Antifungal Prophylaxis for Solid Organ Transplant Recipients: Seeking Clarity Amidst Controversy

Nina Singh

Organ transplant recipients comprise a growing and an increasingly important group of immunocompromised hosts. Between the period 1990–1993 and the period 1994–1997, the number of transplantation procedures performed in the United States alone increased 41% for liver, 81% for kidney-pancreas, 102% for pancreas, 120% for lung, and 136% for intestinal transplantations [1]. Invasive fungal infections remain one of the most significant infectious complications among organ transplant recipients. Although mycelial fungi (e.g., phaeohyphomycetes) have emerged as important pathogens within the last decade, most invasive fungal infections in these patients are due to Aspergillus and Candida [2–4]. Management of invasive mycoses, particularly aspergillus infections, has proven remarkably challenging.

Antifungal prophylaxis for solid organ transplant recipients remains a complex and controversial issue. There is a striking paucity of randomized trials in the literature. Consequently, institutional practices involving antifungal prophylaxis vary widely. Nevertheless, knowledge accrued regarding epidemiology and risk factors and published data, albeit largely from cohort studies and case series, can contribute substantially toward devising rational antifungal prophylactic strategies. In this overview, I discuss the demographic characteristics and predisposing variables for fungal infections that are the pathophysiological basis for my recommendations and the approaches I outline, the disadvantages of antifungal prophylaxis, and, finally, briefly outline directions for future studies.

High-Risk Patient Populations and Epidemiological Considerations

Clinical events (e.g., augmented immunosuppression associated with high-dose corticosteroids and OKT3 monoclonal antibodies) tend to enhance the risk of invasive fungal infections, regardless of the type of solid organ transplant. However, there are risk factors sufficiently unique to account for the diversity among different types of organ transplant recipients in the incidence of fungal infections, and also in the predilection toward specific fungal pathogens, time of onset, and risk of dissemination. The frequency of invasive mycoses among organ transplant recipients and the predominant fungal pathogens are outlined in table 1. Although candidal infections are a significant complication in liver and pancreas transplant recipients, the impact of aspergillosis is greatest in the context of liver and lung transplantation. An estimated 9.3% of deaths in lung transplant recipients and 16.9% in liver recipients are due to invasive aspergillosis [3].

Liver transplant recipients. Invasive aspergillosis has been described in 1%–8% of liver transplant recipients [5, 27–30]. Aspergillus infections in liver transplant recipients are notable for their early occurrence. The median time to onset after transplantation was 17 days in one study [28] and 16 days in another [27]. In the study by Bonham et al. [31], 8 (31%) of 26 CNS lesions that occurred within 30 days of transplantation were infectious, and Aspergillus caused 6 (75%) of these lesions. In other studies, 81%–100% of the liver transplant recipients who developed invasive aspergillosis were still in the intensive care unit after transplant surgery [27–29].

Virtually all liver transplant recipients with invasive aspergillosis have had evidence of significant hepatic and/or renal dysfunction [3, 5, 29]. In a study comprising 26 proven cases of invasive aspergillosis, poor allograft function was documented in all cases; the median serum bilirubin level was 21.8 mg/dL [28]. Thrombocytopenia in liver transplant recipients is a marker of severity of hepatic dysfunction [32]. It has been proposed that platelets may play a critical role in the host defense against Aspergillus by augmenting polymorphonuclear leukocyte–mediated damage to the fungal hyphae. The nadir in posttransplantation thrombocytopenia correlated with a higher risk of invasive fungal infections in liver transplant recipients [32]. Fulminant hepatic failure, as an indication for transplantation, was associated with a higher risk of invasive fungal infections after liver transplantation [33]. Systemic fun-
Table 1. Incidence of major invasive fungal infections (FIs) among organ transplant recipients and proportion of those infections that are due to Aspergillus and Candida.

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Incidence of invasive FIs, %</th>
<th>Proportion of FIs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aspergillus</td>
</tr>
<tr>
<td>Renal</td>
<td>1.4–14</td>
<td>0–10</td>
</tr>
<tr>
<td>Heart</td>
<td>5–21</td>
<td>77–91</td>
</tr>
<tr>
<td>Liver</td>
<td>7–42</td>
<td>9–34</td>
</tr>
<tr>
<td>Lung and heart + lung</td>
<td>15–35</td>
<td>25–50</td>
</tr>
<tr>
<td>Small bowel</td>
<td>40–59</td>
<td>0–3.6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18–38</td>
<td>0–3</td>
</tr>
</tbody>
</table>

NOTE. Data are derived from [2–26].

4 Fungal infections other than aspergillosis and candidiasis in transplant recipients include, predominantly, cryptococcosis (0%–6%), zygomycosis (0%–3%), infections due to phaeohyphomycetes (up to 1%), and infections due to geographically restricted or endemic dimorphic fungi (0%–4%).

Invasive aspergillosis developed in 9 (21%) of 42 patients undergoing liver transplantation for acute liver failure; 5 of the fungal infections were due to Aspergillus [33]. Finally, approximately one-fourth of the cases of invasive aspergillosis have occurred after retransplantation [28].

Renal dysfunction, particularly that requiring dialysis, portends a significantly greater risk for the development of invasive aspergillosis after liver transplantation. Fifty-eight percent of the liver transplant recipients with invasive aspergillosis in one report [28] and 80% in another [27] were undergoing either hemodialysis or continuous venovenous hemofiltration prior to Aspergillus infection. Requirement of dialysis was an independently significant predictor of invasive fungal infections in a study of liver transplant recipients [34]. Therefore, although renal failure may merely be a marker of the critically-ill nature of these patients, it is also plausible that functional abnormalities of granulocytes and macrophages associated with renal dysfunction augment the risk of developing invasive aspergillosis. Regardless, institution of dialysis is a readily discernible clinical event that identifies liver transplant recipients at risk for Aspergillus infections.

For liver transplant recipients studied between 1981 and 1990, use of OKT3 monoclonal antibody was shown to be an independent risk factor for invasive aspergillosis [5]; in that study, none of the patients with aspergillosis infections had received OKT3 monoclonal antibodies. Use of OKT3 monoclonal antibody after liver transplantation has declined substantially in the current immunosuppressive era. At many institutions, including mine, OKT3 monoclonal antibodies are used only for 1% of the patients. In a multicenter study conducted between 1990 and 1996, only 8% of the patients with invasive aspergillosis had received OKT3 monoclonal antibodies [28]. Effective prophylactic strategies for cytomegalovirus infection have also led to a significant decline in the occurrence of this infection in liver transplant recipients, consequently reducing its role as a predictor of invasive fungal infections in more recent reports [28].

Liver transplant recipients appear to be uniquely predisposed to dissemination of Aspergillus beyond the lungs and for CNS involvement [35] (table 2). One report [35] described extrapulmonary spread of Aspergillus in 11 (92%) of 12 liver transplant recipients, 6 (38%) of 16 hematologic patients, and 9 (45%) of 20 non–liver transplant patients with invasive aspergillosis (P < .02). Overall, disseminated disease has been described in 50%–60% of liver transplant recipients with invasive aspergillosis [3, 31].

Liver transplant recipients are also recognized to be at high risk for invasive candidiasis; invasive candidiasis accounts for 62%–91% of all invasive fungal infections after liver transplantation [4, 38–40]. Risk factors for invasive candidiasis in liver transplant recipients largely reflect the technical difficulties of the surgical procedure and an overall greater severity of illness in the patient. Longer operation time, blood loss, repeated operation, retransplantation, antibiotic usage, and renal failure are among the most significant risk factors for invasive candidiasis [4, 38, 39]. Return to surgery prior to invasive candidiasis was an independently significant predictor of death in liver transplant recipients with candidemia [40]. It is noteworthy that whereas studies before 1990 described invasive candidiasis in 16%–30% of the patients, several reports in the 1990s have reported lower rates, ranging from 5% to 10% (even in the absence of systemic antifungal prophylaxis) [4, 7, 28, 39, 41]. Although unproven, this decrease probably reflects greater technical expertise and perhaps a lower requirement of corticosteroids in the modern immunosuppressive era.

Lung transplant recipients. Aspergillus infections in lung transplant recipients demonstrate several unique features. Direct communication of the transplanted lung with the environment and impaired local host defenses, including mucociliary clearance, render airway colonization a common occurrence in these patients [42]. During surgery, the bronchial arteries are disrupted at the site of anastomosis [43]. Until collaterals from bronchial circulation develop, the anastomotic healing is dependent upon blood supply from pulmonary circulation of the transplanted lung. The anastomotic site with transient vascularization therefore remains susceptible to ischemic injury, necrosis, and potentially infection with Aspergillus.

Following lung transplantation, Aspergillus can be detected in airway specimen cultures for 9%–68% (average, 29%) of the patients [2, 9–11, 44]. I personally reviewed the cases of 2001 lung transplant recipients described thus far and found the following: 219 (23%) of 969 patients had airway colonization with Aspergillus without disease, 23 (4%) of 615 had tracheobronchitis, and 85 (6%) of 1542 had invasive aspergillosis. Tracheobronchitis is an entity observed specifically in lung transplant recipients [45]. Characterized by endobronchial lesions ranging from mild bronchitis to ulcers and pseudomembranes, isolated tracheobronchitis is probably early or locally invasive disease with the potential to progress to disseminated infection. Lesions in the vicinity of or involving the anastomotic site can result in fatal bronchopleural fistulas [8]. In cases reported in the
due to are frequently isolated from airway specimen cultures, invasive obleterative bronchiolitis, rejection, and increased immunosup-plantation [12, 46]. Other risk factors for invasive aspergillosis deemed to be at higher risk for invasive aspergillosis after trans-colonized with aspergillosis [6]. Notably, patients with cystic ®brosis who are isolation of aspergillosis [12]. In another report, were treated with antifungal agents with or without debride-latory cultures were performed, 56% of the protic www.ccmj.ca/lookup/doi/10.1093/clinics/68.10.606\#bm.586

although airway colonization with Aspergillus is associated with a low positive predictive value for invasive aspergillosis, it portends a higher risk for subsequent invasive infection. Patients with airway specimen cultures positive for Aspergillus within 6 months of lung transplantation were 11-fold more likely to develop invasive aspergillosis [12]. In another report, isolation of Aspergillus from a respiratory specimen was associated with a 22-fold greater risk for subsequent invasive aspergillosis [6]. Notably, patients with cystic fibrosis who are colonized with Aspergillus before transplantation are not deemed to be at higher risk for invasive aspergillosis after transplantation [12, 46]. Other risk factors for invasive aspergillosis in lung transplant recipients include cytomegalovirus infection, obliterative bronchiolitis, rejection, and increased immunosuppression [6, 12, 47, 48].

Although Aspergillus species other than Aspergillus fumigatus are frequently isolated from airway specimen cultures, invasive disease in lung transplant recipients has almost exclusively been due to A. fumigatus [9]. In a report where surveillance respiratory cultures were performed, 56% of the Aspergillus species detected were non-fumigatus. However, invasive disease was described only in patients colonized with A. fumigatus [9].

The median time to onset of aspergillus infections in published reports was 120 days. Overall, 49% of the infections have occurred within 3 months, 68%, within 6 months, and 79%, within 9 months of lung transplantation. When patients with airway colonization are excluded, the mortality rate among lung transplant recipients with invasive aspergillosis is 68% (table 2).

Pancreas transplant recipients. Although aspergillosis occurs infrequently, candidiasis is a major infection in pancreas transplant recipients. Intra-abdominal abscesses and deep wound- and surgical site–infections due to Candida occur in 7%–14% of pancreas transplant recipients and have been associated with significantly poorer allograft and patient survival [13, 14, 36, 49]. One-year survival was 70% for patients with intra-abdominal fungal infections, compared with 92% for those without infection (P = .0007) [14]. Significant risk factors that have been documented for candidal infections in these patients are as follows: donor age (vs. recipient age), enteric (vs. bladder) drainage, pancreas after kidney transplantation (vs. pancreas transplantation alone), preoperative peritoneal dialysis (vs. hemodialysis), and pancreas retransplantation [14, 36].

Heart transplant recipients. Heart transplant recipients are generally perceived to be at a lower risk for aspergillus infections than are lung or liver transplant recipients. The incidence of invasive aspergillosis among heart transplant recipients has been reported to vary widely (1%–15%), with an overall frequency of 5.2% (102 of 1948) in studies reported thus far [15–17, 50, 51]. It should be noted, however, that these reports have almost all included patients who underwent transplantation in the 1970s or 1980s, patients who contracted infections in an outbreak setting, or patients for whom antilymphocyte preparations, including OKT3 monoclonal antibodies, were used as part of induction immunosuppressive therapy [15–17, 50, 51]. These variables in aggregate may account for the high prevalence of aspergillosis among this patient population. Unique risk factors predisposing heart transplant recipients to invasive aspergillosis have not been identified.

Other solid organ transplant recipients. In the absence of graft failure requiring reinstatement of hemodialysis or intense immunosuppressive therapy, invasive aspergillosis occurs infrequen-ly in kidney transplant recipients (table 1). The frequency of candidal infections among kidney transplant patients is also low (table 1). Invasive fungal infections have been described in 40%–59% of small bowel transplant recipients. Most of these infections are invasive candidiasis (table 1). The risk factors for candidal infections in intestinal transplant recipients, however, have not been well defined.

Approaches to Prophylaxis and Antifungal Agents

Antifungal prophylaxis, if highly effective, inexpensive, non-toxic, and easily administered, would be far less controversial. The foremost issue pertinent to antifungal prophylaxis, therefore, is who should receive it. In my opinion, high incidence coupled with significant mortality support the use of prophyl-

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Mean incidence of invasive aspergillosis, % (range)</th>
<th>Incidence of Aspergillus colonization, %</th>
<th>Mean time to onset, d (range)</th>
<th>Proportion of infections due to disseminated aspergillosis, % (range)</th>
<th>Mortality rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>2 (1–8)</td>
<td>0.5</td>
<td>17 (6–1197)</td>
<td>50–60</td>
<td>87</td>
</tr>
<tr>
<td>Lung</td>
<td>6 (3–14)</td>
<td>23</td>
<td>120 (4–1410)</td>
<td>15–20</td>
<td>68</td>
</tr>
<tr>
<td>Heart</td>
<td>5.2 (1–15)</td>
<td>NA</td>
<td>45 (12–365)</td>
<td>20–35</td>
<td>78</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.7 (0.9–4)</td>
<td>1.7</td>
<td>82 (20–801)</td>
<td>9–36</td>
<td>77</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.3 (1.1–2.9)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td>Small bowel</td>
<td>2.2 (0–3.6)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE. Data are derived from [2, 3, 5, 8, 9, 11, 13, 15–17, 24–26, 28, 36, 37]. NA, not available.

* From the time of transplantation.
laxis for invasive aspergillosis in liver and lung transplant recipients and for invasive candidiasis in liver and pancreas transplant recipients. Currently, given the relatively low incidence of invasive fungal infections and uncertain clinical benefits of prophylaxis, routine employment of antifungal prophylaxis cannot be justified for other solid organ transplant recipients. I believe that strategies for antifungal prophylaxis should not be universal but instead should be targeted toward high-risk patients.

**Recommendations for Prophylaxis for Invasive Aspergillosis**

*Liver transplant recipients.* In liver transplant recipients, the risk factors for invasive aspergillosis and the period of vulnerability to aspergillosis infection have been precisely defined. Thus, a targeted or preemptive prophylactic approach lends itself well to these patients. The following key facts, however, need to be borne in mind. First, detection of *Aspergillus* species in respiratory samples from liver transplant recipients almost always indicated invasive disease [5]. Indeed, the infection may already have widely disseminated beyond a pulmonary focus by the time *Aspergillus* is detected in respiratory cultures [27]. Therefore, liver transplant recipients with airway specimen cultures positive for *Aspergillus* should not be considered candidates for prophylaxis but should be considered for therapy for invasive aspergillosis. Second, liver transplant recipients at risk for invasive aspergillosis are often critically ill, and invasive infection ensues very rapidly in these high-risk patients [27–29]. Prophylactic antifungal agents in this setting must be potent and be able to rapidly achieve the systemic drug levels considered adequate for activity against *Aspergillus*.

The efficacy of prophylaxis for aspergillosis with itraconazole (in capsule or solution form) and low-dose amphotericin B deoxycholate (AmBd) in dosages of 0.1–0.5 mg/kg/d is unconvincing in liver transplant recipients. The capsule formulation of itraconazole has an absolute bioavailability of ~55%. An acidic environment and the presence of food in the stomach increases bioavailability. Although steady-state itraconazole concentrations tend to be lower in all immunocompromised individuals [52], poor bioavailability can be particularly problematic in critically ill liver transplant recipients, in whom the integrity of the gut is compromised, bile is diverted, and a fed state is usually not possible in the early transplantation period.

Reformulation in hydroxypropyl-β-cyclodextrin has significantly improved the oral bioavailability of itraconazole. A randomized, controlled trial has compared the oral solution of itraconazole with placebo for prevention of systemic fungal infections in liver transplant recipients [53]. The study, however, was inadequately powered to demonstrate the efficacy of itraconazole against invasive aspergillosis; there were no documented aspergillus infections in 33 patients who received itraconazole or in 38 controls who received placebo. In a larger, placebo-controlled European trial that included neutropenic patients, however, the rate of systemic infections due to *Aspergillus* did not differ between patients who received the oral solution of itraconazole (4 [2%] of 201) and those who received placebo (1 [0.5%] of 201) [54]. An iv preparation of itraconazole in cyclodextrin has recently become available. Its efficacy as prophylaxis and therapy awaits testing in clinical trials including transplant recipients.

Higher dosages of AmBd (1–1.5 mg/kg/d) are of unproven efficacy as prophylaxis for aspergillosis. Regardless, the potential for nephrotoxicity precludes the use of AmBd in these dosages for transplant recipients. The lipid formulations of amphotericin B, on the other hand, have several characteristics that make them attractive antifungal agents for prophylaxis for high-risk liver transplant recipients. These formulations are less nephrotoxic and are at least equivalent, or perhaps superior, to AmBd in efficacy against invasive mycelial infections [55, 56]. Liposomal amphotericin B maintained the immunostimulatory antifungal effects that were lost with high doses of AmBd [57]. Although varying in pharmacokinetics and disposition, a difference in efficacy between currently available lipid formulations of amphotericin B in the transplant setting has not been documented. A small, noncomparative study including liver transplant recipients, however, found no difference in efficacy or toxicity between amphotericin B lipid complex (ABLC) and liposomal amphotericin B (LAmB) [58]. Therefore, cost and, to a lesser degree, infusion-related toxicity would probably determine the choice between these 3 drugs. All lipid formulations of AmBd are substantially more expensive than AmBd: LAmB is the most expensive, ABLC less expensive, and amphotericin B colloidal dispersion the least expensive [59]. Amphotericin B colloidal dispersion, however, is associated with a higher rate of infusion-related toxicity than are ABLC and LAmB.

Optimal doses of lipid formulations of amphotericin B as prophylaxis for aspergillosis infections in the transplant setting have also not been defined. A study that compared 2 dosages of LAmB (1 and 4 mg/kg/d) for the treatment of invasive aspergillosis in neutropenic and bone marrow transplant patients found no difference in efficacy between them [60]. However, case series and anecdotal reports of cases in liver transplant recipients have documented failure of prophylaxis with LAmB at a dosage of 1 mg/kg/d for aspergillosis infection [61, 62].

Thus, although firm recommendations regarding prophylaxis for infections due to *Aspergillus* cannot be made without further research, prophylaxis for invasive aspergillosis in liver transplant recipients, if deemed necessary, may be considered. Recommended is a lipid formulation of amphotericin B at a dosage of least 3 mg/kg/d, preferably 5 mg/kg/d, targeted toward high-risk patients (as identified in table 3) for a period of 4 weeks after transplantation. The need for continuing prophylaxis beyond this period should be assessed individually, on the basis of the persistence of risk factors. However, I caution that lipid formulations of AmBd are expensive, and there are limited data to support these recommendations.

*Lung transplant recipients.* The timing of aspergillus infec-
tions in lung transplant recipients is not as precisely defined as in liver transplant recipients. The period of greatest vulnerability extends over several months. Thus, the cost and feasibility of administering a parenteral antifungal agent for a prolonged time render this a less desirable option for prophylaxis. Alternative modalities include aerosolized polyene agents and orally administered antifungal drugs.

Given that most aspergillus infections are pulmonary and airway colonization precedes tracheobronchial or invasive infections in lung transplant recipients, aerosolized AmBd prophylaxis would appear to be a rational choice. In an animal model of immunocompromised rats, 1.6 mg of aerosolized AmBd/kg administered 2 days before infection prevented death in all experimental animals in the following week, whereas 90% of the controls died [64]. Furthermore, it is proposed that AmBd is delivered more efficiently to the lungs, attaining higher lung concentrations when administered as an aerosol than by the systemic route [65]. Seven doses of intravenous AmBd at 4 mg/kg achieved a concentration of 4.3 µg/g in the lung tissue, whereas the same concentration was achieved with only 2 doses of aerosolized AmBd at 1.6 mg/kg [65]. Aerosolized AmBd doses up to 60 mg/kg were tolerated in animal models without any toxicity and no detectable serum levels. The combination of aerosolized amphotericin B followed by an azole was more effective as prophylaxis for aspergillus infection than was aerosolized AmBd alone [66]. It has been proposed that aerosolized liposomal formulations of AmBd may enhance the retention of AmBd in the lung tissue [67]. Lung concentrations achievable with the lipid formulations of amphotericin B were several-fold higher than those of AmBd [67, 68].

Although randomized trials have not been conducted, a number of reports have demonstrated significant reduction in the frequency of aspergillus infections in lung transplant recipients treated with aerosolized AmBd [69–71]. Nebulized ABLC was also reported to be efficacious in a study of lung transplant recipients [72]. Thus, although the real efficacy of aerosolized amphotericin B remains to be determined, the advantages of this approach include lack of systemic toxicity, low expense, ease of administration, and lack of a need to monitor drug levels or side effects. Though therapeutic failures have been reported, itraconazole has generally been effective against the less fulminant forms of invasive aspergillosis in lung transplant recipients (e.g., tracheobronchitis) and as prophylaxis for colonized patients [44].

Therefore, an option for prophylaxis for lung transplant recipients is aerosolized amphotericin B for several weeks after transplantation or until the bronchial anastomosis has healed (in one report all anastomotic infections occurred within 60 days of lung transplantation [8]). It should be noted that Aspergillus conidia that reaches the small airways and alveolar spaces have a diameter of 2.5–3.5 µm [73]. The optimal size of the aerosols generated is 1–5 µm; particles >5 µm in diameter are likely to be retained in the upper airways and may not reach the lower respiratory tract [73].

Alternatively, preemptive prophylaxis with itraconazole for 4–6 months (with or without aerosolized amphotericin B) may be considered for patients with airway specimen cultures that are positive for Aspergillus within 6–9 months of transplantation. Treatment of tracheobronchitis or prevention of invasive disease in colonized patients has generally been accomplished with a prolonged course of itraconazole [70, 74], and this duration of prophylaxis spans the period of greatest vulnerability to infection (i.e., the first 6 months after transplantation). Patients with airway specimen cultures positive for Aspergillus who have all forms of invasive aspergillosis, including anastomotic site infections and tracheobronchitis, should be excluded from this prophylaxis; these patients should receive treatment and not prophylaxis for aspergillosis.

The oral solution of itraconazole may be preferable to capsules because of its greater bioavailability. Although tissue concentrations of itraconazole may be more predictive of efficacy than are serum concentrations, it has been suggested that trough serum levels of itraconazole of at least 500 ng/mL are required for effective antifungal prophylaxis for neutropenic

Table 3. Suggested approach to antifungal prophylaxis for organ transplant recipients.

<table>
<thead>
<tr>
<th>Type of transplant</th>
<th>Fungal pathogen targeted</th>
<th>High-risk characteristic(s)</th>
<th>Antifungal agent(s)</th>
<th>Suggested duration of prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Aspergillus</td>
<td>Poor allograft function, particularly primary nonfunction of the allograft; retransplantation fulminant hepatic failure; retransplantation; dialysis</td>
<td>Liposomal AmB</td>
<td>4 w</td>
</tr>
<tr>
<td>Liver</td>
<td>Candida</td>
<td>Repeated operation; higher intraoperative transfusion requirement; longer operation time; renal failure</td>
<td>Fluconazole</td>
<td>4 w</td>
</tr>
<tr>
<td>Lung</td>
<td>Aspergillus</td>
<td>Airway specimen cultures positive for Aspergillus; particularly for patients with rejection, increased immunosuppression, CMV infection, and obliterative bronchiolitis</td>
<td>Itraconazole ± aerosolized AmB</td>
<td>4–6 mo</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Candida</td>
<td>Enteric drainage procedure; pancreas transplantation after kidney transplantation; preoperative peritoneal dialysis; pancreatitis after reperfusion; pancreatic retransplantation</td>
<td>Fluconazole</td>
<td>4 w</td>
</tr>
<tr>
<td>All organs</td>
<td>Coccidioides immitis*</td>
<td>History of coccidioidal pulmonary infection or reactive coccidioidal serology before transplantation</td>
<td>Triazole antifungals</td>
<td>Prolonged or perhaps indefinite</td>
</tr>
</tbody>
</table>

NOTE: AmB, amphotericin B; CMV, cytomegalovirus; ±, with or without.

* According to the recommendations of Hall et al. [63].
patients [75]. The itraconazole dosage used to achieve similar concentrations may be considered for lung transplant recipients. It should be noted that itraconazole will increase cyclosporine, simvastatin, and itraconazole has been associated with simvastatin-induced rhabdomyolysis in a lung transplant recipient [77].

**Recommendations for Prophylaxis for Invasive Candidiasis**

At least 2 randomized studies have assessed the efficacy of fluconazole as prophylaxis for invasive fungal infections in liver transplant recipients [78, 79]. A randomized trial from Europe compared fluconazole with oral nystatin for 28 days after transplantation as antifungal prophylaxis for liver transplant recipients [78]. Although the incidence of colonization with *Candida* and superficial fungal infections was lower among fluconazole recipients a difference in the frequency of invasive candidiasis was not observed between the 2 groups. Nystatin has often been administered alone as part of selective bowel decontamination for liver transplant recipients. However, its efficacy in decreasing systemic fungal infections is questionable; a high incidence of invasive candidiasis has been documented among patients who received nystatin therapy [4]. Another study found that fluconazole for 10 weeks was associated with a significant decrease in the incidence of invasive fungal infections [79]. However, this study reported an unusually high incidence of invasive mycoses (43%), most of which were superficial fungal infections. The frequency of invasive candidiasis in this fluconazole group was similar to the frequency among patients at other centers who received no systemic antifungal prophylaxis [79].

The need for fluconazole prophylaxis, in my opinion, should be assessed on the basis of institutional trends in the incidence of invasive candidiasis. Universal fluconazole prophylaxis is unwarranted and should be discouraged. Given the low frequency of invasive candidiasis at many liver transplant centers and the potential for the emergence of resistance, prophylaxis should be employed selectively. When it is used, prophylaxis should be directed only to high-risk patients (as identified in table 3) and for only 4 weeks after transplantation.

Fluconazole prophylaxis has been anecdotally reported to be

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**Table 4.** Data from published studies on systemic antifungal prophylaxis for solid organ transplant recipients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of transplant</th>
<th>Study design</th>
<th>Prophylactic approach</th>
<th>Antifungal regimen</th>
<th>n</th>
<th>Major finding(s)</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[81]</td>
<td>Liver</td>
<td>Randomized, DB, PC</td>
<td>Universal</td>
<td>LAmB, 1 mg/kg/d for 7 d</td>
<td>58</td>
<td>Significant decrease in fungal infections, primarily candidiasis</td>
<td>Study inadequately powered to assess efficacy for aspergillosis</td>
</tr>
<tr>
<td>[62]</td>
<td>Liver</td>
<td>Cohort</td>
<td>Universal</td>
<td>LAmB, 1 mg/kg/d for 7-10 d</td>
<td>21</td>
<td>2 (%) of 21 patients developed invasive aspergillosis</td>
<td>Findings suggest this regimen lacks efficacy</td>
</tr>
<tr>
<td>[61]</td>
<td>Liver</td>
<td>Cohort</td>
<td>Targeted, Universal</td>
<td>LAmB, 1 mg/kg/d for 7-10 d</td>
<td>21</td>
<td>2 (%) of 21 patients developed invasive aspergillosis</td>
<td>Findings suggest this regimen lacks efficacy</td>
</tr>
<tr>
<td>[79]</td>
<td>Liver</td>
<td>Randomized, DB, PC</td>
<td>Universal</td>
<td>Flu, 400 mg/d for 10 w</td>
<td>212</td>
<td>Significant decrease in fungal infections</td>
<td>Unusually high incidence of fungal infections was documented in the control group</td>
</tr>
<tr>
<td>[82]</td>
<td>Liver</td>
<td>Historically controlled</td>
<td>Targeted</td>
<td>Flu, 100 mg/d</td>
<td>45</td>
<td>Reduction in invasive candidiasis</td>
<td>6.6% of the Flu vs. 2.7% of the controls had mycelial infections</td>
</tr>
<tr>
<td>[53]</td>
<td>Liver</td>
<td>Randomized, controlled</td>
<td>Universal</td>
<td>Ltr, oral solution</td>
<td>71</td>
<td>Significant reduction in invasive candidiasis</td>
<td>Inadequately powered to assess efficacy for aspergillosis</td>
</tr>
<tr>
<td>[78]</td>
<td>Liver</td>
<td>Randomized, controlled</td>
<td>Universal</td>
<td>Flu, 100 mg/d; Nys for 28 d</td>
<td>143</td>
<td>Colonization with <em>Candida</em> and superficial fungal infections decreased</td>
<td>No decrease in invasive candidiasis documented</td>
</tr>
<tr>
<td>[76]</td>
<td>Heart</td>
<td>Historically controlled</td>
<td>Universal</td>
<td>Ltr capsule, starting day 5 for 3-12 mo</td>
<td>96</td>
<td>Significant reduction in invasive aspergillosis</td>
<td>Other risk factors (e.g., intensity of immunosuppression) not available</td>
</tr>
<tr>
<td>[44]</td>
<td>Lung</td>
<td>Cohort</td>
<td>Targeted</td>
<td>Flu or Itr, 400 mg/d</td>
<td>38</td>
<td>No systemic fungal infections documented</td>
<td>Uncontrolled study design</td>
</tr>
<tr>
<td>[83]</td>
<td>Lung</td>
<td>Historically controlled</td>
<td>Universal</td>
<td>Ltr</td>
<td>49</td>
<td>Trend toward a decrease in invasive aspergillosis</td>
<td>Retrospective control subjects; however, matched with patients for rejection and CMV infection</td>
</tr>
<tr>
<td>[69]</td>
<td>Lung</td>
<td>Historically controlled</td>
<td>Universal</td>
<td>Aerosolized AmB</td>
<td>126</td>
<td>Significant decrease in aspergillosis</td>
<td>Confounding variables (e.g., immunosuppression) not reported; no stated rationale for continued decrease in aspergillosis at 12 mo</td>
</tr>
<tr>
<td>[74]</td>
<td>Lung</td>
<td>Cohort</td>
<td>Universal</td>
<td>Flu, 400 mg/d</td>
<td>52</td>
<td>No fungal infections documented during prophylaxis</td>
<td>Small sample size, uncontrolled study design</td>
</tr>
</tbody>
</table>

**NOTE.** AmB, amphotericin B; CMV, cytomegalovirus; DB, double-blind; Flu, fluconazole; Ltr, itraconazole; LAmB, liposomal AmB; Nys, nystatin; PC, placebo-controlled.

*a* Prophylaxis administered to 21 of 100 high-risk patients.

*b* Itraconazole used until first fungal infection or hospital discharge or for 56 days.

*c* Prophylaxis initiated upon detection of *Candida* or *Aspergillus* in airway specimen cultures or culture isolation of *Aspergillus* before transplantation.

*d* During posttransplantation admission.
effective after pancreas transplantation [14, 18]. Given the significant morbidity and adverse effect on patient outcome that are associated with candidal infections, prophylaxis with fluconazole for 4 weeks may be considered for high-risk pancreas transplant recipients. Prophylaxis for candidal infections may also be reasonable for small bowel transplant recipients; however, the risk factors for candidemia have not been well defined in this subgroup of patients.

**Pitfalls of Antifungal Prophylaxis**

The potential for the emergence of resistant fungi is among the most worrisome concerns pertaining to antifungal prophylaxis and is particularly relevant in the context of azole prophylaxis. Widespread fluconazole use is arguably the most significant factor contributing to an ecological shift toward non-albicans Candida species and the emergence of azole-resistant Candida causing infection. Failure to demonstrate infection due to fluconazole-resistant Candida in short-term analyses in one report [79] is not necessarily reassuring since the emergence of resistance often requires prolonged and widespread usage. Likewise, short-term cost analyses reporting an economic benefit with fluconazole prophylaxis are misleading [80]. The potential morbidity due to infections with azole-resistant Candida and the expense of managing these infections could far outweigh such advantages in the future.

**Limitations of Existing Literature and Future Directions**

The existing reports on antifungal prophylaxis are largely uncontrolled studies with small sample sizes (table 4). Historically, controlled studies have frequently failed to stratify patients by confounding variables (e.g., intensity of immunosuppression; table 4). Variable and, at times, imprecise criteria have been employed to define fungal infections. In this regard, a concerted attempt by the European Organization for Research and Treatment of Cancer to devise explicit and uniform diagnostic criteria for invasive fungal infections in neutropenic patients is laudable [83]. Finally, the correlation of the efficacy of prophylaxis with clinical outcome is an important end point. However, mortality rates have not been uniformly reported in published studies. Patients at risk for invasive fungal infections are often critically ill and may die of their illness regardless of the efficacy of prophylaxis. At least 3 randomized studies [78, 79, 81] could not document an impact on mortality, despite a significant reduction in invasive fungal infections in liver transplant recipients.

Despite these weaknesses, existing data have some noteworthy implications for future trials. For example, the studies by Lorf et al. [61] and Varo et al. [62], despite their uncontrolled design, convincingly show the lack of efficacy of low-dose LAmB as prophylaxis for invasive aspergillosis, which suggests that higher doses need to be considered in clinical trials including liver transplant recipients.

**Conclusion**

The approaches recommended here for antifungal prophylaxis are based upon the principle of directing prophylaxis to high-risk patients for the period relative to transplantation when risk is thought to be greatest. Although theoretically sound, it should be emphasized that these recommendations are my perspective, based on biological plausibility and a review of existing literature. Validation of the efficacy of these approaches in future investigations and reassessment of their relative merits are warranted should definitive studies become available. The recommendations should not be construed as a standard of care, but merely as guidelines for consideration.

**References**

1. UNOS Scientific Registry data as of 8 September 1998.
60. Ellis M, Spence D, de Pauw B, et al. An EORTC international multicenter randomized trial (EORTC number 19923) comparing 2 dosages of lipo-