Original Article

Critically Ill Recipients of Weight-Based Fluconazole Meeting Drug-Induced Liver Injury Network Criteria

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Abstract

Background: Fluconazole-associated liver injury is estimated to occur in <10% of patients; however, effect of weight-based fluconazole dosing on liver injury is unknown. Furthermore, no studies have systematically applied the Drug-Induced Liver Injury Network (DILIN) Criteria to identify patients who may have drug-induced liver injury in an intensive care unit (ICU) setting. **Objective:** This study evaluated how often patients met DILIN criteria when receiving fluconazole daily doses of <6 mg/kg versus ⩾6 mg/kg. **Methods**: This dual-center, retrospective cohort study was performed in hospitalized critically ill fluconazole recipients. We compared liver function tests (LFTs) upon fluconazole initiation to peak LFTs within 2 weeks after discontinuation using DILIN criteria. The primary objective was to evaluate the number of patients meeting DILIN criteria when receiving fluconazole daily doses of <6 mg/kg versus ⩾6 mg/kg. Secondary objectives were to evaluate incidence of patients meeting DILIN criteria in patients with renal dysfunction, cirrhosis, septic shock, or those receiving a loading dose. **Results**: Of 248 patients included, 90% had a documented fungal infection or received empiric therapy for suspected invasive candidiasis. In patients receiving <6 mg/kg of fluconazole, 55% (110/199) met DILIN criteria versus 46.9% (23/49) in the ⩾6 mg/kg cohort ($P = .20$). Only 14.5% of patients meeting DILIN criteria also met the definition for hepatocellular damage. Weight-based fluconazole dose and creatinine clearance <50 mL/min were not independent risk factors for meeting DILIN criteria. However, 77.3% of patients with cirrhosis met DILIN criteria (OR 4.84 [95% confidence interval, CI, 2.61-9.28]) and 76.3% with septic shock met DILIN criteria (OR 4.56 [95% CI, 2.44-8.88]). **Conclusion**: Weight-based fluconazole dosing did not affect the number of critically ill recipients who met DILIN criteria. However, DILIN criteria may overestimate the incidence of fluconazole-associated liver injury in critically ill patients.

Keywords
adverse drug reactions reporting/monitoring, critical care, medication safety, fluconazole, drug-induced liver toxicity, hepatotoxicity

Background

In the United States, drug-induced liver injury is the leading cause of acute liver failure, which has a mortality rate of 30% without transplantation.[1] The Drug-Induced Liver Injury Network (DILIN) developed standardized definitions to identify cases of suspected drug-induced liver injury. Currently, inpatients and outpatients who meet DILIN criteria are referred to investigators and followed prospectively to determine the likely causality of hepatotoxicity of the implicated drug.[2] In a study published by DILIN investigators, of the 899 patients enrolled with likely drug-induced liver injury, the most common implicated agents were herbal and dietary supplements (n = 145), amoxicillin/clavulanate (n = 91), isoniazid (n = 48), nitrofurantoin (n = 42), and trimethoprim-sulfamethoxazole (n = 31). While fluconazole was implicated as a possible causative agent, only 4 patients were determined to have possible fluconazole hepatotoxicity.[3]

The definition of hepatotoxicity has varied widely in published studies from undefined elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and

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alkaline phosphatase (Alk P), to more standard definitions calculating the degree above the upper limit of normal (ULN) of AST, ALT, Alk P, and/or total serum bilirubin.[4-8] The DILIN has since developed a standardized definition to identify cases of drug-related liver injury and has been using this tool to identify cases of suspected drug-induced liver injury. Therefore, we chose this tool to identify cases of fluconazole-associated liver injury with the standardized DILIN definition in this intensive care unit (ICU) population.

While there is a variety of definitions studies have used to identify liver toxicity, the categorization of hepatotoxicity as hepatocellular, cholestatic, or mixed is fairly consistent. Fluconazole liver injury is usually hepatocellular but may present as cholestatic or mixed.[9,10] While fluconazole has been implicated in drug-induced liver injury, no specific risk factor, including weight-based dosing, in the fluconazole regimen has been linked to drug-induced liver injury.[11]

We evaluated the incidence of patients meeting DILIN criteria with fluconazole dosing of <6 mg/kg vs ≥ 6 mg/kg in an ICU population. This fluconazole dose is based on the Infectious Diseases Society of America (IDSA) recommendation for fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) for empiric therapy for suspected candidiasis and candidiasis treatment in nonneutropenic patients.[12] Our secondary objectives were to evaluate the incidence of fluconazole patients meeting DILIN criteria in patients with renal dysfunction (creatinine clearance [CrCl] $<$ 50 mL/min), cirrhosis, septic shock, or those receiving a loading dose of fluconazole.

Methods

Study Design

We performed a dual-center, retrospective cohort study involving patients admitted to any ICU at two academic medical centers in San Antonio, Texas, from January 1, 2009, to December 31, 2012. Eligible patients received fluconazole for 3 or more days with at least 1 dose administered in the ICU. Patients were excluded if they were pregnant, had concomitant acetaminophen toxicity, received fluconazole within 1 week of liver transplantation, missed 2 or more doses of fluconazole during the treatment period, received fluconazole for candiduria, or had missing baseline or follow-up liver function tests. Patients with candiduria were excluded as asymptomatic candiduria rarely requires treatment. This study was approved by the institutional review boards of the University of Texas Health Science Center at San Antonio, the University of the Incarnate Word, and the research and development offices of University Health System and the South Texas Veterans Health Care System.

Data Collected

We collected data on baseline patient demographics, fluconazole indication, dose, and duration. All patient charts were reviewed for alternate etiologies of liver toxicity, including the presence of hepatitis A, B, or C, cirrhosis, or nonalcoholic steatohepatitis. To evaluate the development of drug-induced liver injury, AST, ALT, Alk P, total serum bilirubin, and international normalized ratio (INR) were collected on days 0, 3, 7, and weekly thereafter during fluconazole therapy. Index date was the start date of fluconazole. Peak values were recorded during therapy and for up to 14 days after fluconazole discontinuation.

Baseline Characteristic Definitions

Patients were considered to have received a loading dose if the first fluconazole dose was higher than the average maintenance dose. Vitals at ICU admission were recorded, and patients were considered to have sepsis if they met 2 of the 4 systemic inflammatory response syndrome (SIRS) criteria and had evidence of infection. SIRS criteria include temperature >100.4°F or <96.8°F, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or $Paco_2 <32$ mm Hg, and white blood cell $>12\,000/mm^3$ or $<4000/mm^3$. Patients were considered to have septic shock if they met sepsis criteria at ICU admission and received norepinephrine or vasopressin at any time during fluconazole treatment. CrCl was calculated by the Cockcroft-Gault method on the index date. Ideal body weight (IBW) was calculated and used for CrCl calculations unless actual body weight (ABW) was less than IBW or if ABW was $>30\%$ of IBW. In the former case, ABW was used. In the latter case, an adjusted body weight (AjBW) was calculated and used: $AjBW = IBW + 0.4(ABW - IBW)$.

Indications

Treatment indications were divided into 5 different categories: (1) empiric therapy if treatment started without a known cause, (2) oropharyngeal or esophageal candidiasis, (3) superficial fungal infections for vaginitis or tinea, (4) prophylaxis for chemotherapy treatment, or (5) documented invasive systemic infection for treatment of fungemia, fungal pneumonia, meningitis, pyelonephritis, coccidioidomycosis, positive intra-abdominal culture, and spontaneous fungal peritonitis.

Drug-Induced Liver Injury Definitions

Patients were considered to have met DILIN criteria if they met one of the following criteria: (1) AST or ALT $>5\times$ ULN or $>5\times$ baseline abnormal value, or, (2) alkaline phosphatase $>2\times$ ULN (or pretreatment baseline if baseline level is abnormal), or (3) total serum bilirubin level >2.5 mg/dL along with elevated AST or ALT or alkaline phosphatase, or (4) INR >1.5 with elevated AST or ALT or alkaline phosphatase.

DILI was further characterized by injury type or "R." "R" is equal to the ratio of serum ALT (as a multiple of its ULN) to serum Alk P (as a multiple of its ULN). The following normal values were used: AST $\leq$ 42 units/L, ALT $\leq$ 30

units/L, and Alk P ⩽ 113 international units/L. The injury was defined as hepatocellular if R ⩾ 5, cholestatic if R ⩽ 2, or mixed if R > 2 and R < 5. Baseline values from date of initiation or 1 day prior to initiation were compared with peak values during fluconazole therapy and for up to 14 days after fluconazole discontinuation.

Outcome Measures

Our primary objective was to evaluate the incidence of patients meeting drug-induced liver injury criteria with weight-based fluconazole dosing in an ICU population. Weight-based fluconazole dosing was stratified based on patients receiving <6 mg/kg vs ⩾6 mg/kg. Prespecified subgroup analyses were performed for patients with renal dysfunction (CrCl < 50 mL/min), cirrhosis, septic shock, and patients receiving a loading dose of fluconazole to assess the effects of these characteristics on meeting DILIN criteria. Furthermore, we also stratified the patients into those receiving fluconazole < 400 mg or ⩾ 400 mg and compared the rate of patients meeting DILIN criteria. We also collected data on other antifungals patients received or were switched to from fluconazole.

Statistical Analysis

Data were analyzed using JMP 10.0 (SAS Corporation, Cary, North Carolina). All nominal data were analyzed using chi-squared or Fisher exact, as appropriate. Continuous variables were tested for normality using the Shapiro-Wilk W test. All continuous data were determined to be nonparametric, analyzed using the Wilcoxon rank sum, and reported as median and interquartile range (IQR). An a priori alpha level of <0.05 was used to define statistical significance. Last, a multivariable nominal logistic regression model was constructed with the following variables: weight-based fluconazole dose, cirrhosis, CrCl < 50 mL/min, and septic shock. Variables that were significant in the nominal logistic regression model were considered independent predictors of meeting DILIN criteria.

Results

Study Participants

A total of 767 ICU patients were billed for 3 doses of fluconazole during the 4 study years, and 248 patients met inclusion criteria. Patients who were missing labs (n = 155), only received two days of fluconazole (n = 25), missed two or more fluconazole doses OR if patient was receiving fluconazole prior to hospital admission (n = 188), candiduria indication only (n = 70), liver transplant <1 week prior to index date (n = 76), acetaminophen overdose (n = 5) were excluded. Overall, there were 199 patients in the <6 mg/kg group and 49 patients in the >6 mg/kg group

Table 1 shows the baseline characteristics of the study participants. In the <6 mg/kg vs ⩾6 mg/kg groups, respectively, there were more male patients (72% vs 55%), a higher median (IQR) weight (80.3 [69.4-97.6] vs 59.1 [50.8-64.3] kg), and a lower median CrCl (59.8 [30.7-92.8] vs 76.0 [46.8-121.0] mL/min). In addition, the percentage of patients with cirrhosis was 39.7% and 18.3% in the <6 mg/kg group and ⩾6 mg/kg group, respectively. The median (IQR) Model For End-Stage Liver Disease (MELD) score for patients with cirrhosis was 28 (20-36) and 19 (10-25.5) in the <6 mg/kg group and ⩾6 mg/kg group, respectively. The median of each patient's average fluconazole dose was 222 mg (200-400 mg) and 400 mg (400-508 mg). Patients received a median of 3.44 mg/kg of fluconazole in the <6 mg/kg dose group compared with 7.18 mg/kg in the ⩾6 mg/kg dose group ($P < .0001$).

There was no statistical difference in the primary end point of incidence of patients meeting DILIN criteria while receiving <6 mg/kg vs ⩾6 mg/kg of fluconazole (Table 2). Overall, a total of 133 (53%) ICU patients met DILIN criteria and the majority of patients with DILIN were categorized as having cholestatic liver injury (Table 2). Of those patients who met DILIN criteria, 39 patients had elevations of greater than 5 times in AST or ALT, 37 patients had elevations of greater than 2 times in Alk P, 85 patients had an elevated total serum bilirubin level, and 58 patients had an elevated INR. Eighty-six patients met more than 1 component of the DILIN criteria.

Of the secondary end points, only patients with septic shock showed a statistically significant difference in meeting DILIN criteria with <6 mg/kg vs ⩾6 mg/kg of fluconazole, respectively (85% vs 50%, $P = .0045$) (Table 3). Interestingly, those receiving lower mg/kg doses of fluconazole (<6 mg/kg) had nonsignificant higher incidence of meeting DILIN criteria. To account for the effect of these subgroups on the incidence of meeting DILIN criteria, a nominal logistic regression model was performed. Presence of cirrhosis and presence of septic shock were both independent predictors of meeting DILIN criteria (septic shock: OR 4.56 [95% confidence interval, CI, 2.44-8.88], cirrhosis: OR 4.84 [95% CI, 2.61-9.28]). However, neither weight-based fluconazole dose nor CrCl < 50 mL/min increased the odds of meeting DILIN criteria (Table 4).

We completed a separate analysis to see whether patients were likely to meet DILIN criteria when grouped by fluconazole < 400 mg vs fluconazole ⩾ 400 mg. DILIN criteria was met in 76 of 133 patients (57%) of patients receiving <400 mg of fluconazole and 57 of 115 patients (50%) receiving ⩾ 400 mg of fluconazole ($P = .25$). In addition, we reran a nominal logistic regression model with the patients grouped by fluconazole dose of <400 mg vs fluconazole dose of ⩾400 mg or more. In the nominal regression model, presence of cirrhosis and presence of septic shock were still the only independent predictors of meeting DILIN criteria (septic shock: OR 3.89 [95% CI, 2.02-7.73], cirrhosis: OR 8.10 [95% CI, 3.81-18.74]).

Table 1. Characteristics of Patients Exposed to <6 mg/kg vs ⩾6 mg/kg Fluconazole.

	Fluconazole < 6 mg/kg (n = 199)	Fluconazole ⩾ 6 mg/kg (n = 49)
Median age, years (IQR)	57 (49-64)	56 (46.5-64)
Male[a]	144 (72.4%)	27 (55%)
Race		
Caucasian	139 (69.9%)	31 (63.3%)
Hispanic	17 (8.5%)	5 (10.2%)
Black	15 (7.5%)	5 (10.2%)
Asian	2 (1.0%)	0 (0.0%)
Native American	0 (0.0%)	1 (2.0%)
Other	26 (13.0%)	7 (14.3%)
Median weight, kg (IQR)[a]	80.3 (69.4-97.6)	59.1 (50.8-64.3)
Social & medical history		
Any alcohol use	58 (29.9%)	16 (33.3%)
Diabetes	75 (37.7%)	14 (28.6%)
HIV	11 (5.6%)	4 (8%)
Sepsis at ICU admission	138 (69.3%)	37 (75.5%)
Septic shock	60 (30.1%)	20 (40.8%)
Liver dysfunction		
History of liver disease[b]	88 (44%)	14 (28.6%)
Cirrhosis[a]	79 (39.7%)	9 (18.3%)
Liver transplant	22 (11.1%)	2 (4%)
Median Model For End-Stage Liver Disease (MELD) Score for patients with cirrhosis (IQR)[a]	28 (20-36)	19 (10-25.5)
Renal function at ICU admission		
Median creatinine clearance, mL/min (IQR)[a]	59.8 (30.7-92.8)	76.0 (46.8-121.0)
Creatinine clearance (CrCl) <50 mL/min[a]	84 (42.4%)	13 (26%)
Dialysis: at least one session received	47 (23.6%)	6 (12.2%)
Drug exposure during fluconazole therapy		
Any acetaminophen exposure	106 (53.3%)	61 (63.3%)
Acetaminophen scheduled	11 (5.6%)	6 (12%)
Exposure to select hepatotoxic medications[a,c]	7 (3.5%)	6 (12.2%)
Warfarin	4 (2.0%)	2 (4.1%)
Fluconazole therapy characteristics		
Median of average maintenance dose, mg (IQR)[a]	222 (200-400)	400 (400-508)
Median of weight-based average dose, mg/kg (IQR)[a]	3.44 (2.52-4.56)	7.18 (6.53-8.81)
Average maintenance dose >400 mg[a]	1 (0.5%)	13 (26.5%)
Number of patients receiving LD	45 (23%)	6 (12%)
LD, mg[a]	400 (400-800)	800 (750-800)
Median of weight-based LD, mg/kg (IQR)[a]	6.01 (4.50-8.40)	14.6 (11.8-19.1)
Number of patients receiving LD >12 mg/kg[a]	0 (0.0%)	5 (10.2%)
Median number of days of treatment (IQR)[a]	6 (4-9)	10 (5-14)
Median number of days to LFT peak (IQR)	6 (3-12)	7 (3-13)

Note. Data represent number (%) of patients, unless otherwise indicated. IQR = interquartile range; ICU = intensive care unit; LD = loading dose; LFT = liver function test.

[a] $P < .05$.

[b] Hepatitis A, hepatitis B, hepatitis C, cirrhosis, or nonalcoholic steatohepatitis.

[c] Fosphenytoin, phenytoin, isoniazid, rifampin, or valproic acid.Primary and Secondary End Points.

Some patients were exposed to another antifungal prior to fluconazole therapy or were changed from fluconazole to an alternate antifungal. Of note, 3 patients in each group were exposed to amphotericin B ($P = .09$). Of the patients exposed to amphotericin B, 2 patients in the low dose group met DILIN criteria. Twenty-five patients in the low dose group were exposed to micafungin, compared with 7 patients in the ⩾6 mg/kg dose group ($P = .81$). Of the patients who received micafungin, 16 patients in the <6 mg/kg group, and 3 patients in the ⩾6 mg/kg fluconazole dose group met DILIN criteria. One patient switched from fluconazole to voriconazole met DILIN criteria.

Table 2. Number of Patients Meeting DILIN Criteria by Weight-Based Dose and Type of Injury Present.

	All patients n = 248	Fluconazole < 6 mg/kg n = 199	Fluconazole ⩾ 6 mg/kg n = 49
Patients meeting DILIN criteria[a]	133 (53.6%)	110 (55%)	23 (46.9%)
Hepatocellular	36 (14.5%)	31 (28.1%)	5 (21.7%)
Mixed	17 (6.9%)	14 (12.7%)	3 (13.0%)
Cholestatic	80 (32.3%)	65 (59.1%)	15 (65.2%)

Note. Data represent number (%) of patients. DILIN = Drug-Induced Liver Injury Network.
[a]$P = .20$ when comparing patients receiving fluconazole <6 mg/kg to fluconazole ⩾ 6 mg/kg.

Table 3. Number of Patients Meeting Drug-Induced Liver Injury Network Criteria by Subgroups.

	Fluconazole < 6 mg/kg	Fluconazole ⩾ 6 mg/kg	*P* value
Creatinine clearance <50 mL/min	52/84 (61.90%)	8/13 (61.54%)	1.00
Cirrhosis	60/79 (75.95%)	8/9 (88.89%)	.68
Sepsis at intensive care unit admission	78/138 (56.52%)	17/37 (45.95%)	.27
Septic shock	51/60 (85.00%)	10/20 (50.00%)	.0045
Loading dose received	23/45 (51.11%)	2/6 (33.33%)	.67

Note. Data represent number (%) of patients.

Table 4. Effect of Creatinine Clearance < 50 mL/min, Weight-Based Fluconazole Dose, Septic Shock and Cirrhosis on Meeting Drug-Induced Liver Injury Network Criteria.

	Odds ratio (95% confidence interval)	*P* value
Creatinine clearance < 50 mL/min	1.33 (0.73-2.40)	.35
Weight-based fluconazole dose ⩾ 6 mg/kg	0.83 (0.40-1.70)	.61
Septic shock	4.56 (2.44-8.88)	<.0001
Cirrhosis	4.84 (2.61-9.28)	<.0001

Discussion

This dual-center, retrospective cohort study with ICU patients suggests no increased risk of meeting DILIN criteria with ⩾6 mg/kg doses of fluconazole compared with <6 mg/kg fluconazole, suggesting that doses could be maintained at ⩾6 mg/kg for efficacy without increasing the risk for fluconazole-related hepatotoxicity.

What is most interesting is that 50% of ICU patients met DILIN criteria which is markedly higher compared with 10% in a previous meta-analysis.[13] There are several likely reasons why we identified a high number of patients meeting DILIN criteria in the ICU: DILIN criteria definition is very broad and has not been systematically applied to an ICU population, a high number of patients had septic shock, or there may be an increased baseline risk for drug-induced liver injury in this population.

DILIN criteria could overestimate the rate of drug-induced liver injury as the definition includes AST, ALT, Alk P, serum total bilirubin, and INR. For example, in a previous meta-analysis, the definition of hepatotoxicity did not consistently use bilirubin or INR and estimated drug-induced liver injury to occur in 10% of patients.[13] Furthermore, other prospective, clinical trials have a variety of definitions for hepatotoxicity that range from undefined elevations of AST, ALT, and Alk P, to more defined definitions that calculate the degree above the ULN of AST, ALT, Alk P, and/or total serum bilirubin.[4-8] In addition, our population had a prevalence of cirrhosis of 35% compared with 0.27% in the general population, potentially biasing our results as patients with cirrhosis have a higher likelihood of meeting the laboratory value thresholds included in the DILIN criteria than patients without cirrhosis.[14] Presence of cirrhosis was shown to be an independent predictor of development of meeting DILIN criteria in our model. However, as fluconazole dose did not increase the odds of meeting DILIN criteria, this suggests that these patients may be more likely to meet DILIN criteria regardless of fluconazole dose.

In addition, the number of fluconazole patients in the ICU meeting DILIN criteria contrasts sharply with the number of patients with fluconazole exposure referred to investigators for potential fluconazole-induced liver injury. Out of the 899 patients referred to the DILIN with likely drug-induced liver injury, only 4 patient's injury could be attributed to fluconazole.[3]

The presence of septic shock could be a confounding variable. In our study, 76% of patients with septic shock met DILIN criteria. Specifically, 61 out of 80 patients with septic shock met DILIN criteria, where only 72 out of 168 (43%) patients without septic shock met DILIN criteria ($P < .0001$). A nominal logistic regression model was performed based on this finding, and the presence of septic shock was found to be an independent predictor of meeting DILIN criteria ($P < .0001$). These results support the theory that the DILIN criteria might be inappropriate to apply to critically ill patients when trying to link liver dysfunction to a drug-related adverse event.

To further support this theory, previous literature has shown fluconazole-induced liver injury to be primarily hepatocellular, but a majority of our patients were classified as having cholestatic injury (80 of the 133 [60%]) (Table 2). Septic shock can impair hepatic perfusion causing hypoxic hepatitis leading to hepatocellular injury. Sepsis-associated cholestasis can also occur from an inflammatory reaction to endotoxin translocation from the intestinal lumen. Inflammatory cytokines alter bile acid uptake and reduces secretion of the bile.[15] Thus, the mechanism of septic shock could cause patients to meet DILIN criteria outside of elevations 5 times the ULN of AST or ALT.

Parenthetically, the authors observed several clinical situations that could influence the mg/kg dose of fluconazole. First, 80% of our patients received < 6 mg/kg which is not consistent with IDSA recommendations for empiric or documented treatment of systemic fungal infection. Over 90% of patients included in this study were given fluconazole for this indication. Lower doses of fluconazole could have been given due to several reasons: a difference in weight between groups, the incidence of renal dysfunction, and the high prevalence of cirrhosis (Table 1). Our results are similar to previous published data on appropriate dosing of fluconazole for empiric or treatment of systemic fungal infections. A previous retrospective cohort study identified a high prevalence of suboptimal dosing of fluconazole given empirically (55% of patients were given less <6 mg/kg).[16] Second, there was a median weight difference of nearly 20 kg between groups. The median weight in the <6 mg/kg was 80 kg and the average mg/kg maintenance dose was 3.44 mg/kg. To empirically treat this patient with a 6 mg/kg dose, a health care provider would need to order 480 mg. It is likely that the dose was rounded down as fluconazole 400 mg is a commercially available parenteral dose. On the contrary, health care providers may also choose to lower the fluconazole dose based on renal or liver dysfunction. It should be noted that in patients with fluconazole doses < 6 mg/kg, 42.4% had a CrCl <50 mL/min and 39.7% had cirrhosis, versus 26% and 18%, respectively, in the ⩾6 mg/kg, highlighting a prescribing bias— lower doses may have been used in the setting of organ dysfunction.

There are several possible limitations of this evaluation. Due to the retrospective nature of the study, many patients were excluded. The most common exclusion criteria met was lack of availability of required labs. This exclusion rate may have overestimated the incidence of drug-induced liver injury captured by this study. The investigators sought to minimize this bias and misclassification bias by including patients who had baseline labs the day of or day prior to fluconazole initiation and at least 1 follow-up lab within 2 weeks of discontinuation. Second, DILIN assesses incidence and resolution of liver injury and therefore excludes patients with previous liver or bone marrow transplant, underlying liver disease defined as autoimmune liver disease, or sclerosing cholangitis. However, we included these patients due to the small number of patients meeting these criteria. There is also a risk of a type II error due to small sample size. Finally, this study only identified the occurrence of meeting DILIN criteria but not the resolution of the liver injury.

The high rate of patients meeting DILIN criteria is important for multiple reasons. First, there are no standardized tools currently available to evaluate drug-induced liver injury in ICU patients. Second, using DILIN criteria may lead to an overestimation of drug-induced liver injury. This finding may also lead to inappropriate discontinuation of necessary drugs or inappropriate dosage reduction. This overestimation could result in unnecessary investigations into potential drug causes that could be clinically insignificant or reversible. These additional tests, specialized consults, and imaging may lead to unnecessary increases in cost of care and length of stay.

Conclusion

We found that 50% of patients receiving fluconazole met DILIN criteria. This is likely an overestimation of fluconazole-induced liver injury due to the breadth of the DILIN definition when applied to a critically ill population with other risk factors and background disease states contributing to liver dysfunction. However, using ⩾6 mg/kg fluconazole doses did not increase the risk of meeting DILIN criteria while presence of cirrhosis and septic shock did.

Furthermore, the investigators found that providers rarely used weight-based dosing of fluconazole in the ICU, even for empiric or confirmed treatment of invasive candidiasis. Clinicians should be cautious of using DILIN criteria in the ICU setting because it may overestimate hepatotoxicity. Investigations for more specific assessment tools for drug-induced liver injury in ICU patients need to be created and validated. Finally, clinicians should be prepared and willing to investigate other nondrug causes of liver injury in this setting.

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