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## Targeted *versus* Universal Antifungal Prophylaxis among Liver Transplant Recipients

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### Abstract

Guidelines recommend targeted antifungal prophylaxis for liver transplant recipients based on tiers of risk, rather than universal prophylaxis. The feasibility and efficacy of tiered, targeted prophylaxis is not well-established. We performed a retrospective study of liver transplant recipients who received targeted prophylaxis (n=145; voriconazole (54%), fluconazole (8%), no antifungal (38%)) vs. universal voriconazole prophylaxis (n=237). Median durations of targeted and universal prophylaxis were 11 and 6 days, respectively (p<0.0001). The incidence of invasive fungal infections (IFIs) in targeted and universal groups was 6.9% and 4.2% (p= 0.34). Overall, intra-abdominal candidiasis (73%) was the most common IFI. Post-transplant bile leaks (p=0.001) and living donor transplants (p=0.04) were independent risk factors for IFI. IFIs occurred in 6% of high-risk transplants who received prophylaxis and 4% of low-risk transplants who did not receive prophylaxis (p=1.0). Mortality rates (100 days) were 10% (targeted) and 7% (universal) (p=0.26); attributable mortality due to IFI was 10%. Compliance with prophylaxis recommendations was 97%. Prophylaxis was discontinued for toxicity in 2% of patients. Targeted antifungal prophylaxis in liver transplant recipients was feasible and safe, effectively prevented IFIs, and reduced the number of patients exposed to antifungals. Bile leaks and living donor transplants should be considered high-risk indications for prophylaxis.

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### Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*.

### Description of Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Studies defining low-risk populations and rate of IFIs in the absence of prophylaxis

Table S2. Studies defining high-risk populations and rate of IFIs with prophylaxis

## Introduction

Prior to the 2000s, invasive fungal infections (IFIs) were diagnosed in up to 40% of liver transplant recipients and associated with mortality rates ranging from 25 – 70%(1). IFIs were caused predominantly by *Candida* species (spp.) (60%- 80%). Infections due to *Aspergillus* spp. (1%– 8%), other moulds, and *Cryptococcus* spp. were less common(2). Most IFIs occurred within the first month after transplant(1, 3), and were associated with surgical factors, including the complexity of the transplant(1). The epidemiology of IFIs has changed in the recent era of liver transplantation, as surgical techniques and immunosuppressive and antifungal prophylaxis strategies have evolved(4). Over the past 10 years, the rate of IFIs has decreased to <10%(5–8), and risk factors such as retransplant, post-transplant renal failure requiring renal replacement therapy, and reoperation have been consistently identified(2). While the predominant pathogens remain consistent with older cohorts, the majority of infections due to *Aspergillus* spp. now occur 90 days post-transplant(3). More recent data have established the safety of withholding antifungal prophylaxis in low-risk patients.(4)

Taken together, guidelines from the American Society of Transplantation (AST) and Infectious Diseases Society of America (IDSA) currently recommend a three-tiered approach to antifungal prophylaxis following liver transplantation: 1) no prophylaxis for low-risk patients; 2) prophylaxis targeted against *Candida* spp. for patients with complicated operations, choledochojejunostomy anastomosis, or peri-operative *Candida* colonization; or 3) prophylaxis targeted against *Candida* and *Aspergillus* spp. for patients with risk factors of retransplantation, renal replacement therapy post-transplant, and reoperation(9–11). At present, there is a lack of data establishing the feasibility and efficacy of the AST/IDSA recommendations. Moreover, the appropriate antifungal agent, dose, and duration have not been determined(9–11).

During a period of construction at our institution in mid-2007, several cases of invasive mould infections were diagnosed among organ transplant recipients residing in the transplant intensive care unit (ICU). In response to these developments, our program instituted a policy of universal antifungal prophylaxis with voriconazole for newly transplanted liver recipients during their stays in the transplant ICU. In 11/1/2010, we revised our approach from universal voriconazole prophylaxis to a targeted algorithm that was adapted from AST/IDSA guidelines (Figure 1)(9, 12, 13). In the algorithm, patients were assigned to receive no antifungal prophylaxis, fluconazole, or voriconazole. In this study, we analyzed the comparative efficacy of targeted *versus* universal prophylaxis, and assessed the safety and efficacy of voriconazole, an agent that has not been investigated as a prophylactic agent in liver transplant recipients.

## Methods

### Study design and patients

We performed a retrospective study of consecutive adult patients undergoing liver transplantation at the University of Pittsburgh Medical Center (UPMC) between November 1, 2008 and December 1, 2012 to compare IFI rates in patients receiving either targeted or

universal antifungal prophylaxis. Patients were excluded if they underwent multi-organ transplantation or dual transplant with lung(s) or heart, had an IFI at the time of transplant, died on the day of transplant, or if the transplant was performed at an outside institution. The University of Pittsburgh Institutional Review Board approved the study.

### Antifungal prophylaxis

Patients were divided into two groups, based on antifungal prophylaxis regimen. The universal prophylaxis group consisted of patients transplanted between 11/1/2008 and 10/31/2010, during which the standard practice was voriconazole 200 mg oral twice daily for all patients. Voriconazole was started within one day of transplant and continued for the duration of the immediate post-transplant ICU stay. In November 2010, we instituted our tiered, targeted approach to antifungal prophylaxis (Figure 1). The targeted prophylaxis group consisted of patients transplanted between 11/1/2010 and 12/1/2012.

### Definitions

IFIs were defined according to EORTC/MSG criteria(14); superficial fungal infections, mucocutaneous candidiasis and *Candida* colonization were not included. Death was attributed to IFI if there was ongoing positive fungal culture or infectious process at the time of death. Compliance with prophylaxis algorithms was defined by the use of the recommended agent. As there was a 3-month roll-out for the change in antifungal prophylaxis strategy, compliance in the targeted prophylaxis group was assessed after this period. The primary outcome of this study was the development of IFI within 100 days of transplantation. The secondary outcomes were attributable mortality for IFI, all-cause mortality at 100 days, compliance with antifungal prophylaxis algorithms, and toxicity of voriconazole.

**Immunosuppressive regimen and prophylaxis**—The standard immunosuppression during the study period consisted of methylprednisolone at the time of transplant followed post-operatively by tacrolimus, mycophenolate, and prednisone. For patients with underlying renal insufficiency (SCr > 1.5 mg/dL)(15), an early calcineurin-sparing regimen consisting of basiliximab induction followed by steroid taper and mycophenolate was used. Peri-operative antibacterial prophylaxis consisted of ampicillin-sulbactam for 72 hours; for patients allergic to  $\beta$ -lactam agents, aztreonam and vancomycin were recommended. Beginning in May 2011, patients known to be colonized with vancomycin-resistant *Enterococcus* received tigecycline for prophylaxis. Throughout the study period, trimethoprim/sulfamethoxazole was given for one year post-transplant. Prior to November 2011, pre-emptive valganciclovir was administered to all liver transplant recipients with CMV viremia, regardless of donor and recipient serology status; all other patients received acyclovir prophylaxis for the first month post-transplant. After November 2011, CMV seronegative recipients of livers from seropositive donors received universal prophylaxis with valganciclovir for 6 months; other patients received pre-emptive valganciclovir.

**Statistical analysis**—Instat Software (Graphpad Software Inc., San Diego, CA) was used. Comparisons of dichotomous and continuous variables were performed using Fisher's exact test and Mann-Whitney *U* test, respectively. *P*-values <0.05 were considered

significant. To identify risk factors for IFIs, variables suggested by univariate analysis ( $p < 0.05$ ) were entered into a multivariate logistic regression model; the type of antifungal prophylaxis (targeted vs. universal) was included in the model to address its impact on IFI. Stata/SE 12.1 was used to compute  $p$ -values, odds ratios and 95% confidence intervals. Kaplan–Meier curves were used to calculate event-free survival; curves were compared by log-rank test. Significance was defined as  $p$ -value  $< 0.05$  (two-tailed).

## Results

### Patient characteristics

Three hundred ninety-eight transplants were performed at UPMC during the study period. Sixteen transplants were excluded (7 multivisceral transplants, 3 cotransplants with lung or heart, 5 deaths on day of transplant, and 1 IFI at time of transplant), leaving 382 transplants in 367 unique patients available for analysis (15 patients were re-transplanted in the study period). For purposes of our review, each transplant was considered to represent a patient at-risk for IFI. Two-hundred thirty-seven and 145 transplants were performed in the universal and targeted prophylaxis time periods, respectively. Among the universal prophylaxis group, 99.6% (236/237) of patients received voriconazole prophylaxis. Among the targeted prophylaxis group, 38% (55/145) of patients received no antifungal prophylaxis, and 54% (78/145), 8% (11/145) and  $< 1\%$  (1/145) of patients received voriconazole, fluconazole and itraconazole, respectively; the patient who received itraconazole had a remote history of pulmonary histoplasmosis. Patient demographics, baseline characteristics, and risk factors for IFIs are noted in Table 1. Patients in the targeted prophylaxis group were more likely to receive a kidney-liver dual transplant ( $p=0.003$ ), undergo an operation exceeding 11 hours (without need for substantial transfused blood products) ( $p=0.02$ ), or have a bile leak post-transplant ( $p=0.04$ ).

### Invasive Fungal Infections

Twenty transplant recipients developed twenty-two IFIs (2 patients had two infections), for an overall rate of 5.2% (20/382). Twenty-three pathogens were recovered from the 20 patients. Ten patients in both the targeted and universal prophylaxis groups were diagnosed with an IFI (6.9% (10/145) vs. 4.2% (10/237), respectively;  $p=0.34$ ). Details of IFIs are presented in Table 2. All patients developed their first episode of IFI within 30 days of transplant. Forty percent (8/20) of patients had breakthrough IFIs while receiving universal or targeted prophylaxis ( $n=4$  each). Thirty-five percent (7/20) of patients developed IFI after prophylaxis had been discontinued (median of 17 days after the antifungal prophylaxis was stopped) and 25% (5/20) developed IFI in the absence of prophylaxis. Seventy-eight percent (18/23) of pathogens were *Candida* spp.; the predominant spp. were *C. glabrata* (39%, 9/23) and *C. albicans* (22%, 5/23). There were two infections due to *Cryptococcus neoformans*, and one infection each due to *Saccharomyces cerevisiae*, *Aspergillus fumigatus* and *Rhizomucor*. Eight-five percent (17/20) of patients developed peritonitis or another intra-abdominal infection. In each instance, intra-abdominal infection was caused by a *Candida* spp. or *S. cerevisiae*; 19% (3/16) of patients with intra-abdominal candidiasis had candidemia due to the same spp. *C. neoformans* and *A. fumigatus* caused pulmonary infections. *Rhizomucor* caused disseminated infection in an HIV/HCV co-infected patient.

All patients with IFI were given algorithm-compliant prophylaxis, but prophylaxis was discontinued early in two patients. The reasons for discontinuation were voriconazole toxicity and an inability to continue voriconazole due to a lack of insurance coverage. Fifty percent (5/10) of patients with IFI in the targeted group did not receive antifungal prophylaxis, in keeping with the recommendations of the algorithm.

Risk factors for IFIs are presented in Table 3. Prophylaxis group (targeted versus universal) designation was not associated with IFI on univariate analysis, nor was MELD score ( $p=0.78$ ). Of the 46 patients in the targeted prophylaxis group with a MELD > 30, 59% (27/46) received prophylaxis and 41% (19/46) did not; the only patient who developed an IFI (IFI rate of 2%, 1/46) did not receive prophylaxis prior to the IFI. From the entire cohort, 12% (47/382) of patients developed acute cellular rejection (ACR) requiring pulsed corticosteroid therapy. There was no association between IFI and ACR; 8% (4/47) and 5% (16/335) of patients with ACR and no ACR developed IFI, respectively;  $p=0.29$ . Development of a bile leak within 30 days of transplant and living donor transplant were the only risk factors for IFI by univariate analysis ( $p=0.0004$  and  $0.008$ , respectively), and the only independent predictors of IFI by multivariate analysis ( $p=0.001$  and  $0.04$ , respectively; odds ratios = 7.13 and 2.96, respectively). Overall, 27% (6/22) of patients with post-transplant bile leak and 14% (7/49) of liver donor transplant recipients developed an IFI. Fifty-seven percent (4/7) of living donor recipients who developed IFIs had a bile leak.

The IFI rate in high-risk patients (defined as possessing a risk factor in Figure 1, living donor, or bile leak) who received prophylaxis was 6% (12/202) compared to 4% (2/46) in low-risk patients (defined as the absence of risk factors) not receiving prophylaxis ( $p=1.0$ ).

## Mortality

The overall mortality at 100 days and 1 year was 8% (32/382) and 16% (62/382), respectively. The 100 day mortality rate was 10% (15/145) in the targeted prophylaxis group and 7% (17/237) in the universal prophylaxis group ( $p=0.26$ , log-rank test; Figure 2A). The 100-day mortality rate among patients with IFI was 15% (3/20) compared to 8% (29/362) among patients without IFIs ( $p=0.25$ , log-rank test; Figure 2B). The attributable mortality rate for IFIs was 10% (2/20). The HIV/HCV coinfecting patient who died due to disseminated *Rhizomucor* infection was in the universal prophylaxis group; the diagnosis was established at autopsy. A patient in the targeted prophylaxis group died due to persistent *C. glabrata* intra-abdominal infection.

## Compliance with prophylaxis algorithms

Overall compliance with the recommendations for antifungal prophylaxis was 97% (341/353). In the universal prophylaxis group, the median duration of prophylaxis in patients who would have been defined as high-risk was 9 days, with a 5% (5/107) IFI rate; corresponding data for low-risk patients were 4 days and 4% (5/130), respectively. After excluding the 20 patients with IFI, the duration of prophylaxis among patients who received an antifungal in the targeted group was significantly longer than in the universal group (median: 11 vs. 6 days, IQR 5–25 and 3–10, respectively;  $p<0.0001$ ). No IFIs occurred during the 3-month roll-out period or in patients receiving non-compliant prophylaxis.

## Toxicity

Antifungal prophylaxis was discontinued early due to concerns of toxicity in 2% (7/327) of patients; all received voriconazole prophylaxis. The reasons for early discontinuation were hepatotoxicity (3 patients), mental status changes (2), diarrhea (1), and supratherapeutic tacrolimus levels due to a voriconazole interaction (1). Only the supratherapeutic tacrolimus level was definitively ascribed to voriconazole.

## Discussion

This large study of antifungal prophylaxis in liver transplant recipients has two particularly important findings. First, targeted antifungal prophylaxis was as effective as universal prophylaxis. Comparable outcomes were achieved in the targeted prophylaxis group, even though 38% of patients did not receive an antifungal agent, and significantly higher percentages of patients had more complicated surgeries (prolonged lengths of transplant and kidney/liver dual transplants) and post-transplant complications (bile leaks). Our results are consistent with, and expand upon, previous findings. The observation that IFIs in low-risk patients were sufficiently uncommon as to not require prophylaxis (Supplemental Table 1) (4, 8, 16) supports AST and IDSA recommendations for targeted prophylaxis in liver transplantation (9–11). Specific definitions of “high-risk” liver transplant recipients differ dramatically across studies; nevertheless, our data clearly verify that antifungal prophylaxis in this population is effective (Supplemental Table 2) (5–8, 17–19). In particular, our IFI rate of 6% among high-risk patients compares favorably to rates of 15–35% in studies of high-risk patients not receiving prophylaxis (6, 20). Most importantly, the low attributable mortality in our study and others (Supplemental Table 2) suggests that prophylaxis attenuates the severity of IFIs that do develop (21, 22).

A second important finding is that bile leaks within the first 30 days post-transplant and living donor liver transplants were newly-identified, independent risk factors for IFI. Bile leaks have not commonly been assessed in studies of IFIs following liver transplantation. Biliary candidiasis and peritonitis are potentially problematic in liver transplant recipients since *Candida* has an affinity for growth in the biliary tract. Indeed, in one study, *Candida* was recovered in 44% of bile samples collected from patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) (23). Bile extracts significantly decrease the susceptibility of *C. albicans* to various antifungals *in vitro* (24). In mouse models, *C. albicans* mutant strains that are attenuated for gastrointestinal colonization are more susceptible to bile salts than wild-type strains (25). Moreover, the gall bladder and biliary tree is a reservoir for the persistence of *C. albicans* within mice following antifungal therapy (24). Living donor liver transplants are highly technical procedures that are uncommonly performed in the United States (26); data from the Organ Procurement and Transplantation Network note that only 3.6% (252/7025) of liver transplants in 2013 were from living donors (<http://optn.transplant.hrsa.gov/latestData/rptData.asp>). Compared to deceased donor transplants, a higher percentage of our living donor transplants underwent operations lasting >11 hours (51% versus 11%,  $p < 0.0001$ ), and recipients were at higher risk for bile leak (16% versus 4%,  $p = 0.003$ ). These findings are concordant with results from a retrospective cohort study of 9 institutions in the United States (26). It is likely that the risk of IFI is

increased in living donor liver recipients by both the complexity of the surgery and disruptions to the biliary tract. Taken together, our data suggest that antifungal prophylaxis should be instituted immediately following living donor transplant and when a bile leak is suspected or diagnosed. In fact, incorporating living donor transplant into our algorithm may result in a number of patients receiving antifungal treatment prior to the development of a bile leak.

Along related lines, previously identified risk factors for IFIs such as renal failure requiring dialysis, *Candida* colonization, fulminant hepatic failure, choledochojejunostomy, prolonged operation, receipt of numerous blood products, and reoperations were not identified as significant in this study. The data offer further support for the effectiveness of antifungal prophylaxis in these high-risk settings. In contrast to two recent studies(27, 28), we did not identify pre-transplant model for end stage liver disease (MELD) score to be associated with IFIs. In fact, the IFI rate in patients with MELD score  $\geq 30$  was only 3.4% and did not significantly differ between targeted and universal groups. Therefore, prophylaxis was effective even among patients in whom fulminant liver failure was the indication for transplant.

To the best of our knowledge, our study is the first to report the efficacy and tolerability of voriconazole as prophylaxis in liver transplant recipients. Among patients at high risk, the rate of IFIs was 6%, which is consistent with recent studies of other antifungal agents (Supplemental Table 2). Voriconazole is less expensive than echinocandins and lipid amphotericin B formulations and offers the advantage of oral administration. It is less nephrotoxic than amphotericin B products and provides broader-spectrum activity than fluconazole (covering moulds) or echinocandins (covering *Cryptococcus neoformans* and certain non-*Aspergillus* moulds)(29). There are obvious concerns with the use of voriconazole in liver transplant patients, including hepatotoxicity(30), significant interactions with calcineurin inhibitors(31), and highly variable pharmacokinetics(30). Voriconazole was discontinued in only 3 patients due to suspected hepatotoxicity, and in a single patient due to an interaction with tacrolimus. However, more prolonged use of voriconazole than in our cohort may result in higher toxicity rates(32, 33). Our study does not suggest that voriconazole is superior to any other prophylactic agent, as the number of patients receiving other antifungals was too limited to draw any conclusions. Furthermore, the literature (Supplemental Table 2) suggests that other agents may achieve similar prophylactic efficacy.

The pathogens causing IFI in our study were consistent with previous reports(2, 5–8, 18, 19). Yeasts (*Candida* spp., *Cryptococcus neoformans* and *Saccharomyces cerevisiae*) accounted for 91% (21/23) of disease-causing isolates. The remaining 9% (2/23) of pathogens were moulds (*Aspergillus fumigatus* and *Rhizomucor*). Our findings that *C. glabrata* and *C. albicans* were the predominant fungi, and that intra-abdominal candidiasis was the most common type of IFI, were in keeping with other studies of liver transplant recipients(Supplemental Table 2). The 19% (3/16) rate of candidemia among patients with intra-abdominal candidiasis was also in agreement with earlier studies(34, 35). Like *Candida*, *S. cerevisiae*(baker's yeast) caused an intra-abdominal infection. *S. cerevisiae* has

been reported to cause invasive infections in immunocompromised patients, but infections in liver transplant recipients are exceedingly rare(36, 37).

*C. neoformans* caused pulmonary infections in 2 patients who were at low-risk for IFIs. Indeed, *C. neoformans* is recognized to cause disease among low-risk patients(4, 8).Cirrhosis, a common indication for liver transplantation, has been shown to predispose to cryptococcosis even in the absence of further immunosuppression(38).In addition, 52% of solid organ transplant recipients who develop cryptococcosis have serologic evidence of cryptococcal infection pre-transplant; seropositive patients develop disease earlier after transplant than patients without pre-transplant *Cryptococcus* antibodies(39).Liver transplant recipients appear particularly predisposed to infection within the first 30 days post-transplant (40). The two cryptococcal infections in our study were diagnosed 8 and 18 days post-transplant, suggesting that they may have been acquired pre-transplant but not eradicated due to impaired complement activity or other immune defects associated with cirrhosis(38, 40).It is plausible, then, that cryptococcosis developed rapidly following transplant with the administration of immunosuppressive agents. Donor-derived infection is possible, but less likely, since early-onset cryptococcosis has been predominantly reported to involve the allograft or surgical site(40). The identification of risk factors for cryptococcosis in our population would facilitate the development of prophylactic strategies. Pulmonary infections are the most common manifestation of aspergillosis. Although the majority of aspergillosis now occurs 90 days post-liver transplant, our case highlights that early-onset infections remain important(3). Finally, two cases of zygomycosis in liver transplant patients were reported previously from our center, corresponding to an incidence (in all solid organ transplant recipients) of 2 infections per 1000(41). The HIV/HCV patient in the present study who developed disseminated *Rhizomucor* disease died within 8 days.

Our data may inform recommendations for the duration of antifungal prophylaxis. The efficacy of short-course antifungal therapy in our universal prophylaxis group suggests that a duration of 30 days is unnecessary for a large proportion of patients. Neither the AST/IDSA guidelines nor the available literature (Supplemental Table 2) provide consistent recommendations for duration (9–11).Some studies examined defined, albeit widely variable, durations (range of 5 days to 10 weeks), while others recommended continuing prophylaxis until risk factors were no longer present or the patient was discharged from the hospital (Supplemental Table 2). We currently advocate an individualized approach, with antifungal regimens discontinued upon discharge from the ICU (as a marker of medical stability) and resolution of ongoing surgical complications.

There are several limitations to our study, in addition to those raised above. First, this was a retrospective review and data were limited to existing medical records. Our single-center experience should be cautiously extrapolated to other programs. Of particular note, our center has extensive experience with using voriconazole in lung and liver transplant recipients(42), and is comfortable managing voriconazole interactions with calcineurin inhibitors. Second, we did not routinely perform voriconazole therapeutic drug monitoring (TDM) during prophylaxis. A study of lung transplant recipients who received voriconazole prophylaxis at our center demonstrated a correlation between trough concentrations 1.5 µg/mL and IFI/fungal colonization (42). The comparable efficacy of voriconazole in our



experience and other antifungal agents in previous studies of liver transplant recipients suggests TDM might not be necessary. Nevertheless, the issue warrants future study. Third, we did not routinely test infecting strains for antifungal susceptibility. The role of fluconazole or voriconazole prophylaxis in selecting for resistant pathogens like *Rhizomucor* or potentially resistant pathogens like *C. glabrata* remains unproven. Nevertheless, programs should be aware that widespread use of these agents may have an impact on institutional ecology. In this regard, the reduction in numbers of patients exposed to antifungal agents by targeted prophylaxis may be beneficial.

In conclusion, targeted antifungal prophylaxis in liver transplant recipients was feasible and safe, effectively prevented IFIs, and associated with attributable mortality similar to overall mortality among patients without IFI. The incorporation of bile leaks within 30 days post-transplant and living donor transplants into a prophylaxis algorithm as high-risk indications may further reduce the rate of IFIs. Future studies should validate tiered approaches to targeted prophylaxis, define optimal antifungal agents and durations of administration, and establish cost-effectiveness. Ideally, these issues should be addressed in a carefully-designed multi-center study.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>ABL</b>	amphotericin B lipid complex
<b>AmB</b>	liposomal amphotericin B
<b>AmBd</b>	amphotericin B deoxycholate
<b>AST</b>	American Society of Transplantation
<b>ATB</b>	antibiotics
<b>CAS</b>	casposfungin
<b>CMV</b>	cytomegalovirus
<b>CrCL</b>	creatinine clearance
<b>FLU</b>	fluconazole
<b>H</b>	hours
<b>HIV</b>	human immunodeficiency virus

<b>ICU</b>	intensive care unit
<b>IDSA</b>	Infectious Diseases Society of America
<b>IFI</b>	invasive fungal infection
<b>ITR</b>	itraconazole
<b>IV</b>	intravenous
<b>LAmB</b>	lipid amphotericin B preparations
<b>LT</b>	liver transplant
<b>MELD</b>	model for end stage liver disease
<b>PRBC</b>	packed red blood cells
<b>PO</b>	by mouth
<b>Q</b>	every
<b>RRT</b>	renal replacement therapy
<b>SCr</b>	serum creatinine
<b>SOLN</b>	solution
<b>TDM</b>	therapeutic drug monitoring
<b>UNOS</b>	United Network Organ Sharing
<b>UPMC</b>	University of Pittsburgh Medical Center
<b>VORI</b>	Voriconazole

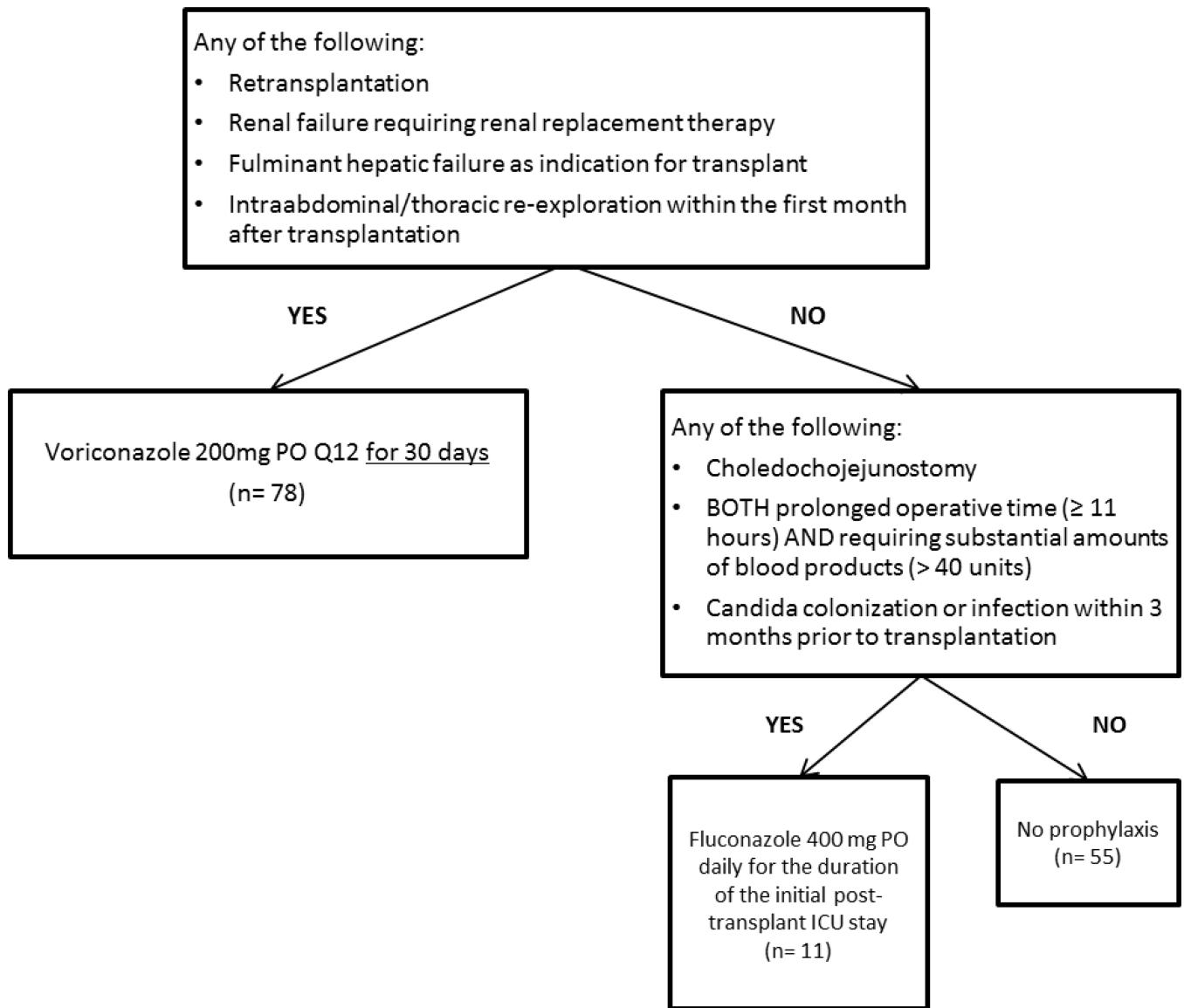
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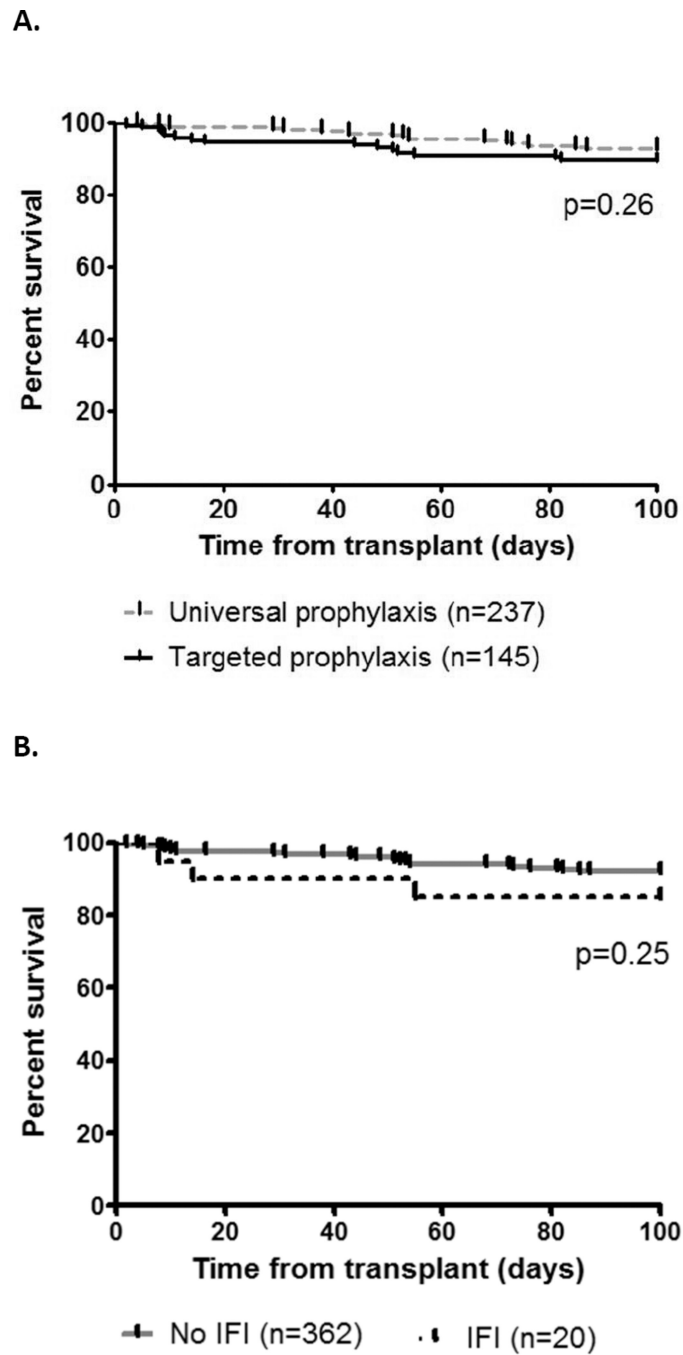
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**Figure 1.**  
Algorithm for targeted antifungal prophylaxis



**Figure 2.** Survival among liver transplant recipients, stratified by type of antifungal prophylaxis (Fig. 2A) and presence or absence of IFIs (Fig 2B)

**Table 1**

Patient demographics, baseline characteristics and risk factors for invasive fungal infections.

	<b>TOTAL (N=382)</b>	<b>Universal Prophylaxis (N=237)</b>	<b>Targeted Prophylaxis (N=145)</b>	<b>P-value</b>
<b>Age, years (mean ± standard deviation)</b>	55.7 ± 10.7	55.8 ± 11.0	55.4 ± 10.2	0.73
<b>Male</b>	65% (248/382)	64% (152/237)	66% (96/145)	0.74
<b>Caucasian</b>	94% (359/382)	95% (224/237)	93% (135/145)	0.66
<b>Indication for transplant<sup>a</sup></b>				
<b>Fulminant hepatic failure</b>	2% (9/382)	3% (6/237)	2% (3/145)	1.0
<b>Cryptogenic cirrhosis</b>	7% (26/382)	8% (18/237)	6% (8/145)	0.53
<b>Nonalcoholic steatohepatitis</b>	10% (37/382)	10% (24/237)	9% (13/145)	0.86
<b>Hepatocellular carcinoma</b>	14% (52/382)	12% (28/237)	17% (24/145)	0.22
<b>Hepatitis C virus infection</b>	17% (66/382)	19% (45/237)	14% (21/145)	0.27
<b>Alcoholic liver disease</b>	21% (80/382)	22% (52/237)	19% (28/145)	0.60
<b>Others</b>	30% (114/382)	27% (64/237)	34% (50/145)	0.13
<b>Re-transplant</b>	8% (29/382)	6% (15/237)	10% (14/145)	0.24
<b>Re-transplant within 30 days</b>	1% (3/382)	1% (2/237)	1% (1/145)	1.0
<b>HIV</b>	1% (5/382)	2% (5/237)	0% (0/145)	0.16
<b>MELD (mean ± standard deviation)</b>	26.4 ± 8.2	25.8 ± 8.1	27.4 ± 8.4	0.07
<b>End-stage renal disease prior to transplant</b>	16% (62/382)	16% (37/237)	17% (25/145)	0.67
<b>Candida colonization within 4 weeks prior to transplant</b>	7% (26/382)	7% (17/237)	6% (9/145)	0.84
<b>Kidney/liver dual transplant</b>	4% (14/382)	1% (3/237)	8% (11/145)	0.003
<b>Living donor</b>	13% (49/382)	12% (28/237)	14% (21/145)	0.53
<b>Choledochojejunostomyanastomosis</b>	10% (40/382)	10% (23/237)	12% (17/145)	0.61
<b>Operation length &gt; 11 hours</b>	16% (63/382)	13% (31/237)	22% (32/145)	0.02
<b>Intra-operative use of &gt;40 units blood products</b>	11% (42/382)	12% (28/237)	10% (14/145)	0.61
<b>Operation length &gt;11 hours <u>AND</u> intra-operative use of &gt;40 Units blood products</b>	4% (17/382)	4% (10/237)	5% (7/145)	0.80
<b>Bile leak within 30 days post- transplant</b>	6% (22/382)	4% (9/237)	9% (13/145)	0.04
<b>Reoperation within 30 days post transplant</b>	25% (96/382)	22% (53/237)	30% (43/145)	0.12
<b>Renal replacement therapy within 30 days post-transplant</b>	27% (104/382)	27% (63/237)	28% (41/145)	0.72

<sup>a</sup>The targeted prophylaxis total adds up to 147 transplants because 2 patients with fulminant hepatic failure also had other indications for transplant

HIV = human immunodeficiency virus; MELD= Model for End-Stage Liver Disease



**Table 2**

Invasive fungal infection case descriptions.

Age (years)	MELD score	IFI risk factors	Living Donor	Bile leak	Prophylaxis	Days of Prophylaxis prior to IFI	Days From Transplant to IFI	Fungal organisms	Types of infection	Treatment	Outcome <sup>a</sup>
<b>Universal Antifungal Prophylaxis</b>											
50	33	RRT post-transplant	-	-	Vori	22	22	<i>Saccharomyces cerevisiae</i>	Peritonitis, infected Hematoma (proven)	FLU	Alive
55	34	None	Y	Y	Vori	5	12	<i>C. tropicalis</i>	Bile leak peritonitis (proven)	FLU	Alive
51	46	HIV, <i>Candida</i> colonized, RRT post-transplant	-	-	Vori	8	8	<i>Rhizomucor</i>	Disseminated infection (proven at autopsy)	None	Died
64 <sup>b</sup>	29	Choledochojejunostomy, RRT post-transplant	-	-	Vori	4	26 62	<i>C. glabrata</i>	Peritonitis (proven) Fungemia, catheter-associated (proven)	VORI CAS	Alive
69	24	None	-	-	Vori	6	25	<i>C. glabrata</i>	Intra-abdominal abscess (proven)	CAS	Alive
71	25	None	-	-	Vori	5	14	<i>C. parapsilosis</i>	Peritonitis (proven)	VORI	Alive
59	14	None	Y	-	Vori	5	22	<i>C. glabrata</i>	Intra-abdominal abscess (proven)	CAS	Alive
23	22	Fulminant hepatic failure, choledochojejunostomy, RRT post-transplant	-	-	Vori	4	4	<i>C. glabrata</i>	Peritonitis (proven)	CAS	Alive
40	29	Choledochojejunostomy	-	-	Vori	3	3	<i>C. glabrata</i>	Peritonitis, infected Hematoma (proven)	CAS	Alive
71	25	None	-	-	Vori	3	8	<i>Cryptococcus neoformans</i>	Pulmonary infection (proven)	VORI	Alive
<b>Targeted Antifungal Prophylaxis</b>											
58	25	None	Y	Y	None	0	6	<i>C. albicans and C. tropicalis</i>	Bile leak peritonitis (proven)	CAS	Died
57	28	Reoperation	-	Y	Vori	10	29 42	<i>C. glabrata</i> <i>Aspergillus fumigatus</i>	Intra-abdominal abscess (proven) Pulmonary infection (probable)	VORI CAS	Alive
66	25	Reoperation	-	Y	Vori	8	8	<i>C. albicans</i>	Bile leak peritonitis (proven)	CAS	Alive

Age (years)	MELD score	IFI risk factors	Living Donor	Bile leak	Prophylaxis	Days of Prophylaxis prior to IFI	Days From Transplant to IFI	Fungal organisms	Types of infection	Treatment	Outcome <sup>d</sup>
58	18	Reoperation	Y	Y	Vori	10	10	<i>C. albicans</i>	Bile leak peritonitis (proven)	VORI	Alive
54	48	RRT post-transplant	-	-	None	0	10	<i>C. glabrata</i>	Fungemia and peritonitis (proven)	CAS VORI	Died
57	13	Reoperation	Y	Y	Vori	7	7	<i>C. parapsilosis</i>	Bile leak peritonitis (proven)	CAS	Alive
58	25	None	-	-	None	0	6	<i>C. albicans</i>	Peritonitis (proven)	VORI	Alive
67	19	None	Y	-	None	0	7	<i>C. albicans</i>	Peritonitis (proven)	CAS	Alive
59	25	None	-	-	None	0	18	<i>Cryptococcus neoformans</i>	Pulmonary infection (proven)	VORI AmB	Alive
57	15	Re-transplant, choledochojunostomy, reoperation	Y	-	Vori	16	16	<i>C. glabrata</i>	Intra-abdominal abscess, fungemia (proven)	VORI	Alive

<sup>d</sup>Mortality at 100 days

Note: 1) Ten patients had candiduria (5 each in the universal and targeted prophylaxis groups). All episodes were asymptomatic and associated with <25,000 colony forming units of *Candida* spp/mL. Most of these patients were evaluated by the Transplant Infectious Diseases service, and none was treated. Therefore, the cases were considered colonization and not included as IFIs. . 2) Among patients with IFI, only 1 patient had CMV viremia (asymptomatic) preceding IFI (3 days before IFI). The remaining patients developed viremia at a median time of 26 days after IFI (and 36.5 days after transplant).

AmB = Liposomal amphotericin B; CAS = Caspofungin; FLU = Fluconazole; HIV = human immunodeficiency virus; MELD= Model for End-Stage Liver Disease; RRT = renal replacement therapy; VORI = Voriconazole

**Table 3**

Risk factors for invasive fungal infections.

Factors	Univariate			Multivariate
	IFI (n=20)	No IFI (n= 362)	P-value Odds ratio (95% Confidence interval)	P-value Odds ratio (95% confidence interval)
Age (years), median	58.1	56.6	0.51	
MELD, median (mean)	25 (26.1)	25 (26.4)	0.78	
Re-transplant	5% (1/20)	8% (28/362)	1.0 0.63 (0.08–4.87)	
<i>Candida</i> colonization before or at time of transplant	5% (1/20)	7% (25/362)	1.0 0.71 (0.09–5.52)	
Reoperation <sup>a</sup>	25% (5/20)	22% (81/362)	0.78 1.16 (0.41–3.28)	
Renal failure prior to transplant	15% (3/20)	16% (59/362)	1.0 0.91 (0.26–3.19)	
Renal replacement therapy post- transplant <sup>a</sup>	25% (5/20)	27% (96/362)	1.0 0.92 (0.33–2.61)	
Fulminant hepatic failure	5% (1/20)	2% (8/362)	0.39 2.33 (0.28–19.60)	
Living donor	35% (7/20)	12% (42/362)	0.008 4.10 (1.55–10.86)	0.04 2.96 (1.05–8.40)
Choledochojejunostomy	20% (4/20)	10% (36/362)	0.15 2.26 (0.72–7.14)	
Operation length >11 hours	25% (5/20)	16% (58/362)	0.35 1.75 (0.61–5.00)	
Intra-operative use of >40 units blood products	0% (0/20)	12% (42/362)	0.15 0.18 (0.01–3.10)	
Operation length >11 hours AND intra-operative use of >40 Units blood products	0% (0/20)	5% (17/362)	1.0 0.48 (0.03–8.30)	
Targeted antifungal prophylaxis	50% (10/20)	37% (135/362)	0.34 1.68 (0.68–4.14)	
Bile leaks within 30 days post-transplant	30% (6/20)	4% (16/362)	0.0004 9.27 (3.15–27.29)	0.001 7.13 (2.31–22.04)

Note: Bile leak within 30 days post-transplant and living donor remained independent risk factors for IFI when the types of antifungal prophylaxis was forced in the multivariate analysis model.

<sup>a</sup>Total numbers of patients who required reoperation or renal replacement therapy post-transplant are lower than in Table 1 because only factors antecedent to the IFI are included

MELD= Model for End-Stage Liver Disease