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Invasive Fungal Infections in Low-Risk Liver Transplant Recipients: A Multi-Center Prospective Observational Study

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Prevention of invasive fungal infections (IFIs) in orthotopic liver transplant (OLT) recipients utilizing postoperative systemic antifungal prophylaxis, typically with fluconazole, is justified among those at high risk for IFI. Use of postoperative antifungal prophylaxis for low-risk OLT recipients is widely practiced but not universally accepted nor supported by data. We conducted a prospective observational study among 200 OLT recipients who were at low risk for IFI and did not receive postoperative antifungal prophylaxis. Patients were considered low risk if they had $\leq$1 of the following conditions: choledochojejunostomy anastomosis; retransplantation; intra-operative administration of $\geq$units of 40 blood products or return to the operating room for intra-abdominal bleeding; return to the operating room for anastomotic leak or vascular insufficiency; preoperative serum creatinine of $\geq$2 mg/dL; and perioperative *Candida* colonization. Patients were followed 100 d post-transplantation for evidence of IFI. Of 193 eligible patients, 7 (4%) developed an IFI. Three (2%) IFIs were due to *Candida* spp. and potentially preventable by standard fluconazole prophylaxis. Three patients developed invasive aspergillosis; one developed late onset disseminated cryptococcosis. Liver transplant recipients at low risk for IFI can be identified utilizing pre-determined criteria, and post-transplantation antifungal prophylaxis can be routinely withheld in these patients.

Key words: Antifungal, fungal infections, invasive candidiasis, liver transplant recipients, prophylaxis

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Introduction

Invasive fungal infections (IFIs) are common following orthotopic liver transplantation (OLT), and are reported to occur in 6–47% of liver transplant recipients (1–4). Recent experience suggests that the overall incidence of this complication has declined due to improved surgical techniques, the availability of newer, more specific immunosuppressive agents with less dependence on glucocorticosteroids and the use of antifungal prophylaxis in certain circumstances (5–8). The dominant fungal pathogens in liver transplant recipients are *Candida* spp., accounting for over 80% of IFIs in this group (9–12). Infections due to *Aspergillus* spp., other moulds and *Cryptococcus neoformans* are much less common, but remain important pathogens in the post-transplant period. The majority of IFIs occur within 2 months following OLT (1,9,13).

The risk of IFI following OLT is associated with well-defined preoperative and intra-operative risk factors including preoperative renal insufficiency, low-serum albumin, previous OLT, *Candida* colonization, choledochojejunostomy anastomosis, long operative time, large intra-operative blood product transfusion requirement, early graft failure and need for surgical reexploration after OLT (6,8,9,11–14). Despite the general recognition of these risk factors for IFI, there has been no consistent center-to-center approach to perioperative systemic antifungal prophylaxis based on risk. Thus, at many centers, systemic antifungal prophylaxis is administered universally to liver transplant recipients independent of risk of IFI, whereas at other centers systemic antifungal prophylaxis is administered selectively to higher risk patients. The major consequences of administering systemic antifungal prophylaxis to all liver transplant recipients are unnecessary antifungal exposure and expense for many patients, and increased potential for antifungal drug resistance, drug interactions and drug-associated toxicity.

We conducted a prospective observational study among a group of liver transplant recipients who were determined to be at low risk for IFI according to a standard definition. We hypothesized that the criteria used to select these subjects would successfully identify those at low risk for developing IFI within the first 100 d following OLT. If validated in a multi-center study, these criteria could be used to identify

a liver transplant population in whom routine antifungal prophylaxis is unnecessary.

Methods

Fifteen sites were selected on the basis of transplant volume (at least 60 liver transplant procedures annually) and site willingness to use a tacrolimus-based initial immunosuppressive regimen. The institutional review board (IRB) of each of the participating sites approved the study. An IRB-approved informed written consent was obtained from patients at each site prior to performing tests exclusively required for determination of eligibility for enrollment into this trial.

Study design and population

All patients who underwent OLT at study sites were screened for eligibility. Patients were eligible if they were ≥18 years of age, if the initial immunosuppressive regimen included tacrolimus, and they were scheduled to receive nystatin 500 000 units 4 times daily as oral nonabsorbable antifungal prophylaxis for the first 60 d post-transplant. Women of childbearing potential were required to use an approved birth control method through 2 weeks beyond the end of the study period. Patients were excluded if they met any of the following criteria: HIV seropositivity; receipt of a systemic antifungal agent within 14 d prior to OLT; history of IFI within 14 d prior to OLT; history of allergy or intolerance to azoles, amphotericin B or tacrolimus; or previous randomization into a high-risk antifungal prophylaxis trial.

Patients with no more than one of the following risk factors at 5 d post-OLT were considered low risk for IFI are were enrolled into this trial: (i) choledochojejunostomy anastomosis; (ii) retransplantation; (iii) intra-operative administration of ≥40 units of cellular blood products including platelets, packed red blood cells, cell saver/auto transfusion blood product; (iv) preoperative serum creatinine ≥2.0 mg/dL or need for any form of dialysis within 48 h prior to OLT; (v) *Candida* spp. isolated from surveillance culture of sputum, urine, wound, surgical drain (e.g. Jackson-Pratt), or intra- postoperative bile drainage obtained between 48 h before until 48 h after OLT; (vi) return to the operating room within 5 d of OLT for laparotomy because of bile or other anastomotic leak, intra-abdominal bleeding, vascular accident other than bleeding (e.g. hepatic artery thrombosis), or primary graft nonfunction. Intra-operative cultures of bile and/or postoperative biliary drainage for fungal organisms were obtained on all patients. All risk factors were assessed either preoperatively or during the interval 5 d post-OLT.

Patients were assessed for IFI on the day of planned hospital discharge and at 100 d post-OLT. These assessments included signs and symptoms of IFI, results of relevant fungal cultures, radiographic results, serologic tests and histopathologic data, if obtained.

To provide a range of estimates of the risk of IFI in low-risk patients in the face of ambiguities in infection ascertainment and the effects of empiric therapy, multiple criteria were used to establish endpoints. For patients who developed an IFI, the date of onset was defined as the date the culture was taken. Patients 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. A less conservative estimate was developed as a secondary endpoint definition, and included patients with IFI combined with those using systemic antifungal therapy for >4 d during any 14-d interval before the end of the study period without evidence of a fungal infection. The combination of these events represents an upper bound estimate of the risk of IFI in this population.

Definitions

Proven IFI was defined as one of the following: (i) at least one positive blood culture for *Candida* spp. or other pathogenic fungi; (ii) a positive culture for a pathogenic fungus from a specimen collected from a normally sterile site; (iii) a positive culture for a pathogenic fungus from a biopsy specimen (taken across a potentially colonized mucosal surface) plus histopathology confirming fungal elements in tissue with local inflammation; (iv) evidence of fungal endophthalmitis based on dilated fundoscopic examination; (v) positive histopathology for fungal elements in a deep tissue biopsy; (vi) positive cryptococcal or histoplasma antigen test and clinical or radiographic evidence consistent with cryptococcosis or histoplasmosis; (vii) a positive culture or histopathologic evidence of an endemic mycosis (e.g. blastomycosis, histoplasmosis or coccidioidomycosis); (viii) a positive culture for a mould (e.g. *Aspergillus* spp., *Fusarium* spp., zygomycete) from a nonsterile body site together with clinical, histopathologic or radiologic evidence consistent with IFI.

Probable IFI was defined as clinical illness consistent with IFI in the absence of other causes of sepsis, together with positive fungal cultures from one or more nonsterile sites, and supporting radiographic or other diagnostic methodologies but without histopathologic confirmation of disease.

Superficial fungal infection was restricted to infection of a nonsterile mucosal surface (e.g. oropharyngeal, esophageal, gastrointestinal, genital) or in the lower urinary tract in the absence of histologic evidence of tissue invasion beyond the mucosa and immediate submucosal tissues.

Death was considered related to IFI if the patient had positive cultures from blood or any other normally sterile site within 48 h of expiration. Postmortem evidence of IFI was used to confirm its relationship to death.

Data collection and statistical analysis

The evaluable population used for analysis included only those subjects who were in the low-risk population. All analyses were done in SAS using Version 8.2 (Cary, NC). Descriptive statistics were used for the baseline characteristics of the patient population. Mean and standard deviation were used for continuous variables while categorical variables were summarized with counts and percentages. Kaplan-Meier estimates were generated for the cumulative incidence at 100 d after OLT of any fungal infection (proven IFI, probable IFI or superficial fungal infection); proven or probable IFI; superficial fungal infection; death (all-cause); proven or probable IFI or death; and proven or probable IFI or use of antifungal therapy. For all 100-d estimates, 95% confidence intervals were computed based on Greenwood's formula for standard error.

Results

Two hundred patients were enrolled between August 1999 and January 2001. Of the 200 patients enrolled, 7 were excluded from analyses because they were ineligible at baseline: 5 were misclassified as low risk and should not have been enrolled, 1 did not have sufficient data to be categorized definitively as low risk, and 1 patient had an entry criteria violation (received fluconazole within 14 d prior to OLT).

Baseline characteristics for the evaluable population of 193 patients are summarized in Table 1. The average age was 51 years (range: 20–73 years), and 81% of the patients were white. Sixty-two percent of these patients

Table 1: Patient characteristics

Characteristic	Evaluable subjects (N = 193)	
Age, mean (std)	51.3	(9.4)
Male, n (%)	121	63%
Race/ethnicity, n (%)		
White, non-Hispanic	156	81%
African American, non-Hispanic	15	8%
American Indian/Pacific Islander	2	1%
Hispanic	14	7%
Asian	2	1%
Other	4	2%
High-risk criteria		
None	119	62%
Choledochojejunostomy anastomosis	13	7%
Retransplantation	2	1%
Intra-operative use of >40 units blood products	20	10%
Pre-op Cr > 2.0 mg/dL; any dialysis 48 h pre-op	9	5%
Candida spp. isolated from surveillance culture	29	15%
Return to the OR within 5 d post-OLT	1	1%

Pre-op = preoperative, Std = standard deviation, OLT = orthotopic liver transplant, Cr = creatinine, OR = operating room.

met none of the high-risk criteria. The most common high-risk criteria in the study population were *Candida* colonization and excess intra-operative blood products. *Candida* spp. were isolated from one or more cultures of sputum, urine, wound, Jackson-Pratt drainage, intra-operative recipient bile or postoperative T-tube drainage in 29 (15%) patients. Twenty (10%) patients received ≥40 units of cellular blood products intra-operatively or returned to the operating room within 5 d for laparotomy for intra-abdominal bleeding.

Ten patients died by day 100, but none of the deaths was attributed to an IFI. Two patients were withdrawn from the study early (at 6 and 11 d after OLT) because they were retransplanted and met high-risk criteria for developing an IFI. One patient withdrew early because he left the country. Of the remaining 180 patients, 61 had their last study evaluation less than 100 d after OLT; the follow-up for these patients ranged from 16 to 99 d post-transplantation. Almost 90% of the evaluable population (n = 193) was followed to day 90 (median follow-up: 100 d).

Fungal infections

Table 2 summarizes the fungal infections and specific risk factors in this cohort. Seven (4%) patients experienced proven IFIs, including 5 (4%) of 119 and 2 (3%) of 74 patients with zero or one risk factor, respectively. No probable IFIs were observed. There were 8 (4%) superficial fungal infections, including 3 (3%) of 119 and 5 (7%) of 74 patients with zero or one risk factor, respectively. Among 7 patients with proven IFI, there were 3 with invasive candidiasis due to C. *albicans*, 3 with invasive aspergillosis, and one with disseminated cryptococcosis. Among patients with candidiasis, one experienced candidemia on day 12 post-OLT. One patient in whom the abdominal fascia was left open post-OLT for technical reasons developed *Candida* peritonitis on day 10. The third patient developed *Candida* cholangitis, but had undergone early post-OLT abdominal re-exploration for bleeding. These latter 2 patients were appropriately categorized as low risk according to study criteria, but developed post-OLT surgical complications that placed them at increased risk for IFI. Among the 3 patients with invasive aspergillosis, 2 episodes occurred very shortly following transplantation (2 and 11 d post-OLT) including 1 patient with screening sputum cultures positive for *Aspergillus fumigatus*. The third patient developed pulmonary aspergillosis 90 d post-OLT. One patient

Table 2: Incident fungal infections

Invasive	Patient.	Organism	Site(s)	Days post-OLTX	Risk factor
	1	*C. albicans*	Blood	12	Choledochojejunostomy
	2	*C. albicans*	Biliary	27	None
	3	*C. neoformans*	Blood /peritoneal fluid	80	None
	4	*C. albicans*	Peritoneal fluid	10	*Candida* colonization
	5	*A. fumigatus*	Lung	2	None
	6	*Aspergillus* spp.	Lung	11	None
	7	*Aspergillus* spp.	Lung	90	None
Superficial					
	8	*Candida* spp.	Urine	6	*Candida* colonization
	9	*Candida* spp.	Urine	58	>40 units blood products
	10	Yeast	Esophagus	19	>40 units blood products
	11	*C. albicans*	Urine	7	None
	12	*C. glabrata*	Urine	15	*Candida* colonization
	13	*C. glabrata*	Urine	18	None
	14	*C. albicans*	Urine	13	None
	15	*C. albicans*	Urine	14	*Candida* colonization

OLT = orthotopic liver transplant.

Table 3: Kaplan-Meier day 100 estimates and 95% confidence intervals for fungal infection and death

	Evaluable subjects (N = 193)	
Events	Day 100 estimate	(95 % CI)
Any fungal infection	0.08	(0.04–0.12)
Proven or probable IFI*	0.04	(0.01–0.07)
Superficial fungal infection	0.04	(0.01–0.07)
Death	0.06	(0.02–0.09)
Proven or probable IFI or death	0.09	(0.05–0.13)
Proven or probable IFI or empiric AFT	0.22	(0.16–0.28)

*There were no probable fungal infections.
AFT = antifungal therapy, IFI = invasive fungal infection.

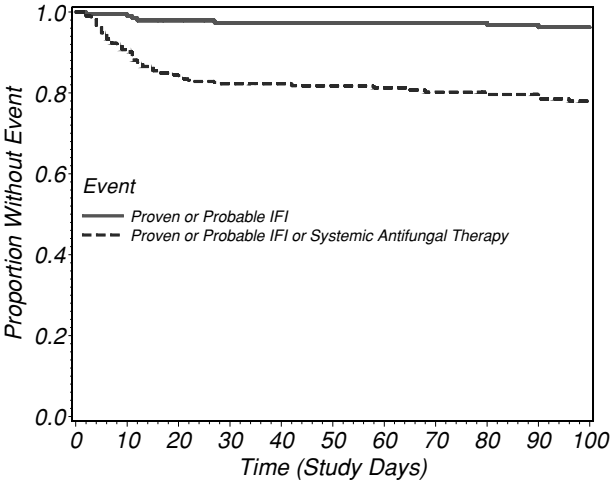

Figure 1: Kaplan-Meier survival curves for IFI-free time on study and IFI-free time on study without systemic antifungal therapy.

developed fungemia and central nervous system involvement due to *Cryptococcus neoformans* on day 80 post-transplantation. Among 8 patients with a superficial fungal infection during follow-up, 7 had *Candida* cystitis (3 *C. albicans*, 2 *C. glabrata* and 2 not identified) and one *Candida* esophagitis proven by histopathology (Table 2). Notably, 3 patients with cystitis had perioperative urine colonization with *Candida*. No patients developed oropharyngeal candidiasis.

The Kaplan-Meier estimate of proven or probable IFI at day 100 post-transplantation was 0.04 (95% CI: 0.01–0.07); the estimate of cumulative incidence of any fungal infection by day 100 post-OLT was 0.08 (95% CI: 0.04–0.12). By including initiation of systemic antifungal therapy and proven or probable IFI in the endpoint definition to obtain a conservative estimate of risk, the day 100 estimate rises to 0.22 (95% CI: 0.16–0.28). These data are presented in Table 3. Figure 1 demonstrates the two Kaplan-Meier survival curves for these patients. The majority (60%) of fungal infections occurred within the first 2 weeks post-OLT: there were four IFIs and five superficial fungal infections on or before day 15 post-OLT.

Antifungal therapy

Thirty-five (18%) of 193 patients received empiric systemic antifungal therapy that was initiated prior to any observed fungal infection and that was administered for at least 5 d within any 14-d interval post-OLT). Three of these patients were found subsequently to have a proven IFI and 3 had a superficial fungal infection.

Discussion

Prevention of IFI is an important goal in the early post-operative management of the liver transplant recipient. Once established, IFIs are associated with high overall mortality in this vulnerable population (2,4,10,15). Unfortunately, there is no standard approach among liver transplant centers concerning the selection of patients who are at the greatest risk for developing this complication and who might derive the most benefit from antifungal prophylaxis. Moreover, there is no consistent approach to the selection of any specific antifungal agent, dose or duration of post-transplantation prophylaxis from center to center. In this study, we report on outcomes for 193 evaluable liver transplant recipients who were determined to be low risk for IFI by using a 6-component definition in the very early postoperative period to determine risk status. These patients were prospectively followed up to day 100 after OLT to establish the incidence of IFI in the absence of systemic antifungal prophylaxis. Our hypothesis was that using well-defined criteria we could identify liver transplant recipients at very low risk for IFI in the early post-transplantation period, and that the validation of these risk stratification criteria in a multi-center study could lead to a more rational and consistent approach to antifungal prophylaxis in all liver transplant recipients.

In an important earlier retrospective study of risk factors for IFI in OLT recipients, Collins (12) and Karchmer (13) determined that the presence of two or more well-defined risk factors defined a high-risk group in whom IFIs occurred in almost 40% of patients post-OLT. Conversely, the presence of fewer than two risk factors was associated with the development of an IFI in less than 5% of patients (13). However, these observations have never been validated in a prospective trial until our study. By documenting the absence of two or more of the six clinical and laboratory criteria defined by Collins, Karchmer and coworkers (12,13), including choledochojejunostomy anastomosis, preoperative renal insufficiency, retransplantation, administration of at least 40 units of cellular blood products, early abdominal

reexploration for bleeding or graft dysfunction, and perioperative (±48 h OLT) colonization with *Candida* spp., our study demonstrated that we could accurately select patients who are at very low risk of post-OLT IFI, and therefore not likely to benefit from post-OLT systemic antifungal prophylaxis. Patients in this low-risk cohort could be easily identified perioperatively. Furthermore, only one criteria (*Candida* colonization) potentially required waiting for up to 5 d post-OLT to determine risk status; the remaining criteria were determined pre- or intra-operatively.

Only seven (4%) of the patients in our low-risk cohort developed an IFI in the first 100 d following transplantation, including 5 without any perioperative risk factors and 2 with only one risk factor. Based on these data, there is little to suggest that patients with one perioperative risk factor are at increased risk of IFI post-OLT, although these numbers are relatively small (74 patients). Furthermore, among these patients, at least 4 would not have been expected to benefit from postoperative antifungal prophylaxis with fluconazole. Specifically, 3 patients developed invasive aspergillosis, including 2 diagnosed very early in the postoperative period (2 and 11 d post-OLT). One of these patients had a sputum culture positive for *A. fumigatus* at baseline and might have been excluded from the low-risk cohort. A third patient developed invasive aspergillosis at 90 d post-OLT, and the fourth patient developed disseminated cryptococcosis in the late (day 80) follow-up period. Among the 3 patients who developed invasive candidiasis post-OLT, only one was truly low risk. One patient underwent abdominal reexploration for postoperative bleeding, and the other had an atypical postoperative course owing to the decision to leave the fascia unclosed. Thus, it is reasonable to expect that no more than 3 (1.5%) of the 193 evaluable patients might have benefited from early post-operative antifungal prophylaxis, and that among a truly low-risk group, only 1 (0.5%) of 191 patients might have benefited from fluconazole prophylaxis.

Antifungal use in the absence of an established fungal infection was a confounding feature of this study. Thirty-five (18%) patients, including 6 who eventually developed a superficial (3 patients) or invasive fungal infections (IFI) (3 patients), received empiric antifungal therapy during the surveillance period before any mycologic or clinical evidence of a fungal infection. The most common reasons given by investigators for administration of empiric antifungal therapy were unexplained fever or leukocytosis, bile leak, or "antifungal prophylaxis" without further justification. For purposes of analysis, these subjects were considered to have met a study endpoint on the basis of significant (greater than 4 d) postoperative antifungal therapy. The use of empiric antifungal therapy and/or prolonged antifungal prophylaxis are common practices among physicians caring for transplant recipients, and our data underscore the frequent and often inappropriate use of antifungal agents, especially with azole antifungals, among patients who are perceived to be at high risk for fungal infection but for whom there is often no evidence of such risk.

Several prospective studies have examined the use of systemic antifungal prophylaxis following OLT, but few have stratified patients according to risk of IFI (16–27). In the largest of these studies, Winston and colleagues demonstrated an advantage for fluconazole 400 mg daily compared to placebo, both administered for 70 d post-OLT, in the prevention of superficial and IFIs in 212 subjects (25). This study did not stratify patients according to risk, but rather included both high- and low-risk patients for randomization to receive either fluconazole or placebo. IFIs were observed in 6% and 23% of fluconazole and placebo recipients, respectively ($p < 0.001$), but there was no difference in survival at the end of antifungal prophylaxis. Nystatin prophylaxis was not administered in that study (25). Tollemar and colleagues also demonstrated an advantage of post-transplant prophylactic liposomal amphotericin B versus placebo (0% vs. 16% IFIs, respectively, $p < 0.01$) in a double-blind trial of nonselected transplant recipients, but again demonstrated no significant survival advantage (24). Other investigators have demonstrated no difference in fungal infection rates following OLT between active drug and placebo recipients (16). Two other groups have demonstrated the ability to prevent IFIs in the postoperative period among higher risk liver transplant recipients utilizing a lipid formulation of amphotericin B, and comparing the results in these patients to historical controls (19,23). Importantly, none of these studies have prospectively stratified patients according to risk of IFI prior to randomization. Lumbreras and colleagues, in a randomized trial comparing fluconazole with nystatin suspension for antifungal prophylaxis among OLT recipients who appeared to be at low risk of IFI found no significant difference in the occurrence of IFI (21).

In summary, this study supports the hypothesis that perioperative assessment utilizing readily identifiable risk factors among subjects undergoing liver transplantation can predict those patients who are at low risk of developing IFI in the first 100 d post-transplantation. We observed no trend toward more IFIs among patients who had one risk factor compared to those with none, suggesting that within this risk stratification system, patients with no more than one risk factor truly reflect a population at low risk for IFI. The strength of this conclusion is somewhat limited by a relatively small number of patients with one risk factor. Considering the very low frequency of IFI that could be prevented by fluconazole prophylaxis (0.5–1.5%) and the absence of mortality associated with IFI in our study population, we believe these criteria identify an OLT population in whom perioperative antifungal prophylaxis is not indicated. Application of these criteria to restrict postoperative systemic antifungal prophylaxis would reduce unnecessary antifungal exposure to this group of patients, pressure for emergence or resistant nosocomial yeasts, and cost. In addition, based on our data, we believe that examination of a similar

approach to assessment of risk for IFI in other solid organ transplant recipients is warranted.

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