# Outcomes of antifungal prophylaxis in high-risk liver transplant recipients

S. Hadley, C. Huckabee, P.G. Pappas, J. Daly, J. Rabkin, C.A. Kauffman, R.M. Merion, A.W. Karchmer. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients.
Transpl Infect Dis 2009: **11**: 40–48. All rights reserved

**Abstract:** Antifungal prophylaxis for liver transplant recipients (LTRs) is common among patients considered at high risk of infection, but optimal prophylaxis duration and drug has not been defined. This study aimed to assess the effects of 14 days of antifungal therapy prophylaxis in reducing proven invasive fungal infections (IFI) in high-risk subjects. Eligible subjects who met 2 or more risk criteria were randomized 1:1 to the treatment arms (liposomal amphotericin B or fluconazole) and were followed for 100 days post transplantation for evidence of IFI. The study was designed to enroll 300 subjects, but was closed early for insufficient enrollment. A total of 71 subjects were enrolled and randomized. Two-thirds of subjects completed 14 days of study therapy. Ten subjects developed proven or probable IFI with *Candida* species (9 subjects) and *Cryptococcus neoformans* (1 subject); rates were similar in the 2 treatment arms. Eleven subjects died, but no death was attributed to study drug or IFI. In summary, high-risk LTRs tolerated antifungal prophylaxis well, and rates of IFI were lower than previously reported in untreated high-risk LTRs.

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Invasive fungal infections (IFI) are a major cause of morbidity and mortality among patients undergoing orthotopic liver transplantation (OLT). Although surgical techniques and immunosuppressive regimens have evolved to reduce mechanical complications and rejection episodes in liver transplant recipients (LTRs), the incidence of IFI remains between 6% and 47% (1–5). Mortality associated with these infections may be as high as 32% (6, 7). *Candida* species account for the majority of infections, followed by *Aspergillus* species, other molds, and *Cryptococcus neoformans* (8–11).

Despite the serious consequences of IFI in LTRs, a definitive strategy for prevention of this complication has not

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These data were presented at the Infectious Diseases Society of America (IDSA) 41st Annual Meeting in San Diego, California, USA, 2003.

yet emerged (12–14). The patient undergoing OLT today is generally sicker than a decade ago, owing to advances in medical therapy of end-stage liver disease and worsening organ shortage. Increased patient complexity necessitates assessment of risk for serious fungal infections after transplantation and subsequent preventative intervention. Well-defined preoperative and intraoperative risk factors associated with IFI have been documented in numerous studies and include preoperative renal failure, low serum albumin, retransplantation, substantial infusions of intraoperative cellular blood products, a choledochojejunostomy anastomosis, *Candida* colonization, early graft failure, and re-exploration after OLT (3, 8, 15–18). Over a 13-year-period in one center, perioperative risk factors were identified in 2 retrospective LTR cohorts and subsequently prospectively validated (8, 16, 19). LTRs with 2 or more perioperative risk factors were at substantially higher risk for IFI than those with 0 or 1 risk factor (34% vs. 3%, respectively) (19). These data suggest that IFI are concentrated in a specific subpopulation of LTRs, and those risks may be assessed and addressed in the perioperative period.

The aim of this study was to evaluate the safety and efficacy of antifungal therapy (liposomal amphotericin B [L-amB] and fluconazole) in patients undergoing OLT who are at high risk for IFI. A companion study assessing the natural history of IFI in low-risk LTRs has been reported (20). Our study was terminated early due to slow enrollment and unlikely completion of the trial in a timely manner. In this report, we describe the aggregate data and implications for future studies.

## Methods

### Study design and population

This prospective, double-blind, randomized trial was designed to evaluate the safety and efficacy of intravenous L-amB 2 mg/kg vs. fluconazole 400 mg daily for 14 days after randomization in 300 high-risk LTRs. The study was approved by the institutional review board (IRB) of each site.

All patients who underwent OLT at study sites were screened for eligibility. An IRB-approved informed written consent was obtained from patients at each site before performing tests exclusively required for determination of eligibility for this trial. Subjects $\geq 18$ years of age satisfied the screening criteria if the initial immunosuppressive regimen included tacrolimus and they were scheduled to receive nystatin 500,000 U 4 times daily as oral nonabsorbable antifungal prophylaxis for the first 60 days post transplant.

Subjects satisfying the screening criteria were considered for enrollment if they met 2 or more of the following high-risk perioperative criteria documented within 5 days of OLT: 1) a choledochojejunostomy anastomosis; 2) retransplantation; 3) intraoperative administration of $\geq 40$ U of cellular blood products (platelets or packed red blood cells excluding cryoprecipitate and plasma); 4) return to the operating room within 5 days for laparotomy for intra-abdominal bleeding or repair of bile or other viscous leak, vascular accident other than bleeding, or acute graft failure; 5) preoperative serum creatinine $\geq 2.0$ mg/dL or need for any form of dialysis within 48 h before OLT; and 6) *Candida* species isolated from cultures obtained within 48 h before or after OLT from one or more of the following sites: sputum, urine, wound, Jackson-Pratt drainage, intra-operative recipient bile/biliary tree, or T-tube drainage.

Eligible subjects were enrolled, stratified by cytomegalovirus (CMV) serostatus, and randomized within 5 days of OLT to receive either intravenous L-amB 2 mg/kg or fluconazole 400 mg daily for 14 days. Subjects were followed at specified intervals for clinical and microbiological events for 100 days post OLT. Surveillance fungal cultures were collected from available sites (sputum, urine, wound, rectum, Jackson-Pratt drains, and T-tube drainage) on study days 3, 7, 10, 14, 28, 42, 70, and 100 post OLT.

### Definitions

The primary endpoint was defined in the protocol to be the incidence of proven IFI within 100 days after OLT. The combined incidence of proven and probable IFI within 100 days after OLT and mortality at 100 days after OLT were both planned secondary endpoints.

Proven and probable IFI were defined based on MSG/EORTC criteria and assessed by a masked data review committee utilizing the same criteria (21).

Death was considered related to IFI based on post-mortem evidence or recovery of a fungus from blood or another sterile site within 48 h of death.

### Power and sample size

The planned study design assumed that the cumulative incidence of IFI at 100 days post transplant (OLT) in high-risk liver transplant patients would be 12% on fluconazole and 2% on L-amB. A sample size of 121 patients per treatment arm was determined to be sufficient to detect this difference at the 2-sided 0.05 significance level with power of 80%.

## Statistical analysis

All final data were maintained and analyzed centrally at Rho Federal Systems Division Inc. Authors had access to data and accept responsibility for content and analysis.

The safety population included all patients receiving at least one dose of study drug. Descriptive statistics of demographic characteristics, subject disposition, adverse events (AEs), and deaths were generated using data from this population. The mean, standard deviation, median, and range were computed for continuous safety variables, whereas frequency and percentage distributions are presented for categorical variables. A Kaplan–Meier estimate with 95% confidence intervals (CI) for the cumulative incidence of death (all-cause) at 100 days after OLT was produced.

Subjects from the safety population who did not meet study entry criteria were excluded from the modified intent-to-treat (MITT) population used for all descriptive analyses of fungal infection outcomes. Kaplan–Meier estimates at 100 days after OLT were generated for the cumulative incidence of (1) subjects with proven or probable IFI and (2) subjects with proven or probable IFI or who received empiric systemic antifungal therapy. For all 100-day estimates, 95% CI were computed based on Greenwood's formula for standard error. To provide a range of estimates of the risk of IFI in high-risk patients in the face of ambiguities in infection ascertainment and the effects of empiric antifungal therapy, multiple criteria were used to establish endpoints. Subjects who developed a proven or probable IFI during the follow-up period were considered to have met the primary study endpoint, thereby representing a conservative lower-bound estimate of risk. Less conservative estimates for risk of fungal infection were produced by combining patients with a proven or probable IFI with those receiving empiric systemic antifungal therapies for > 4 days during any 14-day interval during the study period without evidence of a fungal infection.

For patients who developed IFI, the date of onset was defined as the date the culture was taken.

# Results

## Study population

The study was terminated early because of slow enrollment and unlikely completion of the trial in a timely manner. Between September 1999 and August 2001, 71 subjects were enrolled and randomized at 13 sites. Because of the limited enrollment, all results presented by treatment group are intended to be strictly descriptive rather than inferential and emphasis is placed on the aggregated results. Figure 1 depicts subject flow through the study.

## Analysis populations

Thirty-nine subjects were randomized to the L-amB group, and 32 subjects were randomized to the fluconazole group. Sixty-eight subjects received at least one dose of study drug (safety population). The masked data review committee identified 4 treated subjects who did not meet study entry criteria, and thus 64 subjects (35 L-amB, 29 fluconazole) were included in the MITT population.

## Baseline characteristics

Baseline demographic and clinical characteristics were comparable across treatment groups (Table 1). Sixty percent of subjects were CMV seropositive at baseline. Males outnumbered females in the study (43 vs. 25). The average age was 50 years. The majority of subjects in the study were white/non-Hispanic (78%).

## Summary of study patient disposition

The disposition of subjects in the safety population is presented in Table 2. Sixty-two percent (58% L-amB, 67% fluconazole) of subjects completed 14 days of study drug. Early drug discontinuation was due to AEs (in 8 patient), development of IFI as determined by the site investigator (in 4), death (in 3), discharge from hospital (in 5), and other reasons (in 6) including medical decision, subject refusal to continue study medication but agreement to continue follow up, and lack of intravenous access. AEs leading to early discontinuation of study drug in the L-amB group (5 patients) included renal toxicity (in 3), intolerance to study medication with head and neck discomfort (in 1), and tacrolimus toxicity (in 1). AEs leading to early discontinuation of study drug in the fluconazole group (3 patients) included chest pain and shortness of breath (in 1), tacrolimus toxicity/interaction (in 1), and abdominal discomfort with nausea (in 1). The majority of subjects (79%) completed study follow-up through 100 days post OLT. Reasons for premature discontinuation from the study included death (in 11), loss to follow-up (in 1), patient withdrawal (in 1), and retransplantation (in 1).

## AEs

Overall, recorded AEs were consistent with the known profile of the study drugs and with the disease state of the subject population. The rate of occurrence of AEs was similar in the 2 treatment groups. Events occurring in more than 20% of the study population included tremor (34%), diarrhea (28%), ascites (26%), confusion (24%), hypotension (24%), pleural effusion (24%), pyrexia (24%), graft rejection (21%), nausea (21%), and tachycardia (21%).
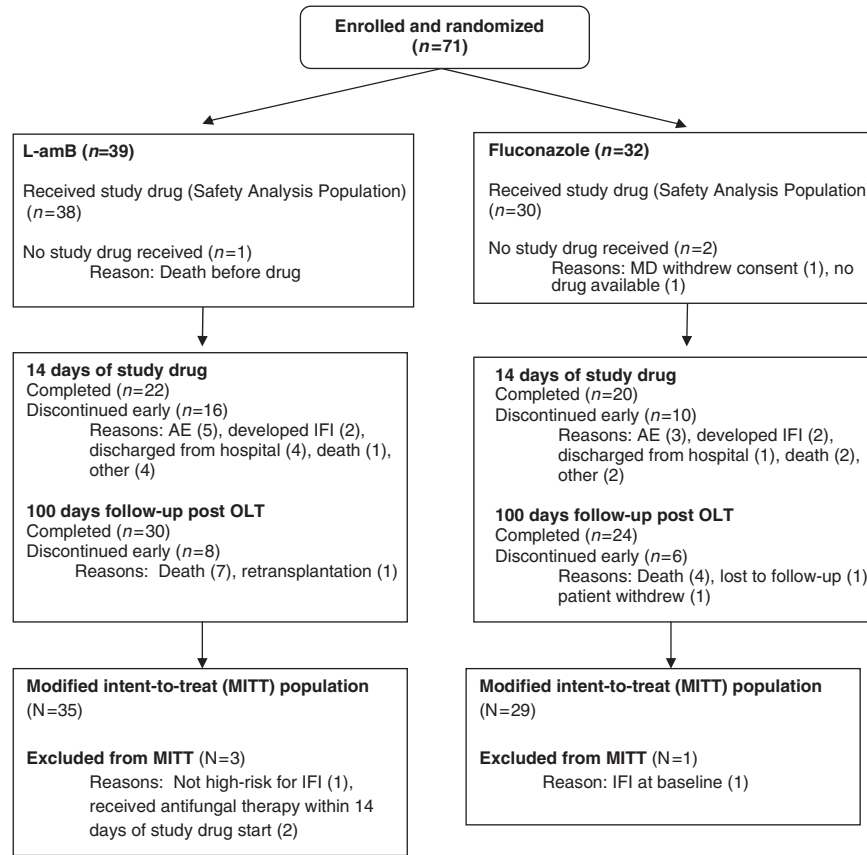
**Fig. 1.** Participant flow through study. L-amB, liposomal amphotericin B; *n*, number; AE, adverse events; IFI, invasive fungal infections; OLT, orthotopic liver transplantation.

## Mortality

Among subjects in the safety population, 11 deaths (7 L-amB, 4 fluconazole) occurred within the 100-day study follow-up window resulting in a Kaplan–Meier estimate for mortality at day 100 of 0.17 (95% CI: 0.10–0.28). Estimates for the L-amB and fluconazole groups were 0.20 (0.10—0.37) and 0.13 (0.05—0.32), respectively. No deaths were attributed to IFI or considered to be related to study drug. The most common cause of death was multi-system organ failure (8 subjects).

## Fungal infections

Ten subjects in the MITT population developed IFI by day 100 (9 proven, 1 probable; 6 L-amB, 4 fluconazole). The number of events was considered too small to make a meaningful comparison. Twelve subjects (8 L-amB, 4 fluconazole) without documented proven or probable IFI received empiric systemic antifungal therapy for additional prophylaxis or empiric therapy for suspected fungal infection or colonization. Kaplan–Meier estimates and 95% CIs for risk of fungal infection at 100 days after OLT for all subjects in the MITT popu-

lation are shown in Table 3. The estimates for the combined population are 17% for proven and probable IFI and 37% considering proven or probable IFI or receipt of empiric sys-

**Baseline demographic and clinical characteristics: safety population**

| Characteristic | All (N = 68) | L-amB (N = 38) | Fluconazole (N = 30) |
|---|---|---|---|
| CMV positive, *n* (%) | 41 (60%) | 23 (61%) | 18 (60%) |
| Age, mean (SD) | 49.9 (9.3) | 48.4 (8.6) | 51.9 (9.8) |
| Male, *n* (%) | 43 (63%) | 24 (63%) | 19 (63%) |
| Race/ethnicity, *n* (%) | | | |
| White, non-Hispanic | 53 (78%) | 33 (87%) | 20 (67%) |
| African-American, non-Hispanic | 6 (9%) | 2 (5%) | 4 (13%) |
| Hispanic | 4 (6%) | 1 (3%) | 3 (10%) |
| Asian | 1 (1%) | 1 (3%) | 0 (0%) |
| Other | 4 (6%) | 1 (3%) | 3 (10%) |

*N*, number; L-amB, liposomal amphotericin B; CMV, cytomegalovirus; SD, standard deviation.

*Table 1*

**Subject disposition: safety population**

| Characteristic | All (N = 68) n (%) | L-amB (N = 38) n (%) | Fluconazole (N = 30) n (%) |
|---|---|---|---|
| Failed to complete 14 days of study drug | 26 (38%) | 16 (42%) | 10 (33%) |
| Primary reason for early discontinuation of study drug | | | |
| Adverse event | 8 (12%) | 5 (13%) | 3 (10%) |
| Patient developed IFI | 4 (6%) | 2 (5%) | 2 (7%) |
| Discharged from hospital | 5 (7%) | 4 (11%) | 1 (3%) |
| Death | 3 (4%) | 1 (3%) | 2 (6%) |
| Other | 6 (9%) | 4 (11%) | 1 (3%) |
| Completed 100 days post-OLT follow-up | 54 (79%) | 30 (79%) | 24 (80%) |
| Prematurely discontinued from study | | | |
| Death | 11 (16%) | 7 (18%) | 4 (13%) |
| Lost to follow-up | 1 (1%) | 0 | 1 (3%) |
| Patient withdrew | 1 (1%) | 0 | 1 (3%) |
| Retransplantation | 1 (1%) | 1 (3%) | 0 |

*N*, number; L-amB, liposomal amphotericin B; IFI, invasive fungal infections; OLT, orthotopic liver transplantation.

*Table 2*

tem antifungal therapy. Nine *Candida* species (*C. albicans* in 2, *C. glabrata* in 4, *C. parapsilosis* in 2, and *C. tropicalis* in 1) and 1 *C. neoformans* infections occurred. The 3 *Candida* infections, occurring in those who received fluconazole prophylaxis, were caused by *C. glabrata*. Most infections occurred early, within 21 days of OLT, and were predominantly intra-abdominal in origin, based on cultures obtained at the time of reoperation or percutaneous aspiration (6 of 10) (Table 4).

### High-risk criteria

Tables 5 and 6 summarize high-risk criteria at enrollment for the MITT analysis population by treatment group and

by development of IFI, respectively. Receipt of $\geq 40\,U$ of cellular blood products, baseline fungal colonization, and elevated serum creatinine were the most common risk factors for eligibility, with similar frequencies in each treatment group. More subjects in the L-amB group returned to the operating room within 5 days of OLT (20%) than in the fluconazole group (7%). The reverse was true for those undergoing retransplantation (6% L-amB, 17% fluconazole). Most of the subjects enrolled had 2 high-risk criteria (42, 66%); 14 (22%), 7 (11%), and 1 (2%) met 3, 4, and 5 high-risk criteria, respectively. Subjects with IFI appeared to be more likely to have choledochojejunostomy type of anastomosis (60% vs. 31%) and retransplantation (30% vs. 7%) than subjects without IFI. The rate of IFI among LTRs with 2 risk factors (4/42; 10%) was lower than among those with 3 or more risk factors (6/22; 27%), suggesting a possible additive effect of risk factors.

## Discussion

A recently updated meta-analysis of the effects of prophylaxis in solid organ transplant recipients demonstrated a significant reduction in IFI in LTRs treated with fluconazole prophylaxis, but no reduction in mortality (22). The authors concluded that antifungal prophylaxis is warranted in high-risk individuals or those in transplant centers with high rates of IFI. Our study is the first to describe the development of IFI in high-risk LTRs receiving antifungal prophylaxis and supports this strategy. This randomized antifungal prophylaxis trial in high-risk LTR was prematurely terminated because of slow enrollment and poor likelihood of meeting enrollment goals within a reasonable time period. Nevertheless, this study resulted in 4 important observations that are related to 1) the tolerance and duration of antifungal prophylaxis treatment; 2) the predominant types of high-risk criteria in subjects who developed IFI and the additive effect of high risk factors; 3) the rate, timing, and types of IFI; and 4) survival of high-risk LTR 100 days post transplant.

**Kaplan–Meier (KM) day 100 estimates and 95% confidence intervals (CI) for risk of fungal infection: modified intent-to-treat population**

| Fungal infection endpoint | Day 100 KM estimate (95% CI) | | |
|---|---|---|---|
| | Combined treatments | L-amB | Fluconazole |
| Proven or probable IFI | 0.17 (0.09–0.29) | 0.18 (0.09–0.36) | 0.15 (0.06–0.35) |
| Proven or probable IFI or empiric systemic antifungal therapy | 0.37 (0.26, 0.50) | 0.43 (0.28, 0.62) | 0.29 (0.16, 0.50) |

L-amB, liposomal amphotericin B; IFI, invasive fungal infections.

*Table 3*

**Proven and probable invasive fungal infections (IFI): modified intent-to-treat population**

| Days from OLT to IFI | Type of infection | Treatment group | Causative organism | Infection site | High-risk criteria |
|---|---|---|---|---|---|
| 3 | Proven IFI | Fluconazole | *C. glabrata* | Intra-abdominal/ peritoneal fluid | Retransplantation, cellular blood products ≥ 40 U, serum Cr ≥ 2.0, dialysis within 48 h, *Candida* species isolated |
| 6 | Proven IFI | Liposomal amphotericin B | *C. parapsilosis* | Blood | Cellular blood products ≥ 40 U, *Candida* species isolated |
| 7 | Probable IFI | Liposomal amphotericin B | *C. parapsilosis* | Right IJ catheter tip | Choledojejunostomy, cellular blood products ≥ 40 U |
| 11 | Proven IFI | Liposomal amphotericin B | *C. albicans* | Intra-abdominal/ peritoneal fluid | Choledojejunostomy, cellular blood products ≥ 40 U, *Candida* species isolated, returned to OR |
| 12 | Proven IFI | Fluconazole | *Cryptococcus neoformans* | Sputum | Serum Cr ≥ 2.0, dialysis within 48 h, *Candida* species isolated |
| 14 | Proven IFI | Liposomal amphotericin B | *C. albicans* | Intra-abdominal/ peritoneal fluid | Choledojejunostomy, retransplantation, cellular blood products ≥ 40 U, serum Cr ≥ 2.0, dialysis within 48 h, *Candida* species isolated |
| 22 | Proven IFI | Liposomal amphotericin B | *C. tropicalis* | Intra-abdominal/ peritoneal fluid | Choledojejunostomy, cellular blood products ≥ 40 U, *Candida* species isolated |
| 36 | Proven IFI | Fluconazole | *C. glabrata* | Intra-abdominal/ bile leak | Cellular blood products ≥ 40 U, serum Cr ≥ 2.0, dialysis within 48 h, *Candida* species isolated |
| 46 | Proven IFI | Fluconazole | *C. glabrata* | Blood | Choledojejunostomy, retransplantation, cellular blood products ≥ 40 U, *Candida* species isolated |
| 93 | Proven IFI | Liposomal amphotericin B | *C. glabrata* | Intra-abdominal/ liver fluid | Choledojejunostomy, cellular blood products ≥ 40 U |

OLT, orthotopic liver transplantation; *C., Candida*; Cr, creatinine; U, units; IJ, intrajugular; OR, operating room.

*Table 4*

Approximately one-third of study subjects did not complete 14 days of assigned study therapy. The 2 most common reasons for early discontinuation were development of AEs in 12% and early discharge from the hospital in 7%. These reasons reflect the underlying conditions of these very ill high-risk LTRs, the toxicities of antifungal therapies, and indicate a need for oral alternatives for high-risk LTRs who do well after surgery and are quickly discharged from the hospital. In our study, the vast majority of AEs were unrelated to study drug; those that were treatment-related were within the expected range for the drugs studied.

Retransplantation and a choledochojejunostomy type of anastomosis were more common perioperative risk factors in subjects who developed IFI. A choledochojejunostomy anastomosis, in which the donor common bile duct is diverted to the recipient's jejunal loop, potentiates the risk of colonization of the biliary system with upper gastrointestinal tract pathogens, such as *Candida* species. Others have found that retransplantation and choledochojejunostomy types of anastomosis are significant risks for fungal infection after OLT (3, 7, 8, 13, 16, 23). Our data suggest that there

may be an additive effect of high-risk factors in the genesis of IFI.

In this clearly defined high-risk group of LTRs who received systemic antifungal prophylaxis in the initial 2 weeks after OLT in addition to topical oral nystatin, the adjusted IFI attack rate by day 100 was approximately 17%. Other studies of antifungal prophylaxis in LTRs have largely not distinguished high- from low-risk subjects. Attack rates for IFI in treated groups in these studies have ranged from 0% to 15% (13, 14, 24–27). In our study, the rate of IFI was approximately half that of previously reported *untreated* high-risk LTRs, which suggests a benefit of prophylaxis (8, 16, 19). In addition, the overall rate of IFI in our study population provides insight into the frequency of IFI for calculating sample size in future studies of prophylaxis.

Invasive candidiasis, predominantly intra-abdominal, was the most common IFI occurring in this study. A choledochojejunostomy type of anastomosis was employed more frequently in the infected group and may play a role in the predominance of intra-abdominal infections overall. Non-*albicans Candida* species caused the majority of IFI.

**High-risk criteria at enrollment by treatment group: modified intent-to-treat population**

| Characteristic | All (N = 64) n (%) | L-amB (N = 35) n (%) | Fluconazole (N = 29) n (%) |
|---|---|---|---|
| Number of high-risk criteria at enrollment | | | |
| 2 | 42 (66%) | 24 (69%) | 18 (62%) |
| 3 | 14 (22%) | 9 (26%) | 5 (17%) |
| 4 | 7 (11%) | 1 (3%) | 6 (21%) |
| 5 | 1 (2%) | 1 (3%) | 0 |
| High-risk criteria | | | |
| Choledochojejunostomy anastomosis | 23 35% | 14 (40%) | 9 (31%) |
| Retransplantation | 7 (11%) | 2 (6%) | 6 (17%) |
| Intraoperative use of > 40 units blood products | 46 (72%) | 25 (71%) | 21 (72%) |
| Pre-op Cr > 2.0 mg/dL  or any dialysis 48 h pre-op | 29 (45%) | 13 (37%) | 16 (55%) |
| *Candida* species isolated from surveillance culture | 45 (70%) | 23 (66%) | 22 (76%) |
| Return to the OR within 5 days post OLT | 9 (14%) | 7 (20%) | 2 (7%) |

N, number; L-amB, liposomal amphotericin B; Cr, creatinine; OR, operating room; OLT, orthotopic liver transplantation.

*Table 5*

In the fluconazole group, all IFI were caused by *C. glabrata,* which has higher rates of fluconazole resistance. As in other studies, the majority of *Candida* infections occurred within the first month after transplantation (7, 8, 14, 16, 20, 26, 28). The timing of infection suggests that a prophylaxis period of one month might be preferable.

In our study, in which a little more than half of the patients received prophylaxis with a drug effective against all yeasts and molds, no infections due to *Aspergillus* or other filamentous fungi occurred in the first 100 days after OLT. This negligible attack rate for *Aspergillus* may simply reflect the follow-up period studied rather than drug efficacy. Singh et al. (17) documented a trend toward invasive aspergillosis occurring more than 3 months after OLT in the majority of patients (55%) studied after 1998. In contrast, 3 of the 7 IFI occurring in the cohort of low-risk

**High-risk criteria at enrollment by development of invasive fungal infections (IFI): modified intent-to-treat population**

| Characteristic | All (N = 64) n (%) | No IFI (N = 54) n (%) | IFI (N = 10) n (%) |
|---|---|---|---|
| Number of high-risk criteria at enrollment | | | |
| 2 | 42 (66%) | 38 (70%) | 4 (40%) |
| 3 | 14 (22%) | 12 (22%) | 2 (20%) |
| 4 | 7 (11%) | 4 (7%) | 3 (30%) |
| 5 | 1 (2%) | | 1 (10%) |
| High-risk criteria | | | |
| Choledochojejunostomy anastomosis | 23 (35%) | 17 (31%) | 6 (60%) |
| Retransplantation | 7 (11%) | 4 (7%) | 3 (30%) |
| Intraoperative use of > 40 units blood products | 46 (72%) | 37 (69%) | 9 (90%) |
| Pre-op Cr  > 2.0 mg/dL or any dialysis 48 h pre-op | 29 (45%) | 25 (46%) | 4 (40%) |
| *Candida* species isolated from surveillance culture | 45 (70%) | 37 (69%) | 8 (80%) |
| Return to the OR within 5 days post OLT | 9 (14%) | 8 (15%) | 1 (10%) |

N, number; Cr, creatinine; OR, operating room; OLT, orthotopic liver transplantation.

*Table 6*

patients followed prospectively were due to invasive aspergillosis, and 2 occurred within 11 days of OLT (20). In high- and low-risk cohorts taken together, the preponderance of early, predominantly non-*albicans Candida* species and *Aspergillus* species infections suggest that a future prophylaxis trial in high-risk LTRs should use broad-spectrum antifungal agents, available in oral form, that are active against all *Candida* species as well as *Aspergillus* species and given for at least 30 days postoperatively.

In this high-risk LTR population, the 100-day survival rate of 79% compares favorably to most previous studies examining mortality in LTRs of varying degrees of risk (6, 7, 16, 29). Moreover, 95% of low-risk patients from the same transplant centers survived 100 days without IFI-related deaths (20). Whether or not antifungal prophylaxis contributed to improved survival in the high-risk cohort cannot be surmised from these data.

In summary, we conducted a randomized controlled antifungal prophylaxis trial for high-risk LTRs assessed perioperatively and followed for 100 days. Despite early termination of the trial and lack of ability to compare treatments in a statistically meaningful manner, our data suggest that a lipid formulation amphotericin B and fluconazole are well tolerated in high-risk LTRs, and when IFI occur, they are caused predominantly by *Candida* species infecting the intra-abdominal space within one month of transplantation. Retransplantation and a choledochojejunostomy type of anastomosis may be particularly strong risk factors for IFI. Future antifungal prophylaxis trials of broadly active oral agents should target selected high-risk LTRs for at least the first month after transplantation.

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