney transplant recipients
– Graft failure requiring hemodialysis
– High and prolonged duration of corticosteroids

independent risk factors for late-onset IA in liver transplant recipients (2,7,11).

Mortality in liver transplant recipients with IA has ranged from 83% to 88% (6,18). Requirement of dialysis and CMV infection are independent predictors of mortality in SOT recipients, including liver transplant recipients with IA (13). More recent studies have reported improved outcomes with mortality ranging from 33.3% to 65% (3,19). Mortality, however, remains high in patients who develop IA after liver retransplantation (82.4%), particularly in those undergoing retransplantation after 30 days of primary transplant (100%; Ref.13).

Renal transplant recipients

IA has been reported in approximately 0.7% and in up to 4% of the renal transplant recipients (6,7,20–25). High doses and prolonged duration of corticosteroids, graft failure requiring hemodialysis and potent immunosuppressive therapy have been shown to be risk factors for IA after renal transplantation (6,23,26). Despite a relatively lower overall incidence as compared to other organ transplant recipients, IA is a significant contributor to morbidity in renal transplant recipients. Mortality in renal transplant recipients with IA has ranged from 67% to 75% (4,6).

Lung transplant recipients

Earlier studies had reported the overall incidence of IA in lung transplant patients ranges from 4% to 23.3% (27). In a recently concluded multicenter prospective study, the first year cumulative incidence of fungal infections in lung transplant was 8.6% (28). This incidence of all fungal infections was in parallel with the reported incidence in donor mismatch allogeneic bone marrow transplant recipients (29). These data highlight the highest risk status of fungal infections in lung transplant recipients despite widespread use of antifungal prophylaxis. IA is the predominant fungal infection in lung transplant recipients (30). The median time to onset of IA in lung transplant recipients from 2002 to 2005 was 508 days posttransplant (30). In lung transplant recipients, the continuous exposure of the organ to the environment, coupled with impaired defenses due to decreased mucociliary clearance and blunted cough reflex, contributes to the vulnerability to IA (31). Other risk factors that confer an increased risk of IA in lung transplant recipients are relative ischemia at the anastomosis (32), receipt of single lung transplant (33), hypogammaglobulinemia (34), CMV infection (35) and pre/postcolonization of the airways with *Aspergillus* (36–38). The presence of bronchiolitis obliterans syndrome as a risk factor for IA is not well determined. However, one study failed to find a higher rate of IA in lung transplant recipients with bronchiolitis obliterans syndrome (39).

The mortality of IA in lung transplant recipients varies according to the clinical presentation, ranging from 23% to 29% in patients with tracheobronchitis to as high as 67–82% in patients with invasive pulmonary disease (10). Recent data would suggest that overall mortality of 20% among patients with IA (30).

Heart transplant recipients

The overall 12 months cumulative incidence of fungal infection in heart transplant recipients was 3.4% in a large prospective cohort study (28). The incidence of IA in heart transplant recipients ranges from 1% to 14% (40). The risk factors for the development of IA include the isolation of *Aspergillus fumigatus* from bronchoalveolar lavage (BAL), reoperation, CMV disease, posttransplant hemodialysis, (41–43). Overall mortality in heart transplant recipients with IA at 1 year was 66.7% in one study (40).

Diagnosis

A substantial delay in establishing an early diagnosis remains a major impediment to the successful treatment of IA. Diagnostic criteria have been established to facilitate the diagnosis of IA. The European Organization of Research and Treatment and Mycosis Study Group had put forth the criteria for the diagnosis of fungal infections in immunocompromised host (44). However, they lack complete applicability in lung transplant recipients owing to the unique clinical syndromes and lack of sensitivity of certain diagnostic tests (serum galactomannan) in lung transplants. The International Society for Heart and Lung Transplantation has developed a working formulation for the diagnosis of invasive fungal infections in lung transplant recipients. This definition excludes the "possible" category from EORTC/MSG criteria and defines the clinical syndromes

Table 2: Recommendations for prophylaxis for invasive aspergillosis in solid organ transplant recipients

Organ	Risk factors	Antifungal prophylaxis	Duration
Liver II-2	Retransplantation Renal failure, particularly requiring renal replacement therapy Reoperation involving thoracic or abdominal cavity	Lipid formulation of amphotericin B (3–5 mg/kg/day) OR an echinocandin	Initial hospital stay or for 4 weeks posttransplant
Lung	**Presence of one of these risk factors (II-2)** Pretransplant *Aspergillus* colonization Posttransplant *Aspergillus* colonization within a year of transplant **Presence of more than one of these risk factors (II-3,III)** Induction with alemtuzumab or Thymoglobulin Single lung transplant *Aspergillus* colonization following cytomegalovirus infection Rejection and augmented Immunosuppression (particularly use of monoclonal antibody posttransplant with *Aspergillus* colonization) Acquired hypogammaglobulinemia (IgG < 400 mg/dL)	Inhaled amphotericin B 6 mg/q8 or 25 mg/day OR Inhaled Abelcet 50 mg OR Inhaled Ambisome 25mg OR Voriconazole 200 mg bid OR Itraconazole 200 mg bid	Preferably guided by interval airway inspection, respiratory surveillance fungal cultures, and clinical risk factors. Once every 2 days for 2 weeks and then once per week for at least 13 weeks Three times/week for 2 months, followed by weekly administration for 6 months and twice per month afterwards 4 months or longer
Heart II-3	Isolation of *Aspergillus* species in respiratory tract cultures Reoperation CMV disease Posttransplant hemodialysis Existence of an episode of IA in program 2 months before or after heart transplant	Itraconazole 200 mg bid OR voriconazole 200 mg bid	50–150 days

of colonization, tracheobronchitis/bronchial anastomotic infection with the inclusion of *Aspergillus* PCR in the microbiological diagnostic criteria. These definitions may be more specific in the epidemiological and intervention studies in lung transplant recipients (45).

Among the diagnostic modalities, cultures of the respiratory tract secretions lack sensitivity and the *Aspergillus* may only be detected in clinical samples in late stages of the disease. On the other hand, a positive culture with *Aspergillus* from respiratory tract samples does not always indicate invasive disease. The significance of a positive culture from an airway sample also varies with the type of organ transplant. Isolation of *Aspergillus* spp. from the respiratory tract of liver transplant recipients is an infrequent event (~1.5%). However, it has a high positive predictive value, ranging from 41% to 72% for the subsequent development of IA (6). *Aspergillus* spp. can be detected in airway samples of ~25–30% of the lung transplant recipients (3,36,46). Although positive airway cultures have a low positive predictive value for the diagnosis of IA in lung transplant recipients, they portend a higher risk for subsequent invasive infection (6). Recovery of *Aspergillus* spp. from an airway sample in lung transplant recipients warrants a bronchoscopic examination to exclude the presence of tracheobronchitis because radiographic and imaging studies may be nonrevealing at this stage.

In heart transplant recipients, the positive predictive value of culturing *Aspergillus* from respiratory tract samples for the diagnosis of IA was 60–70% (43). The positive predictive value of recovering *A. fumigatus* for the diagnosis of IA was 78–91%, whereas it was 0% for other including *A. versioclor, A. terreus, A. glaucus* and *A. candidus* (43). The isolation of *A. fumigatus* from the sputum had a positive predictive value of 50–67% that increased to 88–100% when the sample was a respiratory specimen other than the sputum such as BAL and bronchial aspirate (43).

The utility of the galactomannan test for the early diagnosis of IA has been assessed in a limited number of studies in SOT recipients. In liver transplant recipients where archived sera were tested, the sensitivity of the test was 55.6% and the specificity was 93.9% (47). A prospective study in 154 liver transplant recipients documented a specificity of 98.5% (48). In lung transplant recipients, the galactomannan test had a specificity of 95%, but a

relatively low sensitivity (30%) for the diagnosis of IA (49). Although the test was able to detect the only case of systemic IA, and 29% of the cases of pulmonary IA, it detected none of the cases of *Aspergillus* tracheobronchitis (49). A meta-analysis showed that galactomannan 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 (50).

Sensitivity of the galactomannan assay for the diagnosis of IA in SOT recipients may be improved by testing BAL. In one study, BAL had a sensitivity of 67% and specificity of 98% at the index cutoff value of $\geq$1 for the diagnosis of IA in lung transplant recipients (51). In another study, BAL had a sensitivity of 100% and specificity of 91% at the same index cutoff value for the diagnosis of IA in SOT recipients (52). In another study which combined the data from two previously reported studies the galactomannan sensitivity was 81.8% in patients with IA, and specificity was 95.8% in lung transplant patients who underwent BAL for surveillance for infection or (53).

False positive galactomannan tests have been documented in up to 13% of the liver and 20% of the lung transplant recipients (48,49). Liver transplant recipients undergoing transplantation for autoimmune liver disease and those requiring dialysis were significantly more likely to have false-positive galactomannan tests (48). In a report of lung transplant recipients, false-reactivity of galactomannan was documented in 20% (14/70) of the patients (49). Most false-positive tests occurred in the early posttransplant period, i.e. within 3 days of lung transplantation in 43%, within 7 days in 64% and within 14 days of transplantation in 79% of the patients (49). Patients undergoing lung transplantation for cystic fibrosis and chronic obstructive pulmonary disease were more likely to have positive tests in the early posttransplant period (49). False-positive galactomannan tests in 29% of the liver transplant recipients in the first week posttransplantation were attributed to perioperative prophylaxis with β-lactam agents that included pipercillin-tazobactam and amoxicillin–clauvanic acid in serum. However, this association is not significant in the newer preparations of pipercillin-tazobactam (54). Plasma-lyte sodium gluconate-containing solution but not gluconate-free Plasma-lyte solution may result in false positive galactomannan values in the BAL fluid (43). The use of plasma-lyte sodium gluconate containing solution should be avoided during bronchoscopy for the diagnosis of IA.

1–3,β-D-Glucan is a component of fungal cell wall. It is present in most of the medical important fungi but is notably absent in *Cryptococcus* species and *Zygomycetes* species. The utility of 1–3, β-D-glucan for the diagnosis of IA has not been fully defined. The test, however, was useful for the diagnosis of IA in living-donor liver allograft recipients in one study (55). In lung transplant recipients, serum 1–3,β-D-glucan had the sensitivity of 64% for the diagnosis of invasive fungal infection (56). A panfungal PCR in the blood preceded clinical signs of invasive fungal infections in renal transplant recipients by 27 days (57). Recently two PCR-based molecular diagnostic tests for *Aspergillus* have become commercially available (Viracor-IBT Laboratories, Myconostica). In a study of viracor Pan fungal PCR in BAL of lung transplant recipients, the sensitivity and specificity for the diagnosis of invasive pulmonary aspergillosis was 100% and 88%, respectively (58). However, their precise role in the diagnosis and management of IA in SOT recipients remains to be determined.

Compatible CT findings for the diagnosis of invasive fungal Infection include the specific but poorly sensitive "halo sign" (54), or multiple nodules/masses, particularly if there is central low density as a precursor to cavitation (the air-crescent sign; Ref. 59). These finding are more prevalent in stem cell transplant recipients. The development of pulmonary nodules in the early posttransplant period is highly suggestive of invasive fungal infection in lung and heart transplant recipients (59). Clinicians should therefore have a low threshold for performing a chest CT in this patient group and should also be mindful that endobronchial fungal disease is under-recognized.

Management

Treatment

Prompt initiation of antifungal therapy is critical for achieving optimal outcomes in SOT recipients with IA. Beginning in the early 1990s and for almost a decade, lipid formulations of amphotericin B largely because of a lower potential of nephrotoxicity have been the mainstay for the treatment for IA in SOT recipients. In a study consisting of 47 SOT patients with IA who were treated with lipid formulations of amphotericin B (5–7.4 mg/kg/day), the overall 90-day mortality was 49% and the IA-associated mortality was 43% (13). Another study that compared the efficacy of amphotericin B lipid complex (median dose of 5.2 mg/kg/day) and amphotericin B deoxycholate (median does of 1.1 mg/kg/day) for the treatment of IA in SOT recipients (60), the overall and IA-related mortality rate was 33% and 25% in amphotericin B lipid complex group and 83% and 76% in amphotericin B deoxycholate group (60). In patients intolerant of or in those failing primary therapy with voriconazole, liposomal amphotericin B or amphotericin B lipid complex can be considered as alternative therapy. *Aspergillus* species such as *A. terreus* are typically resistant to the polyenes but susceptible to voriconazole. However, only 5–6% of IA in SOT recipients is due to *A. terreus* (13).

Based on a large randomized trial that compared voriconazole with amphotericin B deoxycholate for the treatment of IA mostly in hematopoietic stem cell transplant recipients and patients with hematologic malignancies, voriconazole has emerged as the preferred agent for primary therapy

Table 3: Antifungal therapy for invasive aspergillosis in adult organ transplant recipients

Drug	Dosing (Adult)	Comments
Primary therapy		
Voriconazole	6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h	Monitoring of plasma drug levels of voriconazole, hepatic aminotransferase levels and calcineurin agent levels is recommended
Alternative agents		
Liposomal amphotericin B (AmBisome®)	3–5 mg/kg/day IV	Higher dosages are not more effective
Amphotericin B Lipid Complex (Abelcet®)	5 mg/ kg/day IV	Higher dosages are not more effective
Caspofungin	70 mg day 1 IV and 50 mg/day IV thereafter	Has been evaluated only as salvage therapy. Its role as single agent therapy is controversial
Micafungin[1]	100–150 mg IV qd	May be used as alternative therapy in cases of intolerance or disease refractory to primary therapy
Posaconazole[1]	200mg qid initially and then 400mg po bid	May be used as alternative therapy in cases of intolerance or disease refractory to primary therapy
Itraconazole[2]	200–400 mg/day orally	Use should be considered only in mild cases intolerant to other therapies. Itraconazole oral solution and capsule are not bioequivalent and should not be used interchangeably. Therapeutic drug monitoring is recommended intolerance or disease refractory to primary therapy

Duration of therapy for aspergillosis has not been optimally defined. Most experts recommend continuing treatment of infection until resolution or stabilization of all clinical and radiographic manifestations. Generally, treatment is continued for a minimum of 6–12 weeks.
[1]Currently micafungin and posaconazole do not have an approved indication for the treatment of invasive aspergillosis.
[2]IDSA guidelines (2008) recommend 600 mg/day for 3 days, followed by 400 mg/day.

of IA (61). Successful outcome at 12 weeks was documented in 52.8% of the patients in the voriconazole group and in 31.6% in the amphotericin B deoxycholate group. The survival at 12 weeks was 70.8% in the voriconazole group and 57.9% in the amphotericin B group (hazard ratio, 0.59; 95% CI 0.40–0.88). Voriconazole-treated patients had significantly fewer severe drug-related adverse events, except for transient visual disturbances.

Since this study, a number of reports of employing voriconazole for the treatment of IA specifically in SOT recipients have appeared in the literature. In three studies that included SOT patients with IA, complete or partial response rates observed with voriconazole were 100%, 100% and 50% (62–64). In another report that included 11 SOT recipients with central nervous system aspergillosis treated with voriconazole, the favorable response rate was 36% and survival was 31% (65). Voriconazole was successfully used in heart transplant recipients as first-line and salvage therapy for IA (66,67). Mean hospital length of stay in SOT recipients with IA in the current era is 29.7 days and initial voriconazole use was associated with decreased length of stay (68). Intravitreal voriconazole has also been used in a lung transplant patient with *Aspergillus* endophthalmitis (69). Voriconazole is now regarded as the drug of choice for primary treatment of IA in all hosts, including SOT recipients (Table 3) and this recommendation is endorsed by the Clinical Practice Guidelines of the Infectious Diseases Society of America (IDSA) for the treatment of IA (level I recommendation; Ref. (70).

Posaconazole is another extended spectrum triazole with activity against *Aspergillus*. Although not approved by the U.S. Food and Drug Administration for the treatment of IA, it has been used as salvage therapy for patients with IA who are refractory to or intolerant of primary antifungal therapy (71) and can be considered as alternative therapy in these settings. Itraconazole is suboptimal therapy for IA in the current era. Plasma drug level monitoring of the triazoles should be considered when using these agents for the treatment of IA.

The echinocandins (caspofungin, micafungin and anidulafungin) inhibit fungal 1,3-β-D-glucan and have *in vitro* activity against *Aspergillus* species. Caspofungin and micafungin are hepatically metabolized while anidulafungin is eliminated by nonenzymatic degradation in the blood, without hepatic metabolism or renal elimination. All three echinocandins, however, have been used anecdotally as salvage therapy in IA as single agent (72) and in combination with other drugs in SOT recipients (73,74). However, only caspofungin is currently approved by the US Food and Drug Administration as salvage therapy for the treatment of IA.

For the treatment of tracheobronchial aspergillosis, current guidelines of the Infectious Disease Society of America recommend systemic voriconazole as primary therapy (70). Aerosolized amphotericin B deoxycholate or lipid formulations of amphotericin B may have some benefits; however, their use for the treatment of tracheobronchial infection has not been standardized and remains investigational (70). There is little experience with caspofungin or other echinocandins in treating tracheobronchial infections.

The role of combination antifungal therapy for IA has not been fully defined at present. Updated guidelines of the Infectious Disease Society of America suggest reserving this option for salvage therapy (70). A prospective, multicenter study in SOT recipients compared outcomes in 40 patients who received voriconazole plus caspofungin as primary therapy for IA with those in 47 patients in an earlier cohort who received a lipid formulation of amphotericin B as primary therapy (13). The two groups were well matched, including the proportion with disseminated disease (10% vs. 12.8%), proven IA (55% vs. 51.1%), or *A. fumigatus* (71.1% vs. 80.9%). Overall survival at 90 days was 67.5% in the cases and 51% in the control group. Mortality was attributable to IA in 26% of the cases and in 43% of the controls ($p = 0.11$). Combination therapy was associated with a trend towards lower mortality when controlled for CMV infection and renal failure. When 90-day mortality was analyzed in subgroups of patients, combination therapy was independently associated with reduced mortality in patients with renal failure and in those with *A. fumigatus* infection, even when adjusted for other factors predictive of mortality in the study population (13). No correlation was found between *in vitro* antifungal synergistic interactions and outcome. None of the patients required discontinuation of antifungal therapy for intolerance or adverse effects however, patients in the combination therapy arm were more likely to develop an increase in calcineurin-inhibitor agent level, or gastrointestinal intolerance (13).

A prospective, randomized, double-blind clinical trial to investigate the efficacy of the combination of voriconazole and anidulafungin for the treatment of IA in allogeneic hematopoietic stem cell transplant recipients and patients with hematologic malignancies has recently been completed (75). Patients were randomized to receive initial treatment with the combination of voriconazole and anidulafungin or voriconazole monotherapy (with placebo). Study treatment was administered for $\geq$2 weeks, followed by voriconazole maintenance to complete 6 weeks. Mortality at week 6 was 26/135 (19.3%) in patients treated with the combination of voriconazole and anidulafungin, compared to 39/142 (27.5%) for monotherapy (95% CI –18.99, 1.51, $p = 0.09$). In a posthoc analysis of 218/277 (78.7%) patients with probable IA based on detection of galactomannan in BAL or serum, mortality at week 6 was 17/108 (15.7%) for combination and 30/110 (27.3%) for monotherapy (95% CI –22.69, –0.41, $p < 0.05$). Safety parameters did not show significant differences between treatment groups. Thus, although the difference in all-cause mortality was not statistically significant, the combination was beneficial in patients with a diagnosis of probable IA based on a positive galactomannan (75).

The combination of voriconazole and caspofungin for the treatment of IA posed a lesser economic burden on institutional resources than 5 mg/kg/day of liposomal amphotericin B (76). Despite relative paucity of data regarding the efficacy, a survey of antifungal therapeutic practices for IA in liver transplant recipients documented that combination therapy is used as first-line treatment in 47% and as salvage therapy in 80% of the transplant centers in North America (77). We believe that potential benefits of combination therapy may be best realized when used as initial therapy, particularly in patients with more severe forms of the disease such as disseminated IA or with poor prognostic factors such as renal failure.

Surgical excision or debridement remains an integral part of the management of IA for both diagnostic and therapeutic purposes (78–83). Specifically, surgery is indicated for persistent, or a life-threatening hemoptysis, for lesions in the proximity of great vessels or pericardium, sinonasal infections, for single cavitary lung lesion which progress despite adequate treatment, for lesions invading the pericardium, bone, invading the subcutaneous or thoracic tissue (70). Pneumonectomy lead to successful outcome in a lung transplant recipient with progressive, refractory angioIA whose disease worsened despite conventional antifungal therapy (84). Surgical resection is also indicated for intracranial abscesses depending upon the location, accessibility of the lesion and neurologic sequelae.

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 cultures if they can be readily obtained, do not yield *Aspergillus*. Lowering of immunosuppression is an important adjuvant measure to surgical and medical treatment of IA. Close monitoring of Cyclosporine A or tacrolimus levels and of allograft function is critical.

Drug interactions of antifungal agents with immunosuppressants

Drug interactions of a number of antifungal agents with immunosuppressants must be carefully considered when treating transplant recipients with IA. The triazole agents are potent inhibitors of the CYP34A isoenzymes and have the potential to increase the levels of calcineurin-inhibitor agents and sirolimus (85). Itraconazole has been shown to increase CsA or tacrolimus levels by 40–83% (86,87).

A 50–60% reduction in the dose of calcineurin-inhibitor agents may be necessary with the concurrent use of voriconazole (85). The use of sirolimus is contraindicated in patients receiving voriconazole. In some reports, however, the two agents have been safely coadministered with sirolimus dose reduction by 75–90% (88,89). Coadministration of posaconazole increased cyclosporine exposure and necessitated dosage reductions of 14–20% for cyclosporine (90). Posaconazole increased the maximum blood concentration and the area under the concentration-time curve for tacrolimus by 121% and 357%, respectively (90).

The pharmacokinetics of caspofungin is unaltered by coadministration of tacrolimus, but caspofungin may reduce tacrolimus concentrations by up to 20% and may increase cyclosporine A plasma concentrations by 35% (91). Elevated liver function tests in healthy volunteers receiving caspofungin and cyclosporine A led to the exclusion of cyclosporine recipients from the initial phase II/III clinical studies of caspofungin (91). In the clinical setting, however, coadministration of caspofungin with cyclosporine A has been well tolerated (92–94). Nevertheless, it is prudent to monitor hepatic aminotransferase enzyme levels in cyclosporine recipients treated with caspofungin. There is no interaction between caspofungin and mycophenolate mofetil.

Anidulafungin clearance is not affected by drugs that are substrates, inducers, or inhibitor of cytochrome P450 hepatic isoenzymes (96). Further, because the drug is negligibly excreted in the urine, drug-drug interactions due to competitive renal elimination are unlikely (96,97). Coadministration with tacrolimus documented no pharmacokinetic interaction between the two agents (96). When administered with cyclosporine A, a small (22%) increase in andifulafungin concentration was observed after 4 days of dosing with cyclosporine A and was not considered to be clinically relevant (96). Micafungin is a weak substrate and a mild inhibitor of the CYP3A enzyme, but not of P-glycoproteins (97). In healthy volunteers, micafungin was shown to be a mild inhibitor of cyclosporine levels (97,98). In patients receiving sirolimus, serum concentrations of this agent was increased by 21% with concomitant use of micafungin and minimal dose adjustment may be needed (99). No drug interactions have been noted between micafungin and mycophenolate mofetil or cyclosporine (97).

Adjunctive immunotherapeutic agents

Enhancement of the host's immune status with immunomodulatory agents is a potentially attractive therapeutic adjunct in the management of IA. Evidence from *in vitro* and animal studies has shown enhanced antifungal activity with cytokine or colony stimulating factors, and modulation of cellular immune responses (100–102). Granulocyte-colony stimulating factor (G-CSF) stimulates proliferation and maturation of committed myeloid precursor cells and also augments neutrophil functions including chemotaxis, phagocytosis and oxidative responses (102,103). Granulocyte macrophage colony stimulating factor (GM-CSF) stimulates the proliferation and differentiation of multiple lineages of cells such as neutrophils, eosinophils and monocyte progenitor cells (104). G-CSF or GM-CSF has been shown to be effective for IA as adjuvant therapy for invasive fungal infections in some studies in patients with hematologic malignancies (105). Although GM-CSF use in SOT recipients appears to be safe, there are no studies that have evaluated its efficacy as adjunctive antifungal therapy specifically in these patients. Routine use of these colony stimulating factors in nonneutropenic SOT recipients with IA is not deemed necessary.

In vitro studies have also demonstrated a potential role of interferon-γ (IFN-γ) against *Aspergillus* (106–109) and case reports in hosts other than SOT recipients have documented possible beneficial effects of the adjunctive use of IFN-γ in invasive fungal infections in, including IA (110–113). Guidelines of the IDSA suggest a role for IFN-γ as adjunctive antifungal therapy for IA in immunocompromised nonneutropenic host (70). The use of this cytokine in organ transplant recipients is of concern, however, given the risk of potential graft rejection.

Prophylaxis

At present, prophylaxis against IA is not routinely recommended in all SOT recipients. Clinical trials of antifungal prophylaxis in liver transplant recipients have comprised small sample sizes in single center studies. An optimal approach to the prevention of invasive fungal infections in these patients, therefore, has not been defined.

Antifungal prophylaxis targeted toward high-risk patients is the most commonly employed approach in liver recipients. A meta-analysis of antifungal prophylactic trials in liver transplant recipients documented a beneficial effect on morbidity and attributable mortality, but an emergence of infections due to non-*albicans Candida* spp. in patients receiving antifungal prophylaxis (114). Because the risk factors and the period of susceptibility to invasive fungal infections is clearly definable, antifungal prophylaxis targeted towards these high-risk patients is also deemed a rational approach for the prevention of IA after liver transplantation. Targeted antifungal prophylaxis using the lipid formulations of amphotericin B in doses ranging from 1 to 5 mg/kg/day has been shown to be effective in observational studies (19,115–117). Currently, targeted prophylaxis in liver transplant recipients is employed most frequently during the initial hospital stay or for the first month post-transplant (77).

The availability of echinocandins with their good tolerability and safety profile has led to an expanded armamentarium of antifungal drugs with a potentially promising role

as agents for targeted prophylaxis for invasive fungal infections in high-risk liver transplant recipients (118). Caspofungin employed as antifungal prophylaxis in 71 high-risk liver transplant recipients was associated with success rate (defined as absence of breakthrough invasive fungal infection after (100) days of caspofungin and absence of premature discontinuation of prophylaxis) of 88.7% (119). However, discontinuation of caspofungin due to drug-related liver toxicity was required in six patients (119). Other studies using caspofungin and anidulafungin as prophylaxis or therapy have documented favorable safety profiles in liver transplant recipients (73). Given the potential for significant drug interactions with the immunosuppressive agents, the role of newer triazoles as antifungal prophylaxis in high-risk liver transplant recipients has not yet been fully defined. The choice of antifungal regimen should also take into consideration that a vast majority of invasive mycoses even in these high risk patients are due to invasive candidiasis for which fluconazole is an appropriate approach for preventive therapy.

An optimal antifungal prophylactic strategy in lung transplant recipients still remains to be determined. Current practices of antifungal prophylaxis in lung transplant recipients are derived from nonrandomized clinical trials of inadequate sample sizes, single center noncomparative case series or case control studies (27,120–126). Although all but one study (127) have employed universal antifungal prophylaxis, a more rational approach would be to use a risk stratification strategy for anti-fungal prophylaxis. To date, no data exist on the preemptive treatment of IA based on positive galactomannan in serum or BAL in lung transplant recipients.

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. Amphotericin B deoxycholate and the lipid formulations (lipid complex and liposomal) have been shown to be safe and well tolerated (121,128); however, aerosolized amphotericin B lipid complex was associated with fewer side effects (121). A 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 (129). 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 (130). Moreover the data on the long term safety of aerosolized preparations of amphotericin B are not available. 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 (27). In a study, age less than 40 years, cystic fibrosis, use of azathioprine, history of liver disease and early initiation of voriconazole were associated with hepatotoxicity. In multivariable logistic regression analysis, perioperative initiation of voriconazole (within (30) days of transplantation) was independently associated with hepatotoxicity (OR 4.37, 95% CI: 1.53–12.43, $p = 0.006$) (131). Itraconazole may be less hepatotoxic than voriconazole in lung transplant recipients receiving antifungal prophylaxis (132). Moreover generic itraconazole is much cheaper than nongeneric voriconazole. Some centers have taken this into account to device the institutional prophylaxis strategy. Due to interactions with calcineurin inhibitors, levels of the immunosuppressive agents need to be measured and doses adjusted routinely when voriconazole is used concomitantly. An association between prolonged voriconazole use and development of skin cancer in lung transplant recipients has been reported (133–135). Although definite association requires further validation, it is prudent to screen these individuals for skin cancer and evaluate the necessity of continued prophylaxis periodically. Long term use of voriconazole prophylaxis may also result in the development of periostitis (136). Higher fluoride levels were reported in patients with periostitis receiving voriconazole (137). The data on posaconazole prophylaxis in lung transplant recipients remain thin but its use may be associated with lower rate of hepatotoxicity.

Pediatric Issues

Most of the data reviewed above regarding the treatment of IA are derived from studies in adults. Data from adult patients cannot be reliably extrapolated to infants and children due to differences in pharmacokinetic and toxicity profiles. For example, children have a higher capacity for elimination of voriconazole and as such higher doses are required compared with adults. Voriconazole exhibits nonlinear pharmacokinetics in most children (138,139). The recommended dose of 7 mg/kg i.v. in children 2–11 years of age provides exposure (area under the concentration-time curve) comparable to that observed in adults receiving 4 mg/kg i.v. (138). For older children (12–13 years of age), adult dosing strategies are often used.

Table 4 summarizes currently available agents for use in the treatment and prevention of *Aspergillus* infection in children. Clinicians need to be aware of data that are emerging for several newer agents, including posaconazole and anidulafungin; as such, the precise place of these agents in the management of pediatric IA is yet to be fully defined. The infectious diseases consult service should always be engaged when children are being treated for IA after organ transplantation.

Key Recommendations

These recommendations are primarily intended for the first year following the lung transplant. No definite

Table 4: Antifungal agents for potential use in children with invasive aspergillosis (listed alphabetically)

Agents	Route of administration and dosages	Comments
Amphotericin B deoxycholate	IV. 1.0–1.5 mg/kg; infuse as single dose over 2 h	
Amphotericin B lipid complex (Abelcet)	5 mg/kg; infuse over 2 h	
Anidulafungin	IV. Load 1.5–3 mg/kg once, then 0.75–1.5 mg/kg/day	Limited pediatric data; not for CNS disease
Liposomal amphotericin B (AmBisome)	IV. 3–5 mg/kg; infuse over 1–2 h	Acceptable front-line therapy
Caspofungin	IV. 70 mg/m^2 loading dose, then 50 mg/m^2 once daily	Not for CNS disease
Itraconazole	IV; PO. 5–10 mg/kg divided into 2 doses	Mild infections in selected older individuals
Micafungin	IV. 4–12 mg/kg once daily (higher doses needed for patients <8 years of age	Not for CNS disease
Posaconazole	PO. Limited data; see adult dosage for children 13 years and older	Limited pediatric data
Voriconazole	IV. 7 mg/kg IV q12h on day 1, then 7 mg/kg IV q12h. PO 10 mg/kg every 12 h for 1 day, then 7 mg/kg every 12 h.	Preferred treatment in most cases; more PK data needed for infants and young children

Adapted from: Recommended doses of parental and oral antifungal drugs. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th Ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009, pp. 767–783.

recommendation can be made for the later years of lung transplantation due to the lack of existing data.

- Use of serum galactomannnan for the screening of invasive apsergillosis is not recommended in lung transplant recipients (II-2).
- The positive predictive value of BAL galactomannan as a screening tool for the diagnosis of IA is best in centers with higher incidences of IA (II-2).
- No recommendation can be made about reinitiating of prophylaxis after 1 year of lung transplant.
- With regards to the choice of the drug and duration of antifungal prophylaxis against *Aspergillus* in lung transplant recipients with risk factors stated in Table 2 following recommendation are made.
- Inhaled amphotericin B or lipid preparation of amphotericin B can be used post operatively in patients with a risk of developing IA. Caution should be exercised in single lung transplant recipients (II-2). The dosage of amphotericin B may vary from 20 mg tid to 25 mg q day. The duration of prophylaxis should be guided by interval airway inspection, respiratory surveillance fungal cultures and clinical risk factors.
- Nebulized ABLC can be used at a dose of 50 mg once every 2 days for 2 weeks and then once per week for at least 13 weeks (II-3).
- Nebulized ambisome can be administered as 25 mg three times/week for 2 months, followed by weekly administration for 6 months and twice per month thereafter (II-3).
- In high risk lung transplant recipients systemic antifungal agents active against *Aspergillus* such voriconazole or itraconazole can be used for prophylaxis. The recommended duration is 4 months (II-2). Liver enzymes should be monitored to assess the hepatic toxicity. Further continuation of the prophylaxis should be guided by the continued existence or emergence of a new risk factor of IA upon evaluation of transplant recipients.
- Screening for squamous cell cancer should be considered in patients receiving voriconazole prophylaxis.

Heart transplant recipients

- Targeted prophylaxis with itraconazole or voriconazole 200 mg bid for 50–150 days may be considered in recipients with one or more risk factors as stated in Table 2 (II-3).

Liver transplant recipients

- Targeted prophylaxis with a lipid formulation of amphotericin B in dosages ranging from 3 to 5 mg/kg/d (II-2) or an echinocandin (II-3) may be considered in patients with high-risk factors as stated in Table 2.

Other solid organ transplant recipients

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

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