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REVIEW

Antifungal Prophylaxis in Liver Transplant Recipients

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Although the overall incidence of fungal infections in liver transplant recipients has declined, these infections still contribute significantly to the morbidity and mortality of patients with risk factors for infection. Although antifungal prophylaxis has been widely studied and practiced, no consensus exists on which patients should receive prophylaxis, with which agent, and for what duration. Numerous studies have attempted to ascertain independent risk factors for invasive fungal infections in liver transplant patients, and these data, in addition to clinical trials, identify several patient groups at exceedingly high risk of fungal infection. These include retransplant patients, patients with renal failure requiring hemodialysis or renal replacement therapy, and those requiring reoperations after transplant. Because the majority of infections occur in the first month after transplantation, prophylaxis should be continued for 4-6 weeks. However, local epidemiology and research should guide decisions regarding choice of agent as well as overall development of interinstitutional guidelines, because the incidence and spectrum of infection may differ dramatically among institutions. ***Liver Transpl 15:842-858, 2009.*** © **2009 AASLD.**

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Fungal infections are one of the most devastating infectious complications of liver transplantation, contributing significantly to both morbidity and mortality in these patients.[1] Management of invasive mycoses, particularly *Aspergillus* infections, has proven remarkably challenging. Of the 5%-40% of liver transplant patients who develop an invasive fungal infection (IFI),[2-4] mortality associated with these infections ranges from 25%-67%,[5] although *Aspergillus*-associated mortality is as high as 60%-90%.[4,6,7] A variety of factors, including environmental exposures, technical/anatomic issues, and the degree of immunosuppression present interact in the causation of fungal infection.[8] An understanding of these interactions and effects is vital for the assessment of risk for serious fungal infections after transplantation and the development of prophylactic strategies.

SEARCH STRATEGY

A PubMed search (through March 2009) was performed using the search terms "prophylaxis," "risk factors," "fungal infection," "*Candida*," "*Aspergillus*," and "antifungals," in combination with "liver transplant." The search was limited to articles in English. All relevant peer-reviewed original articles, meta-analyses, guidelines, consensus statements, and review articles were examined.

EPIDEMIOLOGY AND RISK FACTORS FOR FUNGAL INFECTIONS

Pathogens

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*. *Candida* species account for the majority (60%-80%) of IFIs, followed by *Aspergillus* species (1%-8% of patients), other molds, and *Cryptococcus neoformans*.[3,7]

Risk Factors for Infection

The incidence of IFIs is strongly influenced by patients' clinical conditions, level of immune suppression, sur-

Abbreviations: CMV, cytomegalovirus; IA, invasive aspergillosis; IDSA, Infectious Diseases Society of America; IFI, invasive fungal infection; SDD, selective digestive decontamination;

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TABLE 1. Risk Factors for IFI for All Fungal Pathogens

Risk Factor	N	Odds/Hazard Ratio (95% CI)	Reference
Preoperative Risk Factors			
UNOS status 1 (life support in ICU)	146	6.3 (2.4–16.7)	George et al.[14]
Donor CMV+/recipient CMV–	146	4.8 (2.0–11.8)	George et al.[14]
UNOS class I (life support in ICU)	172	3.5 (1.7–7.0)	Winston et al.[23]
Fungal colonization at baseline	172	2.3 (1.2–4.3)	Winston et al.[23]
Pretransplant SCr ≥ 3 mg/dL	168	1.4 (1.2–1.6)	Collins et al.[11]; Karchmer et al.[17]
Per mg/dL increase in pretransplantation bilirubin	284	1.002 (1.0001–1.0004)	Wade et al.[22]
Pretransplantation HHV-6 seronegativity	247	Not provided	Dockrell et al.[12]
Operative Risk Factors			
Retransplantation	131	6.0 (1.7–21.1)	Fortun et al.[13]
	172	3.7 (2.0–6.8)	Winston et al.[23]
	168	3.2 (1.5–6.5)	Collins et al.[11]; Karchmer et al.[17]
	265	2.9 (1.5–5.7)	Karchmer et al.[17]
	307	Not provided	Castaldo et al.[10]
Choledochojejunostomy	124	4.9 (1.8–13.8)	Karchmer et al.[17]; Hadley et al.[15]
	265	2.8 (1.5–5.2)	Karchmer et al.[17]
Surgical reintervention	131	5.1 (1.8–14.5)	Fortun et al.[13]
Return for Surgery	284	2.98 (1.32–6.7)	Wade et al.[22]
Re-operations (abdominal or intrathoracic)	168	2.5 (1.6–3.8)	Collins et al.[11]; Karchmer et al.[17]
40 units blood/platelets transfused in OR	265	2.6 (1.4–4.9)	Karchmer et al.[17]
Per unit of blood/platelets transfused in OR	124	2.2 (2.1–4.4)	Karchmer et al.[17]; Hadley et al.[15]
Operation time ≥ 11 hours	168	1.2 (1.1–1.4)	Collins et al.[11]; Karchmer et al.[17]
Postoperative Risk Factors			
Dialysis post-LT	80	20.5 (2.9–143.8)	Rogers et al.[20]
HD or hemofiltration post-LT	152	Not provided	Briegel et al.[9]
Units of fresh frozen plasma given post-LT	152	Not provided	Briegel et al.[9]
Fungal colonization (within 3 days after LT)	265	4.7 (2.5–8.9)	Karchmer et al.[17]
Bacteremia	146	4.6 (1.8–11.7)	George et al.[14]
HHV-6 infection	80	8.3 (1.2–58.0)	Rogers et al.[20]
ICU stay >3 days	265	4.5 (1.7–12.1)	Karchmer et al.[17]
Per day of therapy with ciprofloxacin	284	1.09 (1.01–1.17)	Wade et al.[22]
Platelet volume (per unit)	146	1.016 (1.006–1.026)	George et al.[14]
Reintubation	307	Not provided	Castaldo et al.[10]
Any Timepoint			
CMV infection	168	8.5 (3.3–21.7)	Collins et al.[17]; Karchmer et al.[17]
	124	3.4 (1.1–10.2)	Karchmer et al.[17]; Hadley et al.[15]

NOTE: Only trials which included an adequate control group, and only risk factors which were found to be significantly associated with IFI on multivariate analysis, are presented.
Abbreviations: CMV, cytomegalovirus; ICU, intensive care unit; LT, liver transplant; OR, operation room; UNOS, United Network for Organ Sharing; SCr, serum creatinine.

gical factors, and the technical complexity of the surgery. Well-defined risk factors associated with the development of IFIs include preoperative and postoperative renal failure, retransplantation, substantial infusions of intraoperative cellular blood products, a choledochojejunostomy anastomosis, *Candida* colonization, cytomegalovirus (CMV) viremia or disease, and re-exploration after transplantation (Table 1).[9-24]

A few studies have identified specific factors for the development of candidiasis (Table 2). However, many of these risk factors were determined from studies conducted in the early to mid-1990s. Improvements in surgical and medical technique and the medical management of liver transplantation, and decreases in transplant-related nonfungal infections such as CMV have been associated with decreasing rates of invasive candidiasis.[5] A recent prospective, multicenter, case-controlled trial of 35 cases of invasive candidiasis noted that 65% of infections were caused by *C. albicans* and 21% by *C. glabrata*. Patients infected with non-*albicans Candida* were significantly more likely to have received antifungal prophylaxis (50% versus 14%, $P = 0.04$), and infection with these species was correlated with higher mortality. In a logistic regression analysis, a require-

TABLE 2. Risk Factors for Specific Fungal Pathogens

Risk Factor	Organism	N	Odds Ratio (95% CI)	Reference
Preoperative Risk Factors				
SBP prophylaxis with FQ	*Candida*	35	11.0 (3.0–33.8)	Husain et al.[16]
Operative Risk Factors				
Retransplantation	*Candida*	35	11.0 (3.3–36.4)	Husain et al.[16]
	Candida	50	Not provided	Tollemar et al.[21]
>18 units cryoprecipitate transfused in OR	*Candida*	405	3.6 (1.8–7.3)	Patel et al.[19]
Long transplantation time	*Candida*	50	Not provided	Tollemar et al.[21]
Class II HLA partial or complete match	*Candida*	405	2.5 (1.2–5.3)	Patel et al.[19]
Donor from male	*Candida*	50	Not provided	Tollemar et al.[21]
Retransplantation	*Aspergillus*	260	29.9 (2.1–425.1)	Fortun et al.[24]
Postoperative Risk Factors				
Posttransplant HD	*Candida*	35	8.0 (3.1–20.0)	Husain et al.[16]
High number of erythrocyte units transfused posttransplant	*Candida*	50	Not provided	Tollemar et al.[21]
Posttransplant bacterial infection	*Candida*	405	4.6 (2.3–9.2)	Patel et al.[19]
CMV viremia	*Candida*	35	3.0 (1.2–7.3)	Husain et al.[16]
CMV disease	*Aspergillus*, early onset	88	2.3 (1.1–4.9)	Gavalda et al.
	Aspergillus, late onset	260	6.7 (1.0–42.5)	Fortun et al.[24]
Use of muromonab-CD3	*Aspergillus*	2180	6.29 (0.93–42.65)	Kusne et al.[18]
Aspergillus antigenemia post-LT	*Aspergillus*	260	50.0 (3.56–650)	Fortun et al.[24]
Dialysis	*Aspergillus*	131	5.5 (1.5–19.6)	Fortun et al.[13]
Need for dialysis post-LT	*Aspergillus*	260	24.5 (1.25–354)	Fortun et al.[24]

Abbreviations: ATB, antibiotics; CMV, cytomegalovirus; FQ, fluoroquinolone; GI, gastrointestinal; HD, hemodialysis; HLA, human leukocyte antigen; ICU, intensive care unit; IFI, invasive fungal infection; LT, liver transplant; OR, operation room; UNOS, United Network for Organ Sharing; SBP, spontaneous bacterial peritonitis; SCr, serum creatinine.

ment for dialysis, the use of prophylaxis for spontaneous bacterial peritonitis with fluoroquinolones, and retransplantation were significantly correlated with infection. In contrast, factors related to surgical technique, such as length of operation, cold ischemic time, type of anastomosis, and blood loss were not significantly associated with infection.[16]

However, these surgical and medical improvements have not been associated with a decrease in the frequency of invasive aspergillosis (IA).[5] Risk factors for *Aspergillus* infection tend to be associated with posttransplantation impairment of allograft and renal function.[25] About 50% of IA infections occur in the setting of retransplantation, which confers a 30-fold greater risk of infection.[24] Posttransplantation renal failure, especially that requiring dialysis, confers a 5-fold to 25-fold greater risk of IA. Other factors independently correlated with the early development of aspergillosis include the presence of *Aspergillus* antigenemia any time after transplant, CMV disease (because of the immunologic effect of cytokine deregulation), and the use of muromonab-CD3 monoclonal antibody (Table 2).[13,18,24] The presence of thrombocytopenia, which serves as a marker of severity of hepatic dysfunction, may play a critical role in the host defense against *Aspergillus* by augmenting polymorphonuclear leukocyte-mediated damage to the fungal hyphae.[26]

Timing of Infections

The recent trial by Husain et al., which analyzed 35 cases of invasive candidiasis, found the median time to infection to be 13.5 days, with 72% of infections occurring within the first month after transplantation.[16] Earlier studies reported that aspergillosis in patients who had undergone liver transplant occurred predominantly in the early posttransplant period, often prior to the patient leaving the intensive care unit (ICU) after surgery. The median time to onset after transplantation was 17 days in one study and 16 days in another.[7] However, more recent data suggest a shift in epidemiology, with 55% of infections occurring ≥ 90 days after transplant. This shift in timing has important implications for the choice and timing of preventive approaches for invasive aspergillosis.[27]

Changes in Surgical Techniques

In a study of 190 liver transplants performed between 1990 and 2000, Singh and colleagues demonstrated significant decreases in operative length, intraoperative transfusion requirements, use of roux-en-Y biliary anastomosis (i.e., choledochojejunostomy), cold ischemic time, retransplantation, and rate of biopsy-proven rejection over time. Concurrent with these changes was a significant decrease in the incidence of invasive can-

didiasis (9%-1.7%). No patient received antifungal prophylaxis.[5]

DIAGNOSIS OF IFIS

Complicating the decision of whether prophylaxis should be utilized are the challenges in diagnosing IFIs in transplant recipients. Although recently updated guidelines from the Invasive Fungal Infections Cooperative Group in Europe and the Mycoses Study Group in the United States have standardized definitions to be used in the enrollment of patients in clinical trials, they are not meant to guide clinical practice. They define a "proven" IFI as a positive fungal culture or histological demonstration of fungal or hyphal elements in a biopsy from a sterile site. "Probable" and "possible" IFIs are further defined on the basis of specific host factors, clinical manifestations of fungal infection, and mycological findings.[28]

Distinguishing between colonization and infection is challenging, particularly with pathogens that are cultured from nonsterile sites. For example, isolation of *Aspergillus* species from bronchial washings, sputum, or nasal secretions is not always indicative of an invasive pulmonary or sinus *Aspergillus* infection.[29] Although a definitive diagnosis of invasive pulmonary aspergillosis can be made by obtaining a biopsy of lung tissue, thrombocytopenia often limits clinicians' ability to perform this procedure. Generally, the diagnosis is determined with the use of high-resolution computed tomography, in which invasive pulmonary aspergillosis will manifest early on as a nodular opacity with surrounding attenuation, or "halo sign".[29] In late IA nodular lesions, diffuse pulmonary infiltrates, consolidation, or ground-glass opacities can be observed. However, bacteria and other fungal infections may produce similar findings.[30] Notably, liver transplant recipients are uniquely predisposed to dissemination of *Aspergillus* infection beyond the lungs, which occurs in ~50%-60% of cases.[7]

Early differentiation of IFIs due to *Aspergillus* species versus zygomycetes and other molds would allow clinicians to initiate timely, appropriate antifungal therapy. New laboratory methods for detecting IFIs are being considered because other diagnostic methods may not always be definitive. The galactomannan test is an enzyme-linked immunosorbent assay that detects galactomannan, an antigen released from *Aspergillus* hyphae upon invasion of host tissue.[29] Although the currently approved test is performed on serum, the utility of this assay on bronchoalveolar lavage fluid and cerebrospinal fluid has also been assessed in the clinical setting.[31,32] The sensitivity of the test ranges from 30%-100%, with a specificity of ~85%; however, the sensitivity of the assay is decreased in patients receiving mold-active drugs on the day of sampling, and it is important to note that its utility in the setting of prophylaxis has not been defined.[29] False positives can occur, particularly in patients receiving cyclophosphamide or piperacillin-tazobactam.[33,34] False negatives can occur during the concomitant use of antifungals, presumably because the level of galactomannan is related to the fungal burden.[29]

The compound 1,3-β,D-glucan is a component of fungal cell walls that can be detected colorimetrically in clinical samples, and is currently approved by the U.S. Food and Drug Administration (FDA) for use on serum. The test can be used to detect most fungi, except for zygomycetes, with a wide range of sensitivity (50%-95%) and specificity (86%-98%) depending on the assay used and the cutoff value.[29,35,36] However, the test can produce false positives in patients undergoing hemodialysis with cellulose membranes, and in other cases for unclear reasons.[29]

One way to effectively use the 1,3-β,D-glucan or galactomannan assays may be to serially screen patients who are at high risk for IFIs and/or use them to monitor response to therapy as, for instance, galactomannan results decline in patients responding to treatment. Finally, polymerase chain reaction–based testing that is being performed in some centers is a promising methodology, but is not yet FDA-approved.[29]

CLINICAL STUDIES OF ANTIFUNGAL PROPHYLAXIS

Selective Digestive Decontamination

Contrary to infections due to *Aspergillus*, in which inhalation of the pathogen is the presumed route of infection, *Candida* infections usually present as intra-abdominal abscesses, recurrent cholangitis due to biliary strictures, and peritonitis, and are often accompanied by fungemia.[37,38] Eradication of normal flora with the administration of antibiotics predisposes patients to overgrowth of *Candida* in the gastrointestinal tract, with subsequent translocation of *Candida* across the gastrointestinal mucosa.[39] Alternatively, spillage of intestinal contents during the transplant procedure or reoperations in patients with pre-existing *Candida* overgrowth of the gastrointestinal lumen may lead to intra-abdominal candidal infections and subsequent dissemination.[37,38]

The use of selective digestive decontamination (SDD) with nonabsorbable antibiotics, including nystatin, clotrimazole, and oral amphotericin B, has been proposed as a logical tool which maintains the growth of anaerobic bacteria while minimizing the intraluminal growth of *Candida*.[38] However, although the use of SDD eradicates gastrointestinal *Candida* colonization, once SDD is discontinued, re-colonization occurs in a majority of patients.[40]

Of SDD trials of antifungals, most are either noncomparative or compare an SDD regimen to a historical cohort,[41-47] employ two regimens utilizing the same antifungal,[48] or compare different antifungals but without a placebo control.[49,50] Many fail to report the incidence of fungal infections,[51-54] or report an extremely low incidence of fungal infections such that comparisons are not feasible,[55] or report fungal infections but without providing a breakdown of fungal infections ob-

TABLE 3. Clinical Trials Evaluating Prophylactic Antifungal Therapy in Liver Transplant Recipients

Authors	Study Design	Antifungal Strategy	n	Enrollment Criteria	Definitions Utilized	Results	Mortality	Comments
Kung et al.[64]	Retrospective Historical cohort utilized as control	Group A: FLU 100mg Q24H Group B: no prophylaxis in historical cohort Prophylaxis initiated at time of admission to liver unit	Group A: 45 (time period: July 1992 to February 1995) Group B: 72 (1984 to June 1992)	Prophylaxis initiated in all patients with fulminant hepatic failure	Not provided	N/A	Mortality attributable to IC: Group A: 0 Group B: 6 (8%) Mortality attributable to IMI: Group A: 3 (7%) Group B: 2 (3%)	Median operative transfusions: Group A: 5 units Group B: 10 units $P = 0.0026$
Tollemar et al.[61]	Randomized, prospective	Time period: 2/1990- 4/1992 Group A: AmB 1mg/kg IV Q24H Group B: placebo Started during LT and given for 5 days	Group A: 40 Group B: 37	None	Proven IFI: autopsy findings or positive cultures from normally sterile body sites or deep organ biopsy in clinically ill patients. IA: Chest radiograph showed pneumonia and bronchoscopy samples grew *Aspergillus* Suspected IFI: clinically ill patient with unknown etiology and serologic findings of fungi without microscopy or culture findings of fungi from a deep site	Total (over 1st year post-transplant): Group A: 4 (10%) Group B: 11 (30%) $P < 0.05$ At 30 days: Group A: 0 Group B: 6 (16%) $P < 0.01$ 30 days- 1 year: Group A: 4 (10%) Group B: 5 (14%) no P value reported.	Total mortality in first year: Group A: 8 (20%) Group B: 8 (22%) p-value not reported Attributable mortality in first year Group A: 1 (2.5%) Group B: 3 (8%) $P > 0.5$.	Causes of IFI: Group A: *Candida* (1), *Aspergillus* (3) Group B: *Candida* (9), *Aspergillus* (2) Safety: only significant difference was mean serum alkaline phosphatase level at 30 days post-LT Group A: 3.3 X ULN Group B: 1.5 X ULN $P < 0.01$
Lumbreras et al.[65]	Prospective, randomized, multicenter	Time period: Not noted. Group A: FLU 100mg PO Q24H Group B: NYS 10^6 units PO Q6H Both received treatment days 3-28 post-LT	Group A: 76 Group B: 67	LT recipients > 8 years old who had first LT in prior 24 hours were randomized. Excluded: azole allergy, SCr≥3 mg/dL, AF within 1 week of study, preexisting FI	IFI: presence of organ-specific symptoms and + cultures from normally sterile sites Colonization: isolation of fungus from stool, throat, urine in absence of clinical findings Thrush: oral lesions, odynophagia, and positive culture for *Candida* in absence of other pathogens *Candida* cystitis: dysuria, pyuria, and isolation of *Candida* in pure growth at least twice (once after catheter replacement) Esophageal candidiasis: compatible endoscopic appearance and culture + for *Candida* from biopsy specimens	*Candida* colonization occurring during study period: Group A: 25% Group B: 53% $P = 0.04$ Total *Candida* infection: Group A: 9 (12%) Group B: 18 (27%) $P = 0.022$ IC: Group A: 1 (1%) Group B: 4 (6%) $P = 0.12$	Overall: Group A: 10 (13%) Group B: 9 (13%) Death attributable to *Candida*: Group A: 0 Group B: 1	No significant differences between adverse events related to AF
Winston et al.[23]	Prospective, randomized, placebo-controlled	Time period: 5/1992- 9/1993 Group A: FLU 400mg Q24H (IV initially, PO when able to tolerate oral medications) Group B: PLA Prophylaxis started just prior to LT, and continued for 10 weeks after LT. If patient required another LT, prophylaxis given for an additional 10 weeks	Group A: 108 Group B: 104	Patients undergoing LT ≥ 13 years old no clinical evidence of fungal infection no systemic AF in the 2 weeks prior to randomization, not allergic to study drug.	Colonization: the presence of a fungus in ≥1 surveillance cultures of the oropharynx, axillae, inguinal skin folds, urine, and stool or perirectal area in the absence of any clinical symptoms or signs of infection. Colonization was assessed at study entry, weekly during the study period, and at the termination of prophylaxis. Superficial FI: isolation of a fungus from the skin, oropharynx, vagina, gastrointestinal tract, wounds, or urine in association with signs of inflammation, ulcerations, plaques, or exudates that could not be explained by other pathogens. IFI: the presence of fungus in the blood, pulmonary tissue or secretions, sinuses, peritoneal cavity, or other organ structures in association with symptoms and signs of infection that could not be explained by other pathogens.	All FI: Group A: 10/108 (9%) Group B: 45/104 (43%) $P < 0.001$ IFI: Group A: 6/108 (6%) Group B: 24/104 (23%) $P < 0.001$ Fungal colonization* at week 8: Group A: 23/83 (28%) Group B: 52/58 (90%) $P < 0.001$ * not all patients were cultured	Overall: Group A: 12 (11%) Group B: 15 (14%) Death attributable to FI: Group A: 2/108 (2%) Group B: 13/104 (13%) $P = 0.003$ Patients with ≥1of the following considered high-risk: UNOS Class I, fungal colonization at baseline, repeated transplantation. IFI in high-risk patients: Group A: 9/81 (11%) Group B: 38/70 (54%) $P < 0.001$ Proven FIs Group A: 5/81 (6%) of Group B: 38/70 (54%) $P < 0.001$	Adverse events or laboratory abnormalities possibly or probably related to the study drug: Group A: 43/108 (40%) Group B: 28/104 (27%) $P = 0.05$ Neurologic events more common in fluconazole group, including headache, seizures, and tremors. Causes of IFI: Group A: *Candida sp.* (6), *Aspergillus sp.* (1) Group B: *Candida sp.* (20), *Coccidioides immitis* (2), *Aspergillus sp.* (4)

TABLE 3. (Continued)

Authors	Study Design	Antifungal Strategy	n	Enrollment Criteria	Definitions Utilized	Results	Mortality	Comments
Singhal et al.[58]	Prospective	Time period: November 1996 to December 1997 Group A: ABLC 5mg/kg IV Q24H Group B: ABLC 2.5mg/kg IV Q24H Group C: 1 mg/kg IV Q24H Prophylaxis continued until ICU discharge or death	Group A: 10 Group B: 10 Group C: 10	Prophylaxis initiated in all patients requiring either mechanical ventilation or CRRT for ≥5 days post-LT	Proven IFI: histological evidence of fungal invasion or isolation of fungus from a single, normally sterile site Possible IFI: isolation of *Candida* from 3 or more nonsterile sites Colonization: isolation of fungus from 1 or 2 nonsterile sites	1 case of possible IFI (*Candida* isolated from 3 nonsterile sites without signs/symptoms of infection; treatment group unknown)	Total: Group A: 3 Group B: 2 Group C: 1 Attributable: 0/30	
Singh et al.[60]	Retrospective Historical cohort utilized as control	Group A: Lipid formulation of AmB 5mg/kg IV Q24H Group B: no prophylaxis Prophylaxis continued until death, discharge, or discontinuation of RRT	Group A: 11 (time period April 1997 to January 2000) Group B: 22 (time period 1990 to March 1997)	LT patients requiring RRT post-transplant	IC: histopathological evidence of tissue invasion by biopsy, or on autopsy, or isolation of *Candida* in one or more blood cultures, or isolation of *Candida* in normally sterile body fluid or sites, with samples collected intraoperatively or by percutaneous needle aspirate. *Cryptococcus*: Isolation in culture *Aspergillus*: evidence of tissue invasion on biopsy or autopsy plus isolation of *Aspergillus* in culture	IFI: Group A: 0 Group B: 8 (36%) $P = 0.03$ Logistic regression analysis (age, CMV infection, increased immunosuppression, prophylaxis): only prophylaxis associated with protection from IFI ($P = 0.017$)	One-year total: Group A: 6 (55%) Group B: 12 (55%) Attributable: Group A: 0 Group B: 33 (14%) *P* value not reported	Causes of IFIs in Group B: *C. albicans* (2), *C. glabrata* (2), *A. fumigatus* (3), *C. neoformans* (1)
Biancofiore et al.[2]	Randomized, prospective	Time period: January 1999 to August 2000 Group A: AmB 1 mg/kg IV Q24H X 7 days, then ITR 200mg PO Q24H X 3 weeks. Group B FLU 400 mg IV Q24H X 7 days, then ITR 200mg PO Q24H X 3 weeks. Group C PLA IV X 7 days, then PO X 3 weeks Initiated immediately before surgery	Group A: 42 Group B: 43 Group C: 44	129 consecutive LT patients Exclusion: previous systemic antifungals within 2 weeks prior to LT and documented allergy to study drugs	FI: histological evidence of tissue invasion at biopsy or autopsy or a positive culture from a deep tissue specimen, or positive cultures from ≥3 peripheral sites and the presence of budding yeast, pseudohyphae, or a positive culture from a bronchoalveolar lavage specimen with clinical and/or radiological evidence of pneumonitis Colonization: isolation or identification of a mycotic species from a single superficial site or positive serological test results not associated with any clinical or other evidence of invasive disease	FI: Group A: 10 (24%) Group B: 10 (23%) Group C: 13 (30%) *P* value not reported Colonization: Group A: 15 (36%) Group B: 18 (42%) Group C: 30 (68%) $P < 0.01$	Total: Group A: 3/42 (7%) Group B: 2/43 (5%) Group C: 3/44 (7%) Attributable: Group A: 1/42 (2%) Group B: 2/43 (5%) Group C: 2/44 (5%)	Itraconazole oral formulation not specified Causes of IFI: Group A: *Candida* (10), Other (1) Group B: *Candida* (7), *Aspergillus* (2) Group C: *Candida* (11), Other (1)
Fortun et al.[63]	Retrospective Historical cohort utilized as control	Time period: February 1997 to December 1999 Group A: FLU 100mg PO Q24H + AmB 100 mg PO Q6H for first 20 days after LT Group B: FLU 100mg PO Q24H for first 20 days after LT	Group A: 91 (time period February 1997 to December 1999) Group B: 128 (2/1994-1/1997)	None	IFI: clinical signs and symptoms present together with a significant yeast isolation (positive culture from a sample obtained from an sterile place or a positive histology	Invasive infections due to *Candida*: Group A: 5 (6%) Group B: 13 (10%) $P = 0.3$	Not reported	

TABLE 3. (Continued)

Authors	Study Design	Antifungal Strategy	n	Enrollment Criteria	Definitions Utilized	Results	Mortality	Comments
Winston et al.[4]	Prospective, randomized	Time period: Not noted. Group A: ITR 200mg PO SOLN Q8H for 24H followed by 200mg PO SOLN Q12H Group B: FLU 400mg IV Q24H followed by 400mg PO Q24H when able to swallow oral tablets. Prophylaxis initiated as a single preoperative dose and continued for 10 weeks post- LT	Group A: 97 Group B: 91	LT recipients: -between 18 and 75 years old - no clinical or microbiological evidence of fungal infection at time of study entry - no allergy to azole AF -not on specified interacting agents After the study was completed, a subgroup of high risk patients was compared: High risk was defined as ≥1 risk factor: –UNOS classification of 1 -fungal colonization at time of transplantation -repeat transplantation 70 ITR patients and 73 FLU patients had one or more of these risk factors for fungal infection.	Colonization: the presence of a fungus in ≥ 1 surveillance cultures in the absence of any clinical symptoms or signs of infection. Superficial FI: isolation of a fungus from the skin, oropharynx, gastrointestinal tract, or vagina in association with signs of inflammation, ulcerations, plaques, exudates, or other manifestations of infection not explainable by other pathogens. IFI: the presence of fungus in the blood, pulmonary tissues or secretions, sinuses, soft tissues, peritoneal cavity, or other organ structure in association with symptoms and signs of infection not explainable by other pathogens.	Overall FI: Group A: 9 (9%) Group B: 4 (4%) P=0.23 IFI: Group A: 7 (7%) Group B: 3 (3%) P>0.05 Fungal colonization significantly decreased in both groups (p<0.001) Among high risk patients: Proven fungal infection occurred in ITR: 7 of 70 (10%) (5 invasive infections, 2 superficial infections) FLU: 2 of 73 (3%) (2 invasive infections) (P=0.09). Among low-risk patients without any significant risk factors for fungal infection: Proven fungal infection ITR: developed in 2 of 27 (7%) (2 invasive infections) FLU: 2 of 18 (11%) (1 invasive infection, 1 superficial infection) (P = 1.0).	Overall: Group A:12 (12%) Group B: 7 (8%) Death attributable to FI: Group A: 1 Group B: 0	More adverse events in ITR group (51% vs. 21%, $P < 0.001$), mostly due to gastrointestinal effects Causes of IFI: Group A: *Candida sp.* (5), *Aspergillus sp.* (2) Group B: *Candida sp.* (2), *Aspergillus sp.* (1) Mean trough concentrations of ITR at 2, 4, 8 and 10 weeks of treatment were generally lower in the 8 of 9 patients who failed prophylaxis than in patients who did not develop a fungal infection
Fortun et al.[13]	Retrospective review Historical cohort utilized as control	Group A: AmB 100mg IV Q24H + FLU 100 mg Q24H for 20 days Group B: FLU 100 mg Q24H for 20 days AmB prophylaxis continued for 10-15 days	Group A: 149 (time period 1/1998-12/2001) Group B: 131 (1/1994-12/1997)	AmB prophylaxis given to pts with ≥4 risk factors: >30units of PRBCs during transplantation, SCr>2.5mg/dL, need for RRT, retransplantation, surgical reintervention, CMV antigenemia (>10cells/200000) or disease, acute rejection, mould colonization, ATB >5days, ICU stay prior to LT	IC: histopathological evidence of tissue invasion or isolation in normally sterile body fluids Proven IA: tissue histopathology with septate, acute branching hyphae +/− culture from the same site OR positive culture obtained by invasive procedure Probable IA: pulmonary disease with new nodules/cavities on chest radiograph and 2 + sputum cultures or one + bronchoalveolar lavage, washing, or brushing cultures	IFI: Group A: 9 (6%) Group B: 22 (17%) P = 0.007 Multivariate analysis: prophylaxis efficacious in preventing IFI in patients with >4 risk factors, OR 0.1 (95% CI 0.02-0.8)	3 month overall mortality: Group A: 10 (7%) Group B: 18 (14%) P = 0.05 12 month overall mortality: Group A: 15 (10%) Group B: 24 (18%) P = 0.07	Causes of IFI: Group A: *Candida* (3), *Aspergillus* (6) Group B: *Candida* (9), *Aspergillus* (13) 3 IFI cases (one aspergillosis, two candidiasis) developed in patients receiving prophylaxis
Sharpe et al.[52]	Prospective, randomized, double-blind, placebo-controlled, restricted-sequential	Time period: Not noted. Group A: ITR SOLN 5mg/kg PO X 1 preoperatively, then 2.5mg/kg PO Q12H postoperatively Group B: PLA Continued until either fungal endpoint or discharge from hospital or when a total of 56 days of treatment had occurred	Group A: 25 Group B: 37	>17 years old undergoing LT Excluded: unable to take medications enterally, being treated or had signs/symptoms of FI at time of LT, allergy to azole antifungals, received systemic antifungals within 2 weeks prior to study entry or topical oral therapy within 1 week, history of prior FI unresponsive to azole therapy, HIV +, or receiving concomitant systemic interacting medications.	Suspected deep FI: 1 of the following - clinical signs and symptoms with fever of unknown origin unresponsive to broad spectrum anti-bacterials - highly suggestive radiological lesions for deep fungal infection, without mycological evidence by culture or histology - clinical signs and symptoms not highly suggestive of fungal infection but associated with a suggestive fungal isolation Superficial FI: clinical signs and symptoms of oral, esophageal, or vaginal candidosis plus + cultures at site of infection. Only superficial fungal infections treated with systemic antifungal medication were considered a fungal endpoint.	Suspected deep FI (no proven FI): Group A: 1 (4%) Group B: 6 (16%) P = 0.225 Superficial FI: Group A: 0 Group B: 3 (8%) P = 0.141	Overall: Group A: ITR: 1 (4%) Group B: 6 (16%) $P > 0.5$	The one case of suspected FI in itraconazole patient occurred in context of sub-therapeutic plasma levels (<250 ng/mL)

TABLE 3. (Continued)

Authors	Study Design	Antifungal Strategy	n	Enrollment Criteria	Definitions Utilized	Results	Mortality	Comments
Hellinger et al.[59]	Prospective intervention with retrospective chart review Historical cohort utilized as control	Group A: ABLC 5mg/kg IV q24-48hrs Group B: no prophylaxis in historical cohort Prophylaxis continued until hospital discharge	Group A: 250 (time period 2/1999-4/2001) Group B: 58 (2/1998-1/1999)	Prophylaxis suggested for high-risk patients (RRT at time of LT and/or hospital discharge delayed >7 days post-LT due to allograft or renal insufficiency) and intermediate-risk (LT due to fulminant hepatic failure and/or retransplantation) patients Recipients who had either or both of the first 2 risk factors were considered to be at high risk for invasive mold infection, and those who had either or both of the latter 2 risk factors were considered to be at intermediate risk. Recipients with no risk factors were considered to be at low risk.	EORTC definitions utilized	IFI through end of 1st year post-transplant: Group A: 3 (1%) Group B: 3(5%) $P = 0.08$ 2/35 high-risk pts (18 received prophylaxis) developed IFI vs. 1/215 non-high-risk pts ($P = 0.05$)	Only one death due to IFI occurred, in historical group (not attributable to IFI)	Significantly higher incidence of CMV infection and use of pulse corticosteroids for acute rejection in historical group. Only 26% of high-risk pts given prophylaxis, 7% of intermediate-risk Causes of IFI: Group A: Proven aspergillosis (2), probable aspergillosis (1) Group B: Proven aspergillosis (2), proven curvuleria infection (1)
Reed et al.[73]	Retrospective	Time period: 1994-2005 Group A: ABLC 5mg/kg IV Q24H X 5 days Or AmB 1mg/kg IV Q24H X 5 days Group B: No prophylaxis.	Group A: 51 patients; 58 LT (22 AmB and 36 ABLC) Group B: 158 patients; 174 LT	≥ 18 years All patients defined as at high risk for FI. High risk defined as one of the following factors being present: retransplantation within one month post-LT, pre-LT renal failure, fulminant hepatic failure as primary indication for LT, or underwent reoperation within the first month post-LT Perioperative transfusion requirements and donor/recipient CMV status were not always available, so these factors were not included in the definition of "high risk" Excluded 39 patients who were receiving fluconazole at time of LT for non-prophylaxis indications	FI: if conformed to definitions from the Mycoses Study Group of the National Institutes of Allergy and Infectious Diseases (Denning et al 1994) and occurred in the period of 3 months pre-LT through entire admission to 3 months post-discharge Fungus isolated from normally sterile site counted as infection. Respiratory isolates were excluded, unless obtained by bronchoscopy and patient had declining respiratory status, clinical signs/symptoms consistent with acute infection, and no other infectious cause apparent	IFI: Group A: 3 (5%) Group B: 28 (16%) $P = 0.043$ Logistic regression analysis incorporating MELD score, time, and pre-LT renal failure (as only high-risk variable that was significant in pre-model specification), hepatitis C, patient age, gender: Odds ratio for fungal infection in high-risk patients who did not receive prophylaxis= 4.04 ($P = 0.0046$).	Not provided.	Significant baseline differences between groups: Pre-LT fulminant hepatic failure: Group A: 12% Group B: 3% $P = 0.021$ Pre-LT Hepatitis C: Group A: 21% Group B: 43% $P = 0.003$ Causes of IFI: Group A: *Candida* (3) Group B: *Candida* (22), *Aspergillus* (6)

TABLE 3. (Continued)

Authors	Study Design	Antifungal Strategy	n	Enrollment Criteria	Definitions Utilized	Results	Mortality	Comments
Fortun et al.[6]	Prospective, multicenter, noncomparative, open-label trial	Time period: April 2004 to June 2007 Caspofungin 50 mg IV QD (after 70-mg IV LD) x ≥21 days Dose =35 mg IV QD in patients with moderate hepatic insufficiency Dose = 70-mg QD starting on day 2 of study therapy in pts > 80 kg or with concomitant therapy with inducers of drug clearance	71	High risk patients as evidenced by having 1 of these major criteria: a. Retransplantation caused by severe dysfunction of a previous graft, b. need for any renal replacement therapy, including dialysis or venous hemofiltration within a maximum time period of 30 days, c. prior history of fulminate hepatitis leading to LT, or 2 of these minor criteria a. prior postoperative renal failure (defined as creatinine clearance <50 mL/min) within a maximum time period of 30 days, b. transfusion intraoperatively of more than or equal to 40 units cellular blood products, c. presence of a choledocojejunostomy, d. more than or equal to 2 positive clinical site surveillance culture (nasal, pharyngeal, or rectal) for *Candida* from 48 hr before to 48 hr after LT, e. reoperation (laparotomy) within 5 days of LT. Patients with severe hepatic insufficiency (Child-Pugh score >9) were not eligible for enrollment.	successful treatment outcome was defined as the absence of breakthrough IFI during the first 100 days after the onset of caspofungin.	MITT: successful treatment outcome in 88.7%. 2 patients developed IFI: a Mucor and a Candida albicans surgical wound infections, respectively.	8 patients died, 6 during caspofungin administration and 2 during follow-up period, but none were attributed to IFI or caspofungin toxicity	6 patients discontinued caspofungin because of drug-related altered liver function. Altered analytical data compatible with grade IV toxicity was observed in 27.7% of patients at the end of caspofungin prophylaxis and in 15.4% of patients in safety visit (14 days after ending caspofungin administration) (P = 0.13)
Hadley et al.[72]	Prospective, multicenter, double-blind, randomized	Group A: AmB 2 mg/kg Q24H Group B: FLU 400 mg IV Q24 Patients randomized within 5 days of LT, and prophylaxis continued for 14 days	Group A: 35 Group B: 29	Prophylaxis initiated in patients with ≥ 2 risk factors within 5 days of LT (retransplantation, preoperative creatinine > 2.0 mg/dL or need for dialysis within 48 H of LT, choledochojejunostomy, intraoperative requirement of ≥ 40 units of blood products (excluding cryoprecipitate and plasma), *Candida* cultured within 48 H before and after LT from ≥ 1 site (sputum, urine, wound, Jackson-Pratt drainage, intra-operative recipient bile/biliary tree, T-tube drainage), re-operation within 5 days for intra-abdominal bleeding or repair of bile or other viscous leak, vascular accident other than bleeding, or acute graft failure.	IFI definitions based on EORTC/MSG criteria	Proven/Probable IFI (within 100 days after LT): Group A: 6 (17%) Group B: 4 (14%) P value not reported	Overall Mortality: Group A: 7 (20%) Group B: 4 (14%) Mortality attributable to IFI: Group A: 0 Group B: 0	Closed early due to insufficient enrollment ~1/3 of patients did not complete 14 days of prophylaxis Causes of IFI: *Candida* (9), *Cryptococcus* (1) Patients with IFI were more likely to have a choledochojejunostomy (60% vs. 31%) and retransplantation (30% vs. 7%) than those without IFI. Rate of IFI among patients with 3 risk factors was higher than those with 2 (27% vs. 10%)

NOTE: Only published trials with systemically available agents are included.

Abbreviations: ABLC, amphotericin B lipid complex; AF, antifungals; AmB, amphotericin B deoxycholate; AmB, liposomal amphotericin B; ATB, antibiotics; CMV, cytomegalovirus; CVVH, continuous veno-venous hemofiltration; EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycoses Study Group; FI, fungal infection; FLU, fluconazole; GI, gastrointestinal; H, hours; HIV, human immunodeficiency virus; IA, invasive aspergillosis; IC, invasive candidiasis; ICU, intensive care unit; IFI, invasive fungal infection; IMI, invasive mold infection; ITR, itraconazole; IV, intravenous; LD, loading dose; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NYS, nystatin; UNOS, United Network for Organ Sharing; PRBC, packed red blood cells; PLA, placebo; PO, by mouth; Q, every; RRT, renal replacement therapy; SCr, serum creatinine; SOLN, solution; ULN, upper limit of normal.

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served in each study arm. None of the trials target only high-risk patients.

As such, the clinical effectiveness of SDD in reducing systemic *Candida* infections (beyond the potential beneficial effect of selective bowel decontamination) remains unknown.[40] To our knowledge, only one prospective, double-blind trial has evaluated the utility of SDD in preventing invasive fungal infections. Zwaveling and colleagues randomized 55 patients (high-risk and low-risk) who underwent transplantation between 1994 and 1998 to placebo or a SDD regimen which included oral amphotericin B administered at 10 mg four times daily.[56] The regimen was initiated at least 7 days prior to transplant, and was continued for 30 days after transplant (postoperatively, the regimen also included an oral paste with a 2% solution of amphotericin). In the first 30 days after transplantation, significantly fewer infections occurred due to *Candida* (15/29 versus 4/26, $P < 0.05$). However, the total number of postoperative infections and infection-related morbidity was unaffected, and infections caused by gram-positive pathogens increased. Because the specifics of infection type were not broken down per organism, the distribution of urinary tract, wound, or mixed infections is unclear.

Studies of systemic antifungal prophylaxis in liver transplant patients have utilized three antifungal agents: itraconazole, amphotericin B (as various formulations), and fluconazole (Table 3).

Itraconazole

The three available studies regarding the prophylactic use of itraconazole are inconclusive. In one trial of 71 patients randomized to placebo or oral itraconazole solution, the incidence of candidal infection was significantly lower in the treatment arm (9/37 [24%] versus 1/25 [4%], $P = 0.04$). However, no patient had a documented invasive infection. In all patients, *Candida* was isolated from urine, stool, mouth, vagina, and/or respiratory secretions, with corresponding systemic signs of infection.[57] In the only other placebo-controlled trial, no differences in the incidence of fungal infections were found among the three study arms: liposomal amphotericin B for 7 days followed by itraconazole for 3 weeks, fluconazole for 7 days followed by itraconazole for 3 weeks, or placebo.[2] However, neither of these studies targeted prophylaxis toward high-risk patients.

Winston et al. compared itraconazole oral solution to fluconazole 400 mg daily for 10 weeks.[4] Proven IFIs developed in 7 (7%) of 97 patients administered itraconazole and in 3 (3%) of 91 patients administered fluconazole ($P > 0.05$). A post-study analysis noted that proven fungal infection occurred in 7 (10%) of 70 high-risk itraconazole patients (five invasive infections, two superficial infections) and in 2 (3%) of 73 high-risk fluconazole patients (two invasive infections) ($P = 0.09$).

Amphotericin B

The trials analyzing the utility of amphotericin B in prophylaxis vary widely in terms of formulation, dosing, and methods. Several trials did not include appropriate control groups,[58-63] while others utilized a historical cohort design [13,64,65] which should be considered a major caveat to the interpretation of study results, given the above data showing significant advances in surgical technique over time and correlation with decreased rates of infection. This is unfortunate, because two studies utilizing a historical cohort design reveal encouraging results. Fortun et al reported that 22/131 (17%) patients developed fungal infections in the historical arm versus 9/149 (6%) ($P < 0.01$) in the intervention arm, who received cumulative prophylactic doses of 1-1.5 g of lipid formulations of amphotericin. Among patients who underwent dialysis, amphotericin prophylaxis decreased the incidence of aspergillosis from 32% (7/22) to 0% (0/15).[13] However, as an example of the problems with historical cohort designs, 55% of patients in the historical group required > 30 units packed red cells compared to only 7% in the prophylaxis cohort ($P < 0.01$). Singh et al. employed antifungal prophylaxis with a lipid preparation of amphotericin B in 11 of 38 (29%) liver transplant recipients who required dialysis.[65] Although no reduction in mortality was documented, prophylaxis was associated with a significant reduction in IFIs in these high-risk patients. IFIs occurred in 8 of 22 (36%) of the patients who did not receive prophylaxis (historical cohort) and 0 of 11 (0%; $P = 0.03$) of those who did. Antifungal prophylaxis was independently associated with protection from fungal infection ($P = 0.017$).

Several trials analyzed the use of low-dose intravenous (IV) amphotericin products. Tollemar and colleagues randomized 86 patients to 1 mg/kg/day IV liposomal amphotericin B or placebo for 5 days after transplant.[66] IFIs were more common in the placebo group at 30 days (16% versus 0%). However, several reports suggest that low-dose amphotericin B prophylaxis may not adequately suppress infection, especially those caused by *Aspergillus*.[60,67] In one trial, of 58 patients who received 1 mg/kg/day IV liposomal amphotericin B for 7 days after transplant, three patients died of breakthrough *Aspergillus fumigatus* infections (at 8, 19, and 24 days after operation, respectively), and one patient developed *Candida albicans* sepsis at postoperative day 4, which was treated successfully with a dose increase to 3 mg/kg/day.[60] In addition, Singh and colleagues report three cases of invasive aspergillosis that developed while on treatment for candidiasis with low-dose IV amphotericin B deoxycholate (0.5 mg/kg/day).[67] Conversely, no patients without candidemia (and thus not on amphotericin B) developed aspergillosis. The authors suggest that in addition to low-dose amphotericin B being ineffective in the prophylaxis of aspergillosis, perhaps low doses actually predispose a patient to infection. Taken together, it appears that IV liposomal amphotericin B may be an effective prophylactic agent, but that doses > 1 mg/kg/day should be utilized to prevent breakthrough infections.

Fluconazole

Data regarding the use of fluconazole provides a clearer view on the importance of selecting "high risk" patients when considering prophylaxis. Three earlier studies[68-70] employed low-dose (100 mg daily) therapy versus historical controls, nystatin suspension, or combination therapy with oral amphotericin B, whereas four later studies,[2,4,23,71] utilized a higher dosages (400 mg) versus placebo, IV amphotericin B, or itraconazole oral solution. In the earliest (1995) trial by Kung and colleagues, low dose (100 mg per os daily) fluconazole prophylaxis in "high risk" patients (based on having fulminant hepatic failure) reduced mortality due to candidal infections versus a historical cohort (0/45 [0%] versus 6/72 (8%), respectively, no *P* value provided), but potentially increased mortality due to invasive mold infections (3/45 [7%] versus 2/72 [3%], respectively, no *P* value provided). However, significantly fewer transfusions were required in the fluconazole cohort, potentially confounding the results.[69] In a subsequent trial, in which 143 patients were randomized to fluconazole 100 mg or nystatin 4×10^6 U administered daily for 28 days after transplant, fluconazole prophylaxis significantly reduced infections during the prophylaxis period: candidal infections developed in 9/76 (12%) of fluconazole-treated patients versus 18/67 (27%) nystatin-treated patients ($P = 0.022$). However, high-risk patients were not targeted for prophylaxis, and the vast majority of infections were superficial. By 90 days after transplant, four patients in the fluconazole group had developed an invasive infection (two cases of candidal esophagitis and two cases of aspergillosis) versus seven in the nystatin group (four cases of esophagitis, one fungemia, one intra-abdominal infection, and one case of aspergillosis). No differences in mortality were noted.[70]

In perhaps the most comprehensive, well-designed trial, Winston and colleagues performed a randomized, double-blind, placebo-controlled trial in 212 patients which compared 10 weeks of fluconazole 400 mg daily to placebo.[23] Proven infections were significantly lower in the treatment arm (10/108 [9%] versus 45/104 [43%], $P < 0.001$), as were invasive infections (24/104 [23%] versus 6/108 [6%], respectively, $P < 0.001$). Most infections occurred within the first 6 weeks after transplantation. Cyclosporine levels were significantly higher, and more neurologic adverse reactions occurred in patients receiving fluconazole ($P = 0.01$). Although there were significantly fewer deaths due to fungal infection in the fluconazole group, there were no differences in overall mortality ($P < 0.003$ and $P > 0.2$, respectively). Importantly, the authors also independently assessed risk factors for infection and the impact of prophylaxis in high-risk patients. Using stepwise regression analysis, assignment to placebo, baseline fungal colonization, repeated transplantation, and United Network Organ Sharing (UNOS) Status 1 (ICU) were identified as significant risk factors. Proven and invasive fungal infections occurred significantly more often in high-risk placebo recipients versus high-risk fluconazole recipients, but not in patients without risk factors for infection.

Echinocandins

Despite their broad spectrum of activity against both *Candida* and *Aspergillus* species, to date, only one study has evaluated the use of echinocandins as prophylaxis for IFIs.[6] A recent multicenter, noncomparative, open-label trial evaluated the prophylactic use of caspofungin (50 mg daily, in most patients) for ≥ 21 days, in 71 high-risk adult liver transplant recipients. A successful treatment outcome (defined as the absence of breakthrough IFI during the first 100 days after the onset of caspofungin treatment) was obtained in 88.7% of patients, and safety assessment was favorable, suggesting that caspofungin is an efficacious and well-tolerated drug as antifungal prophylaxis in high-risk liver transplant recipients. The extensive exclusion criteria, including patients taking cyclosporine, somewhat limit the clinical applicability of this study.

Current Practices

Antifungal prophylaxis for liver transplant recipients remains a complex and controversial issue, and institutional practices of antifungal prophylaxis vary widely, as illustrated by a recent survey by Singh and colleagues of 106 UNOS-approved transplant programs. Of 67 sites which responded, 46 (70%) performed ≥ 50 transplants annually, and 91% of programs employed some type of antifungal prophylaxis.[72] Despite the 2004 and 2009 (which appear unchanged) guidelines by the Infectious Diseases Society of America (IDSA), only 72% of centers targeted prophylaxis toward high-risk patients, whereas 28% used universal prophylaxis, primarily (86%) fluconazole.[73,74] Prophylaxis was targeted toward *Candida* in 86% of centers. In centers which used mold-active agents for prophylaxis, a variety of agents were utilized, including low-dose lipid formulations of amphotericin B (1 mg/kg/day). Echinocandins were noted to be the leading choice of mold-active agents for antifungal prophylaxis, probably due to their lack of significant drug interactions with the immunosuppressive agents and favorable safety profile. Prophylaxis was continued for the duration of the posttransplant hospital stay in ~40% of centers, for 1 month after transplant in ~20%, for 3 months in ~10%, and for varied durations in the remainder.[72]

ASSESSMENT OF AVAILABLE DATA

How does one distill the available data? Two recent meta-analyses highlight some important points: universal prophylaxis results in a clear but limited effect in reducing proven IFIs. The effects were most pronounced for patients receiving fluconazole in doses of at least 400 mg daily for more than 4 weeks. However, fungal prophylaxis has no effect on overall mortality, or on the numbers of patients placed on definitive treatment for suspected fungal infection. Furthermore, prophylaxis results in a significantly higher proportion of episodes of non-*albicans Candida* infection (Table 4).[75,76] As such, it is clear that universal prophylaxis is

TABLE 4. Meta-Analyses of Antifungal Prophylaxis in Liver Transplant Recipients

Author	No. of Trials	Number of Patients	Regimens Compared	Infection Reduction (95% CI)	Attributable Mortality (95% CI)	Overall Mortality (95% CI)	Comments
Playford et al.[70]	7	793	FLU vs. PLA (2), FLU vs. nonsystemic AF (2), ITR vs. PLA (2), AmB vs. PLA (1)	Proven IFI RR 0.39 (0.18–0.85) Fungal colonization RR 0.51 (0.41–0.62) Fungal colonization with *C. glabrata*/ *C krusei* RR 1.57 (0.76–3.24)	Not reported	RR 0.84 (0.54–1.3)	Formulated algorithm (based on fluconazole prophylaxis data only) in which patients with <2 risk factors (retransplantation, preoperative creatinine > 2.0 mg/dL, choledochojejunostomy, requirement of ≥ 40 units of blood products intraoperatively, fungal colonization from ≤ 2 days prior to and 3 days after transplant, and reoperation within 5 days for reason other than bleeding) deemed low-risk (4% incidence) for IFI. Conversely, patients with ≥2 of the above risk factors, fulminant hepatitis, preoperative steroids, dialysis or renal failure, or postoperative bacterial or CMV infection calculated to be at high risk (25% incidence) for IFI.
Cruciani et al.[69]	6	698	AmB vs. PLA (1), FLU vs. nonsystemic AF (1), FLU vs. PLA (2), ITR vs. PLA (1), AmB→ITR vs. FLU→ITR vs. PLA (1)	Total proven fungal infections RR 0.31 (0.21–0.46) IFI RR 0.33 (0.18–0.59)	RR 0.30 (0.12–0.75)	RR 1.06 (0.69–1.64)	Patients receiving prophylaxis had a higher proportion of non-*albicans* proven fungal infections (56% vs. 33%), mostly consisting of *C. glabrata* (26% vs. 14%) Higher incidence of side effects in prophylaxis arm: RR 1.38 (1.04–1.83)

Abbreviations: AF, antifungal; AmB, liposomal amphotericin B; CI, confidence interval; CMV, cytomegalovirus; FLU, fluconazole; IFI, invasive fungal infection; ITR, itraconazole; PLA, placebo; RR, relative risk.

not a logical approach, because it carries the risk of unnecessary expense as well as the increased potential for antifungal drug resistance, drug interactions, and drug-associated toxicity.

Current Guidelines

The 2004 and the current (2009) IDSA guidelines recommend that only patients with ≥2 key risk factors (retransplantation, preoperative creatinine >2.0 mg/dL, choledochojejunostomy, intraoperative requirement of ≥40 units of blood products, prolonged [>11 hour] intraoperative time [the guidelines actually say >1 hour, which we presume to be an error], and fungal colonization from at least 2 days prior to and 3 days after transplantation) be considered for antifungal prophylaxis.[73,74] The guidelines cite two studies (Hadley et al.[15] and Karchmer et al.[17]) as the basis for the algorithm. The study by Karchmer et al., however, incorporates the patients in the study by Hadley et al., and expanded collection to assess two retrospective liver transplant recipient cohorts over a 13-year period (July 1983 to September 1992). The data revealed a series of perioperative risk factors that could be used to assign patients to low-risk or high-risk strata for the occurrence of IFI during the first 100 days after liver transplantation. Patients with ≥2 perioperative risk factors were at significantly higher risk of IFIs than those with 0 or 1 risk factor (38% versus 4%, respectively).[17] The

validity of low-risk assignment was subsequently studied in a multicenter, prospective observational study in 193 liver transplant patients who were considered low risk by guideline criteria. Seven (4%) patients developed an invasive fungal infection, of which three (2%) were due to potentially preventable infection by *C. albicans*. The other four infections, including one due to late-onset *C. neoformans* and three (2%) due to *Aspergillus* species, would not have been prevented with fluconazole prophylaxis.[77] The authors concluded that these findings validate the low-risk assignment of the IDSA algorithm. Several caveats to this conclusion should be noted. First, no data was provided on how many patients required dialysis after transplant. In addition, only two (1%) patients had undergone retransplantation. Both these risk factors have been repeatedly identified as highly significant, independent risk factors for IFI. As such, both factors most likely warrant prophylaxis by themselves, even those patients who, per the current guidelines,[73] would not qualify because they only have a single risk factor of retransplantation. In addition, no study has verified that patients who fit protocol criteria are at high risk and warrant prophylaxis. This is a crucial distinction, especially considering the numerous changes in liver transplantation practice since the analysis by Karchmer and colleagues. A recent study which attempted to assess the efficacy of 14 days of antifungal prophylaxis in high-risk patients (criteria similar to those in the study by Karchmer et al.) reported rates of IFI of ~15%, which is substantially lower than the 38% rate reported by Karchmer et al. However, it is not clear if this difference was due to the use of prophylaxis, advances in care, or other reasons.[71] Most tellingly, the data from Singh and Husain[5,16] suggest that certain factors, such as those involving outdated surgical techniques, may be excluded from such guidelines, whereas others, such as fluoroquinolone prophylaxis, should be evaluated further.

Guidance from Clinical Trials

Because no gold-standard algorithm exists, stratification of patients at risk for fungal infection must be evaluated and based on a recent and comprehensive data set. Only four studies have evaluated the efficacy of prophylaxis in patients identified before the study as "high risk" (i.e., both patients receiving and not receiving prophylaxis are identified by the same risk factors).[64,65,69,78] The study by Hellinger et al. only included six "high-risk" patients in the historical arm.[64] The trial by Kung et al. provided limited baseline information, and the historical arm included patients who underwent transplantation >20 years ago.[69] However, the trial by Singh et al. demonstrated an impressive and dramatic reduction in IFI in patients requiring dialysis who received prophylaxis versus those who did not (albeit with a small sample size).[65] Finally, the study by Reed et al. revealed a significant decrease in IFI in patients possessing at least one "high risk" criterion who received prophylaxis versus those who did not. The risk factors for ~60%, ~10%, and ~10% of the patients were reoperation within the first month after transplant, retransplantation, and renal failure, respectively (Table 3).[78] These trials further elucidate the high risk portended by retransplantation, dialysis, and reoperation after transplant, as shown in Tables 1 and 2.

Finally, although the trial by Winston et al. suggests that perhaps UNOS classification should be considered a significant risk factor for fungal infection, UNOS status 1 was defined as requiring life support in an ICU.[23] Use of this definition could result in administration of prophylactic antifungals to many patients, although only a few with certain risk factors may represent the primary population at risk. Current UNOS classification defines status 1A candidates as having fulminant liver failure, with the onset of hepatic encephalopathy within 8 weeks of first symptoms and requiring ICU care, and a life expectancy of <7 days. In addition, patients must either be ventilated, requiring dialysis, or have an international normalized ratio of > 2.0. Other qualifications for status 1A candidates are primary nonfunction of a recently transplanted liver and acute decompensated Wilson's disease. Using UNOS status (1 or 1A) as a risk factor for fungal infection has not been validated, and it is not certain which components of the status designation confer the increased risk.

RECOMMENDATIONS AND CONCLUSIONS

Clearly, despite many clinical trials, clinicians are left without clear answers. We propose the following:

(1) SDD is an enticing technique to prevent candidiasis while minimizing systemic exposure to antifungal agents. Unfortunately, the data regarding its efficacy is too limited to allow an evidence-based endorsement. The only prospective, controlled trial stopped enrolling patients in 1998, and although infections due to *Candida* were significantly reduced, there was no overall benefit in reducing total infection-related morbidity.[56] No trial has assessed stratifying patients to receive SDD based on risk for infection; for example, patients receiving broad-spectrum antibiotics prior to transplant may carry a high burden of *Candida* in the gut, and may especially benefit from SDD. Without further compelling evidence in a population that more accurately reflects current surgical techniques, the use of SDD as universal prophylaxis cannot be recommended.

(2) The incidence and timing of posttransplantation infections at one's own institution should be analyzed. Populations with rates of infection ≥ 10% should be considered for prophylaxis. A prime example of the need for this analysis is in the application of the trial by Winston and colleagues, which demonstrated a 43% fungal infection rate in the placebo group.[23] This is an unusually high rate, and as such, institutions with much lower rates of infection may not be able to extrapolate the results to their patients. Institutional variability in the incidence of IFIs is likely, given the variability in surgical techniques and differences in donor criteria (extended donor criteria, for example) and immunosuppressive regimens. However, the finding of significantly

higher rates of IFIs as compared to the literature should prompt an analysis of potential causes. Rigorous definitions for fungal infection should be used (see the international consensus recommendations published by De Pauw and colleagues).[28] Centers should be encouraged to share this data within their own and other institutions.

(3) Recent data suggest that modern surgical and medical practices have dramatically reduced the risk of candidiasis (1.7%, from Singh and colleagues).[5] This data suggests that because the general liver transplant population has a low risk of infection, prophylactic antifungals should only be utilized in those patients at highest risk. The important consequences of this stratification is illustrated by the trial by Husain,[16] which revealed that prophylaxis increased the risk for non-*albicans Candida*, and was associated with higher mortality.

In balancing the line between prophylaxis in appropriate patients and overuse, which may ultimately lead to worse outcomes, three methods may be considered: targeting of highest-risk patients, appropriate dosing, and a limited duration of therapy. In targeting the highest-risk patients, two risk factors have consistently been shown to portend a significantly increased risk of fungal infection (by both *Candida* and *Aspergillus* species) in liver transplant patients: renal failure, especially that requiring dialysis, and retransplantation. As such, these patients should all receive antifungal prophylaxis targeted against *Candida* spp. with fluconazole 400 mg daily. Therapy should be continued for 4-6 weeks, because the vast majority of candidal infections have been shown to occur in the first month after transplantation. The decision of whether prophylaxis should include coverage for *Aspergillus* should be based largely on local epidemiology.

(4) A challenging question is the choice of prophylactic agent in centers with high rates of fluconazole-resistant *Candida* (such as *C. glabrata*). Although choosing an arbitrary numerical cutoff may be appealing, centers should attempt to identify whether certain additional risk factors (such as prior azole use[79]) are present, which may indicate patients who are more likely to develop infection due to fluconazole-resistant species of *Candida*. At this time, the data is not consistent enough to develop strict protocol recommendations that all institutions would find valuable.

(5) If *Aspergillus* is a target pathogen (based on local epidemiology), either caspofungin or amphotericin B should be used for prophylaxis. Given the dramatic difference in nephrotoxicity between amphotericin B deoxycholate and the lipid formulations and the substantial degree of kidney disease in liver patients, lipid formulations are preferred.[80] If lipid formulations of amphotericin B are utilized, doses >1 mg/kg/day are recommended, given the reports of breakthrough aspergillosis with low doses.[60,67] The compiled data from the two historical cohort trials which utilized standard-dose lipid amphotericin B products is as follows: 3/261 (1%) in the intervention arms developed aspergillosis compared to 10/80 (13%) in the preintervention arms, and overall 1-year mortality rates were 41/261 (16%) and 17/80 (21%), respectively.[64,65] In the retrospective trial by Reed et al., no patients who received prophylaxis developed aspergillosis, versus six patients (4%) in the placebo group.[78] We recommend prophylaxis with a lipid formulation of amphotericin B (3-5 mg/kg/day) or caspofungin (70 mg load on day 1 followed by 50 mg/day).

Determining the appropriate duration of antifungal prophylaxis when targeting Aspergillus is deemed necessary is difficult. As stated previously, 55% of *Aspergillus* infections occur ≥ 90 days after transplantation, with 25% occurring after 1 year of transplant.[27] However, perhaps more relevant to the patients who would be considered for anti-*Aspergillus* prophylaxis, 76% of aspergillosis in patients who underwent retransplantation occur within 90 days of transplant (53% within the first 30 days).[81] Administration of amphotericin B for prolonged durations offers significant potential for renal toxicity, even with lipid formulations. Although the recent introduction of orally available agents such as posaconazole and voriconazole which have significant activity against *Aspergillus* offers an attractive alternative to amphotericin B, these agents have not yet been evaluated for this indication. Perhaps the best option is to administer prophylaxis for 4 weeks and to be cognizant of the significant potential for late disease in patients at risk. Given the correlation of late aspergillosis in retransplant patients with disseminated disease and severe outcomes (100% mortality in one analysis), aggressive management of disease should be instituted for patients who present with signs and symptoms of infection.[3,81]

(6) Some liver transplant patients in the ICU may warrant early antifungal therapy based on general risk factors. Although an in-depth discussion is beyond the scope of this article, a recent review distills the available data.[82] For example, ICU patients who undergo repeated abdominal surgeries have a significantly increased risk of candidal infections.[83] In these cases, patients who return to the operating room for repair of leaks, bleeds, or ischemia (Tables 1 and 2) should receive empiric anticandidal therapy. The duration of therapy, however, should not automatically be designated the same as in prophylaxis, because therapy should be continued as long as the patient is considered infected. As such, the distinction between prophylaxis and empiric therapy is important in these cases.

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