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Universal Fungal Prophylaxis and Risk of Coccidioidomycosis in Liver Transplant Recipients Living in an Endemic Area

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Abstract

Liver transplant recipients are at increased risk for symptomatic coccidioidomycosis, primarily due to chronic immunosuppression and impaired cellular immunity. Unfortunately, no consensus exists regarding optimal posttransplant prophylaxis. In a prior study at our institution, we observed both de novo and recurrent coccidioidomycosis despite targeted antifungal prophylaxis. In response, in February 2011 we instituted a universal prophylaxis program consisting of fluconazole 200 mg daily for the first posttransplant year. In the current study, we retrospectively reviewed the medical records of all patients who had liver transplants (LTs) between the initiation of universal prophylaxis and July 11, 2013. Patients receiving a second transplant or dual-organ transplant and those who died or did not have follow-up in the 12-month post-LT period were excluded. Data from the universal prophylaxis cohort were compared with previously published data from the targeted prophylaxis era. Of the 160 patients undergoing LT during the study period, 143 met criteria for data analysis. When compared with the 349 patients in the targeted prophylaxis cohort, patients in the universal prophylaxis group were older and had higher rates of pre-LT coccidioidomycosis, asymptomatic coccidioidal seropositivity, posttransplant diabetes mellitus, and renal insufficiency. Fluconazole-related toxicity occurred in 13 of the universal prophylaxis patients, 7 of whom were required to discontinue use of the medication. Coccidioidomycosis developed in 10 of the 391 patients (2.6%) in the targeted prophylaxis cohort and in none of the patients in the universal prophylaxis group (P=.04). These data strongly support the use of a 1-year antifungal prophylaxis regimen for LT recipients in endemic regions.

Keywords: antifungal; fluconazole; immunosuppression; infection; prevention

Introduction

Coccidioidomycosis is an infection caused by the dimorphic fungi of the *Coccidioides* species, *C immitis* and *C posadasii* (1). This soil-dwelling organism is endemic to areas of the southwestern United States, northern Mexico, and portions of Central and South America (2,3). Soil disruption results in airborne spores; after inhaling these, a majority of immunocompetent hosts remain asymptomatic, but others experience widely varying degrees of respiratory symptoms (4,5). Fewer than 5% of patients experience extrapulmonary infection (6,7). However, solid-organ transplant recipients require lifelong suppression of cell-mediated immunity and are thus particularly susceptible to symptomatic, severe, or disseminated coccidioidal infection (1-3,8).

The literature regarding coccidioidal prophylaxis for organ-transplant recipients is sparse, presumably due to the infection's limited area of endemicity. Available studies suggest rapidly increasing incidence within the endemic region (6,9-12) and report rates of dissemination and mortality as high as 72% in the transplant population (2,8). Transplant centers within the endemic region use various prophylactic antifungal regimens (13), and no consensus exists regarding the optimal approach because no prospective, randomized data have been published.

Our liver transplant program began with a targeted prophylaxis approach based on pretransplant history of coccidioidomycosis or asymptomatic seropositivity, consistent with the widely held view that most cases of posttransplant coccidioidomycosis represented reactivation (1,14). Early data gleaned from the targeted-prophylaxis period supported this practice (13); however, subsequent studies in liver (15) and renal (16)

transplant recipients at our institution showed de novo cocci in patients not receiving prophylaxis. This finding led to the implementation in February 2011 of universal fluconazole prophylaxis for 1 year after liver transplant.

The aim of the current study was to update previous descriptions of posttransplant coccidioidomycosis at our institution and assess the efficacy and tolerability of universal antifungal prophylaxis. Specifically, we reviewed the records of all liver transplant recipients since the initiation of universal prophylaxis and compared these data to those of the targeted prophylaxis cohort (15). We hypothesized that the expanded prophylaxis program would decrease the incidence of coccidioidomycosis.

Methods

Study Design

The electronic medical records of all patients who received liver transplants at our institution between February 4, 2011, and July 11, 2013, were retrospectively reviewed. Patients undergoing retransplant or dual-organ transplant, those who died of causes unrelated to coccidioidomycosis during the first posttransplant year, and those not completing 12 months of follow-up were excluded from the study. Previously published data were used to compose the targeted prophylaxis cohort and were subjected to the same exclusion criteria. This study was approved by our institution's institutional review board.

Data Collection

All electronic medical records, including inpatient and outpatient encounter notes, radiographic and laboratory reports, and patient correspondence were reviewed. Data were recorded for a period of 1 year after transplant in both cohorts. Data recorded included demographics,

comorbidities, cause of end-stage liver disease, history of hepatitis C virus (including previous treatment), history of hepatocellular carcinoma or other malignancy, transplant characteristics (donor type, cytomegalovirus status), location of residence, history of pretransplant coccidioidomycosis (date of infection, symptoms, and laboratory or radiographic findings), posttransplant coccidioidomycosis (date of infection, location, strength of diagnosis, outcome), results of all fungal cultures (coccidioidal and noncoccidioidal), antifungal prophylaxis regimen, posttransplant infection other than coccidioidomycosis, acute rejection (degree of rejection and use of high-dose intravenous corticosteroids), and death and associated cause. Renal dysfunction was defined as a creatinine clearance less than 60 mL/min.

Definition of Coccidioidomycosis

Data from the US Centers for Disease Control and Prevention (17) and internet mapping software (18) were used to determine residence in an endemic region. Coccidioidomycosis was defined according to the consensus revised definitions of invasive fungal disease of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (19). Proven coccidioidomycosis was defined as positive culture, cerebrospinal fluid seropositivity, 2-dilution increase in consecutive serum serologic tests, or histopathologic identification of *Coccidioides* spherules in a biologic specimen obtained during active disease. Probable coccidioidomycosis was defined as coccidioidal seropositivity in the setting of a consistent clinical picture and a host factor for invasive fungal infection (eg, recent neutropenia, prolonged

use of corticosteroids, treatment with T-cell immunosuppressive agents, and congenital immunodeficiency states).

Although clinical features of coccidioidomycosis are heterogeneous and nonspecific, symptoms of fever, cough, dyspnea, chest pain, headache, myalgias, and fatigue were considered characteristic (20). Characteristic radiographic findings are similarly nonspecific but included parenchymal consolidation, peribronchial thickening, multifocal nodularity, hilar or mediastinal lymphadenopathy, and pleural effusion (21).

Pretransplantation Evaluation

Candidates for liver transplant underwent a thorough multidisciplinary evaluation. This included a complete medical history, physical examination, and appropriate laboratory and radiographic studies. All patients were evaluated by an infectious disease specialist to identify previous infections and determine the risk for posttransplant infection.

Coccidioidomycosis Prophylaxis

Before February 2011, patients with a documented history of coccidioidomycosis more than 1 year before transplant received 200 mg oral fluconazole daily for 6 to 12 months. Those with positive coccidioidal serologic results at transplant or active coccidioidomycosis within 1 year of transplant were given 400 mg oral fluconazole daily lifelong. From February 2011 until currently, all patients received antifungal prophylaxis beginning at the time of transplant, regardless of pretransplant history. The protocol consisted of 200 mg oral fluconazole daily for the first posttransplant year. Dose adjustment for renal function consisted of a reduction to 50% for creatinine clearance less than 50 mL/min and was performed at the discretion of the treating physician. Patients with a recent pretransplant

history of coccidioidomycosis (<1 year) or asymptomatic coccidioidal seropositivity at the time of transplant were treated lifelong with fluconazole prophylaxis at a dosage of 400 mg/day. Patients with a remote history of coccidioidomycosis (>1 year) received a prophylactic regimen identical to that of patients without any prior history (200 mg/day, adjusted for renal function); however, this was continued lifelong in cases of seropositivity before transplant. Aside from the alteration in the coccidioidomycosis prophylaxis protocol outlined above, no other changes to the transplant protocol or to the immunosuppressive regimen were made between study cohorts.

Noncoccidioidal Prophylaxis

All patients received daily prophylaxis for *Pneumocystis* pneumonia with trimethoprim/sulfamethoxazole for 6 months. For patients with cytomegalovirus mismatch (donor positive, recipient negative) or those with a history of cytomegalovirus seropositivity in the setting of hepatitis C virus, valgancyclovir was administered at a dosage of 900 mg daily for 6 months. For those not receiving valgancyclovir, acyclovir 400 mg twice daily was administered for 30 days as herpes simplex virus prophylaxis.

Posttransplant Immunosuppression

Postoperatively, patients received a standard immunosuppressive regimen that consisted of intravenous methylprednisolone and tacrolimus. They were then transitioned to oral prednisone, tapered over a 4-month period. Patients with immune-mediated disease (eg, primary biliary cirrhosis, autoimmune hepatitis) continued to receive low-dose prednisone (5 mg/day) indefinitely. Patients with renal insufficiency (increased serum creatinine, more than 2 mg/dL) received concomitant treatment with

mycophenolate mofetil 1,000 mg twice daily to allow for lower tacrolimus dose and blood levels. Symptomatic intolerance of mycophenolate mofetil or observed cytopenia resulted in dose reduction to 500 mg twice daily.

Coccidioides Serologic Testing

In addition to undergoing measurement of *Coccidioides* serology during the pretransplant evaluation, all patients undergo repeat testing on the day of transplant, 4 and 12 months after transplant, and annually thereafter. Symptomatic patients may undergo additional testing at the discretion of the treating provider. Each instance of testing consists of multimodal serologic testing performed in our laboratory, including enzyme immunoassay for immunoglobulin M and G (Meridian Bioscience test kit, Meridian Bioscience, Inc), immunodiffusion for immunoglobulin M and G (Gibson Laboratories test kit, Gibson Laboratories), and complement fixation testing using the laboratory branch method of the Centers for Disease Control and Prevention (antigen obtained from Coccidioidomycosis Serology Laboratory, University of California Davis School of Medicine).

Graft Rejection

In cases of suspected acute cellular rejection, liver biopsy was performed. Treatment of biopsy-proven rejection was individualized to each patient. In moderate-severe rejection, intravenous methylprednisolone sodium succinate was given in 3 doses of 1 g each. Cases of mild rejection were often treated with an increase in oral immunosuppressive medication, at the discretion of the treating provider.

Statistical Analysis

Descriptive statistics were performed to compare data between universal and targeted prophylaxis groups using JMP statistical analysis

software (SAS Institute, Inc). Two-tailed Fisher exact test was used for proportional data, and means were compared with Student *t* test. A *P* value less than .05 was considered statistically significant.

Results

During the study period, 160 patients underwent liver transplant at our institution. Of these, 143 met criteria for inclusion. Exclusion criteria were applied to the 391 patients reported in the previous study, and 349 were included in the current analysis. The details of patient exclusion are provided in Figure 1. Data regarding prophylactic regimens and the details and outcomes of each case of coccidioidomycosis in the targeted-prophylaxis cohort have been previously published (15).

Pretransplant Characteristics

The demographic, comorbidity, and transplant characteristics of our study populations are summarized in Table 1. Patients in the universal prophylaxis cohort were significantly older and had a higher prevalence of hepatocellular carcinoma, chronic kidney disease (pretransplant or posttransplant, combined), and posttransplant diabetes mellitus. The proportion of hepatitis C virus and alcoholic liver disease as cause for end-stage liver disease was equivalent in both groups, but nonalcoholic steatohepatitis was more prevalent in the universal prophylaxis group. Both groups experienced equivalent rates of acute cellular rejection. However, the targeted prophylaxis group was more likely to experience severe rejection requiring treatment with intravenous corticosteroids.

Pretransplant coccidioidomycosis data are summarized in Table 2. Patients in the universal prophylaxis group had a higher prevalence of asymptomatic seropositivity. However, residence in an endemic region was

significantly less likely among these patients, with only 119 of the 143 patients (83.2%) residing in endemic areas.

Prophylactic Antifungal Regimen

In total, 133 (93%) of study patients completed a full year of antifungal prophylaxis: 87 (61%) patients completed 12 months of the 200 mg/day prophylactic dose; 33 (23%) required dose adjustment for renal dysfunction; 7 (4.9%) received 400 mg daily fluconazole for a history of pretransplant coccidioidomycosis. In comparison, 18 patients in the targeted prophylaxis cohort received prophylactic fluconazole. Of these, 11 had a pretransplant history of coccidioidomycosis, and 7 were found to have asymptomatic seropositivity before transplant. Doses varied between 100 and 400 mg daily, based on comorbid diseases (eg, renal dysfunction) and toxicity.

Fluconazole toxicity occurred in 13 of the 143 patients (9%). Seven of these patients permanently discontinued use of fluconazole at a mean of 2.6 months after transplant because of increased transaminase levels. One of them required ongoing antifungal treatment because of a pretransplant history of coccidioidomycosis and was given voriconazole. Four patients transiently decreased or stopped fluconazole prophylaxis because of increased transaminase levels but returned to daily prophylaxis and completed the remainder of the course. At the request of a hematologist, 1 patient permanently discontinued use of fluconazole because of pancytopenia.

Medication nonadherence occurred in 3 patients (2.1%). One patient misunderstood the provided instructions and unintentionally doubled the dose to 400 mg daily. One patient missed 2 weeks of scheduled

treatment with 200 mg daily fluconazole because of difficulty obtaining the medication. One patient stopped prophylaxis altogether within the first 3 months after transplant because the prescription expired. Treatment with fluconazole was resumed on the day this noncompliance was discovered and continued until completion of the first posttransplant year.

Posttransplant Coccidioidomycosis

Posttransplant coccidioidomycosis data are summarized in Table 2. No cases of posttransplant coccidioidomycosis occurred in the universal prophylaxis group. In the targeted cohort, coccidioidomycosis developed in 10 patients (2.9%) within the first year after transplant, and in 9 of these 10 it occurred within the first 6 months. Only 1 patient with a history of pretransplant coccidioidomycosis received 400 mg fluconazole daily. The remaining 9 patients had no prior history of coccidioidomycosis and thus received no prophylaxis. Of these 10 patients, 2 died of disseminated coccidioidomycosis, and neither received antifungal prophylaxis. All 10 cases occurred in patients residing in endemic regions. The reduction in the universal prophylaxis group was statistically significant (P=.04). The incidence of asymptomatic seroconversion at 1 year was also higher in the targeted-prophylaxis group: 8 (2.3%) cases compared with no cases in the universal prophylaxis cohort. None of these 8 cases received fluconazole prophylaxis. This difference was not statistically significant (P=.11).

In a subset analysis of patients at risk for de novo coccidioidomycosis, we excluded patients with a history of pretransplant coccidioidomycosis or asymptomatic seropositivity. Thus, only the 331 patients who received no prophylaxis under the previous targeted protocol were compared with the 106 patients with no risk factors who received

universal prophylaxis. The 1-year incidence of coccidioidomycosis after transplant was 9 of 331 in the targeted prophylaxis group and zero in the universal cohort (*P*=.12).

Other Fungal Infections

Noncoccidioidal fungal infections occurred in 57 of the 349 patients (16.3%) in the targeted-prophylaxis cohort and in 25 of the 143 (17.5%) in the universal prophylaxis cohort (*P*=.79). Table 1 summarizes the noncoccidioidal infections in each cohort. There were more non-*albicans Candida* infections in the universal prophylaxis cohort [20/143 (14%)] than the targeted cohort [23/349 (6.6%)] (*P*=.01).

Discussion

Coccidioidomycosis continues to pose a particular threat to liver transplant recipients residing in endemic regions because the iatrogenic suppression of cell-mediated immunity simultaneously prevents acute cellular organ rejection and the ability to control the infection (22,23). A targeted prophylaxis approach at our institution failed to completely prevent de novo coccidioidomycosis; this failure led to implementation of a 1-year universal antifungal prophylaxis program (15). To our knowledge, this is the first study to directly compare the outcomes of universal fluconazole prophylaxis in liver transplant recipients with those of a targeted prophylaxis approach.

Although numerous prophylactic fluconazole regimens, ranging in duration from 30 days to lifelong and in dosage from 100 to 400 mg per day, have been informally reported by transplant centers in the endemic region (13), the body of literature addressing outcomes is scant and consists primarily of small, retrospective cohort studies. Winston and colleagues (5)

performed the only prospective, randomized study of antifungal prophylaxis in liver transplant recipients. They assigned 236 patients to receive 400 mg of fluconazole daily or placebo for 10 weeks posttransplant. Two patients in the placebo group acquired coccidioidomycosis, and no cases occurred in the fluconazole prophylaxis cohort. However, that study did not directly address the issue of universal versus targeted prophylaxis in that pretransplant assessment of coccidioidomycosis risk was not reported.

In the current study, universal and targeted prophylactic approaches were directly compared. The absence of posttransplant coccidioidomycosis in patients receiving 1 year of universal prophylaxis is encouraging, particularly when compared with the rate of de novo infection in the targeted cohort. A subgroup analysis of patients at risk for de novo coccidioidomycosis showed a statistically nonsignificant decrease in de novo coccidioidomycosis in the universal prophylaxis group; however we believe this lack of difference is primarily due to small sample size. Furthermore, patients in the universal prophylaxis cohort had a higher rate of pretransplant asymptomatic seropositivity and should have therefore been at a higher risk for development of posttransplant coccidioidomycosis. Although not statistically significant, the lack of any asymptomatic seroconversion is equally promising. Finally, although formal analysis in the current study did not extend beyond 1 year, we can report anecdotally that the withdrawal of prophylaxis at 1 year has not resulted in any new cases of coccidioidomycosis.

Although no consensus yet exists regarding universal versus targeted prophylaxis, our results favor the use of a 1-year universal prophylaxis approach in liver transplant recipients residing in endemic areas.

The vulnerabilities of targeted prophylaxis have been well described. Rates of undetected, subclinical coccidioidomycosis as high as 60% at the time of transplant have been reported (3,24), and they are likely attributable to the inadequacy of current screening methods. The acquisition of an accurate and complete medical history is often impeded by inaccurate recall and poor medical literacy (25). Radiographic abnormalities are common but nonspecific (1). Currently available serologic assays lack the sensitivity and negative predictive value to definitively rule out infection and are limited by the lack of a standard diagnostic test (26). Furthermore, immunologic abnormalities in patients with liver dysfunction may lead to poor diagnostic yield in coccidioidal serologic tests (13), and complications of end-stage liver disease, such as ascites and portosystemic encephalopathy, may mask characteristic findings and thus delay diagnosis (13,27).

The search for risk factors, aside from prior infection, that can identify patients in whom coccidioidomycosis is likely to develop has yielded few useful markers, and this paucity has further limited the efficacy of targeted antifungal prophylaxis. Known risk factors for dissemination include male sex, pregnancy, blood group, HLA type, and African American or Filipino race (3). End-stage liver disease is not an established risk factor for the acquisition or dissemination of coccidioidomycosis (3,28,29), but it affects the identification of infection. The treatment of acute cellular rejection with intravenous corticosteroids is a reported risk factor for posttransplant coccidioidomycosis (30,31). In our study, the incidence of corticosteroid-treated acute rejection was significantly higher among the targeted prophylaxis cohort. This finding is interesting, particularly given the observed trend toward a higher incidence of coccidioidomycosis in this

group. However, in previously published data, this group had undergone a subgroup analysis that showed no statistically significant association between posttransplant coccidioidomycosis and the rate of acute rejection (15).

Although patients who undergo transplant and reside in endemic regions are the predominant population for which prophylaxis is indicated, we administered coccidioidomycosis prophylaxis to all patients, regardless of area of residence. Patients residing in nonendemic regions may have a degree of risk by virtue of their exposure during perioperative care. Numerous case reports of donor-transmitted infection reinforce the risk of transient or remote exposure. Donors briefly visiting or formerly residing in Arizona have transmitted infection through organ donation to recipients in nonendemic regions, and this transmission has led to disseminated and often fatal cases of coccidioidomycosis because infection is often not suspected until dissemination has occurred (32,33). Donor factors associated with coccidioidomycosis risk were not systematically recorded in our study. However, within the endemic area, it is difficult to differentiate donor-derived from new-acquisition cases because of the ongoing exposure of the recipient to the endemic area. Hence, this issue remains important for future research.

As with any intervention, the benefit of preventing coccidioidal infection must be weighed against the potential risk of unintended harm. Historically, targeted prophylaxis has been favored within the endemic region because of a concern for fluconazole-related toxicity and the emergence of resistant fungal infections in a chronically immunocompromised population (5,34). Very few of the patients in our

study experienced serious drug-related toxicity requiring dose adjustment or discontinuation. This risk is primarily theoretical and has not been reported in the few published outcome studies of patients receiving fluconazole prophylaxis (5,13,15). However, as shown in our patient population, appropriate dose adjustments and clinical judgment can maximize the benefit and limit the toxicity of fluconazole prophylaxis.

The concern for expanded risk of resistant fungal infections with universal prophylaxis is similarly theoretical. The study by Winston et al (5) found no significant increase in colonization by resistant fungal organisms in a comparison of patients receiving fluconazole prophylaxis with a placebo group. In our study, the overall rate of fungal infection did not differ between the universal (17.5%) and the targeted (16.3%) prophylaxis groups (P=.79). However, the proportion of patients with non-*albicans Candida* was higher in the universal prophylaxis group (14.4%) than the targeted prophylaxis group (6.3%) (P=.01). This finding suggests that the implementation of universal prophylaxis may select for fluconazole-resistant *Candida* species. Antifungal susceptibility tests were not routinely ordered for many of the fungal isolates in our study population and, therefore, cannot be compared.

The potential for pharmacokinetic interactions must also be closely considered. Azole antifungals are potent inhibitors of the cytochrome P-450 enzyme 3A4, which serves as the major pathway for metabolism of tacrolimus (35). Accordingly, therapeutic levels of tacrolimus can be achieved at lower doses in patients concurrently taking fluconazole. However, any change in the dose of fluconazole must be met with careful monitoring of tacrolimus levels and corresponding dose adjustment, because

serum tacrolimus levels will predictably decrease and, if not adjusted appropriately, may precipitate organ rejection. In our protocol, use of fluconazole is intentionally started immediately after transplant and thus initial tacrolimus dosing can account for this interaction. The 1-year timeframe of universal prophylaxis was deliberately chosen to coincide with the highest period of coccidioidomycosis risk; however its conclusion was also designed to coincide with the first annual posttransplant evaluation. At this visit, use of fluconazole is discontinued, the tacrolimus dose is preemptively doubled, drug levels are monitored weekly for 1 month until they have stabilized, and patients are given education about expected changes. This level of vigilance and deliberate planning is essential to mitigating the risk of the fluconazole-tacrolimus drug interaction.

Our study has several important limitations. The retrospective, observational study design allows for only a comment on the correlation between variables. The adjustment of immunosuppressive and antifungal dosing was performed independently by each treating physician and was not prospectively controlled. From the standpoint of demographic and comorbidity data, our cohorts were relatively well matched despite a lack of prospective randomization. However, we used a historical control and patients in the targeted cohort were more likely to have endemic residence and rejection requiring corticosteroids, whereas the universal prophylaxis group had a higher rate of pretransplant asymptomatic seropositivity. The small sample size of our universal prophylaxis cohort and the relatively low overall incidence of coccidioidomycosis also limited our ability to show statistical differences and placed a high statistical emphasis on each incident

case. The difficulty in establishing a definitive diagnosis means that undetected cases could have altered our statistical findings substantially.

We acknowledge that adherence to the described universal prophylaxis protocol was not uniform. Each patient was treated by independent providers whose clinical judgment was individualized on a case-by-case basis. Coordination of care within the health system, patient medication intolerances, and disease-related circumstances (eg, fluctuating renal function) served as additional sources of deviation. Such deviations are important limitations of our retrospective study design.

In conclusion, our data show the efficacy and tolerability of 1-year universal fluconazole prophylaxis for liver transplant recipients. The consequences of posttransplant coccidioidomycosis far outweighed any observed morbidity associated with widespread prophylaxis. These data are limited, and larger prospective studies are needed to characterize the incremental benefit of universal over targeted prophylaxis. However, our results support the implementation of a 1-year universal prophylaxis approach in endemic areas. Despite the apparent success of our expanded prophylaxis program, comprehensive and thorough pretransplant evaluation and posttransplant follow-up care are perhaps even more imperative in the changing landscape of coccidioidomycosis. Future studies will be needed to examine our study population beyond the first posttransplant year and provide ongoing critical analysis of outcomes to further optimize care.

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Table 1. Demographic, Comorbidity, and Transplant Characteristics of All Study Patients

Characteristic	Group: Targeted Prophylaxis (n=349)	Group: Universal Prophylaxis (n=143)	*P* Value
Mean age, y	51.9	55.3	<.01
Sex			
Male	243 (69.6%)	99 (69.2%)	>.99
Female	106 (30.4%)	44 (30.8%)	
Race			
White	276 (79.1%)	116 (81.1%)	.71
African American	8 (2.3%)	2 (1.4%)	.73
Native American	16 (4.6%)	4 (2.8%)	.46
Asian American	5 (1.4%)	2 (1.4%)	>.99
Other	44 (12.6%)	19 (13.3%)	.88
Diabetes history			
Pretransplant	88 (25.2%)	35 (24.4%)	.9
Posttransplant	8 (2.3%)	12 (8.4%)	<.01
Renal disease	44 (12.6%)	82 (57.3%)	<.01
HCC prevalence	91 (26.1%)	57 (39.9%)	<.01
Cancer history			
Non-HCC hepatobiliary	5 (1.4%)	3 (2.1%)	.7
Non-liver solid	20 (5.7%)	13 (9.1%)	.23
Hematologic	4 (1.1%)	4 (2.8%)	.24
ESLD cause			
Hepatitis C infection	170 (48.7%)	70 (49%)	>.99

Table 1 (continued)

Characteristic	Group: Targeted Prophylaxis (n=349)	Group: Universal Prophylaxis (n=143)	*P* Value
ALD	50 (14.3%)	26 (18.1%)	.34
NASH/cryptogenic	38 (10.9%)	27 (18.8%)	.03
Other	91 (26.1%)	20 (14%)[c]	<.01
Donor type			
Deceased	283 (81.1%)	121 (84.6%)	.44
Living	66 (18.9%)	22 (15.4%)	
CMV			
Mismatch	53 (15.2%)	29 (20.3%)	.18
Infection	28 (8%)	16 (11.2%)	.3
Noncoccidoidal fungal infections	57 (16.3%)	25 (17.5%)	.79
Candida albicans	23 (6.6%)[a]	5 (3.5%)[b]	.2
Non-*albicans Candida*	23 (6.6%)[c]	20 (14%)[d]	.01
Candida species, not otherwise specified	8 (2.3%)[e]	0	.11
Other yeast	1 (0.3%)[f]	0	>.99
Mold infection[g]	2 (0.6%)	1 (0.7%)	>.99
Acute rejection			
None	247 (70.8%)	108 (75.5%)	.32
Mild	27 (7.7%)	22 (15.4%)	.01
Required IV corticosteroids	75 (21.5%)	13 (9.1%)	<.01

Table 1 (continued)

Abbreviations: ALD, alcoholic liver disease; CMV, cytomegalovirus; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; IV, intravenous; NASH, nonalcoholic steatohepatitis.

[a]Urinary (n=13), peritoneal (n=6), septic arthritis (n=1), biliary (n=2), pharyngeal (n=1).

[b]Urinary (n=1), fungemia (n=1), sinus (n=1), biliary (n=1), respiratory colonization (n=1).

[c]Urinary (n=18), biliary (n=3), fungemia (n=2).

[d]Urinary (n=17), peritoneal (n=2), biliary (n=1).

[e]Gastrointestinal mucosal infection (n=7), peritoneal (n=1).

[f]*Rhodotorula minuta* urinary infection.

[g]*Aspergillus flavus* biloma (n=1) in universal prophylaxis group. *Aspergillus* pneumonia (n=1) and *Scedosporium* brain abscess (n=1) in targeted cohort.

Table 2. Coccidioidal Characteristics of All Study Patients

Characteristic	Group: Targeted Prophylaxis (n=349)	Group: Universal Prophylaxis (n=143)	*P* Value
Residence in an endemic area	325 (93.1%)	119 (83.2%)	.001
Pretransplant			
Asymptomatic seropositivity	26 (7.4%)	27 (18.9%)	.001
Coccidioidomycosis	11 (3.2%)	10 (7%)	.08
1-Year posttransplant			
Asymptomatic seroconversion	8 (2.3%)	0	.11
Coccidioidomycosis	10 (2.9%)	0[a]	.04

Legend

Figure 1. Flow Chart of Exclusion Criteria Applied to Transplant Study Groups. HCV indicates hepatitis C virus.

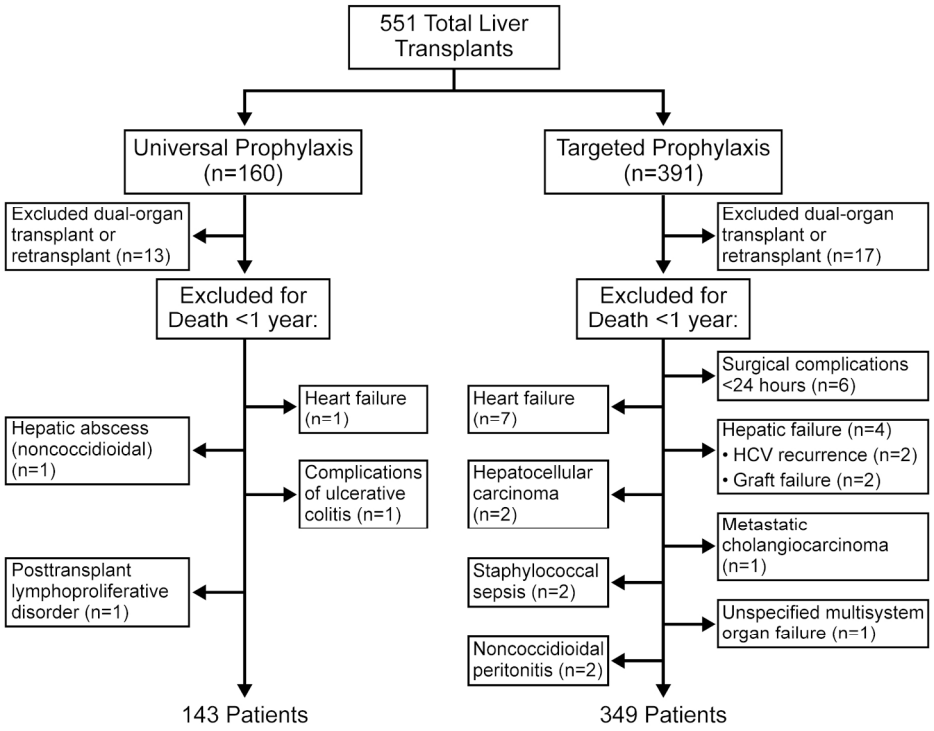

Figure 1. Flow Chart of Exclusion Criteria Applied to Transplant Study Groups. HCV indicates hepatitis C virus.
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