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Creation and Internal Validation of a Clinical Predictive Model for Fluconazole Resistance in Patients With *Candida* Bloodstream Infection

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Background. Fluconazole is recommended as first-line therapy for candidemia when risk of fluconazole resistance (fluc-R) is low. Lack of methods to estimate resistance risk results in extended use of echinocandins and prolonged hospitalization. This study aimed to develop a clinical predictive model to identify patients at low risk for fluc-R where initial or early step-down fluconazole would be appropriate.

Methods. Retrospective analysis of hospitalized adult patients with positive blood culture for *Candida* spp from 2013 to 2019. Multivariable logistic regression model was performed to identify factors associated with fluc-R. Stepwise regression was performed on bootstrapped samples to test individual variable stability and estimate confidence intervals (CIs). We used receiver operating characteristic curves to assess performance across the probability spectrum.

Results. We identified 539 adults with candidemia and 72 *Candida* isolates (13.4%) were fluc-R. Increased risk of fluc-R was associated with older age, prior bacterial bloodstream infection (odds ratio [OR], 2.02 [95% CI, 1.13–3.63]), myelodysplastic syndrome (OR, 3.09 [95% CI, 1.13–8.44]), receipt of azole therapy (OR, 5.42 [95% CI, 2.90–10.1]) within 1 year of index blood culture, and history of bone marrow or stem cell transplant (OR, 2.81 [95% CI, 1.41–5.63]). The model had good discrimination (optimism-corrected c-statistic 0.771), and all of the selected variables were stable. The prediction model had a negative predictive value of 95.7% for the selected sensitivity cutoff of 90.3%.

Conclusions. This model is a potential tool for identifying patients at low risk for fluc-R candidemia to receive first-line or early step-down fluconazole.

Keywords. antifungal resistance; *Candida*; candidemia; clinical predictive model; fluconazole.

Candida species are among the most common pathogens of healthcare-associated bloodstream infections (BSIs), and invasive candidiasis is associated with crude mortality >40% [1]. The Centers for Disease Control and Prevention estimates that 25 000 cases of *Candida* BSIs occur each year [2]. Echinocandins are the first-line agents recommended by the Infectious Diseases Society of America (IDSA) for treatment of candidemia [3]. The use of azoles is currently limited by the increasing proportion of fluconazole-resistant (fluc-R) *Candida* isolates [3–6]. Studies have shown that approximately 6%–7% of all *Candida* BSI isolates are fluc-R [7–10]. However, fluconazole can

be considered an alternative first-line therapy due to its oral bioavailability, safety, overall efficacy, and lower cost when compared to echinocandins if the risk of fluc-R is low according to local epidemiology. Additionally, fluconazole may be used as step-down therapy in patients with nonresistant *Candida* isolates [3].

Although the IDSA guidelines recommend fluconazole as an alternative first-line option, currently there is no approved systematic method to predict low risk of fluc-R *Candida* BSI based on clinical profiles, and clinical predictive models (CPM) developed in the past have several limitations [11]. Antifungal susceptibility testing is the most accurate method to evaluate for fluc-R and determine choice of effective antifungal therapy, but it is a time-consuming process that many hospitals cannot routinely perform. For many hospitals, antifungal susceptibilities can only be obtained by sending isolates to reference laboratories, which delays a definitive switch to oral therapy and discharge [12]. As a result, clinicians often rely on the *Candida* spp as a predictor of fluconazole susceptibility. This strategy has limitations as some species considered to be fully susceptible to fluconazole such as *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis* may develop fluc-R, whereas some isolates of typically resistant non-*albicans* species (eg, *Candida glabrata*) retain susceptibility [13].

This study aimed to develop a CPM to identify patients at low risk for infection with fluc-R *Candida* isolates, making them appropriate candidates for fluconazole as initial or step-down to oral therapy without awaiting susceptibility testing.

METHODS

Setting

We conducted a retrospective cohort analysis at Barnes-Jewish Hospital (BJH), from January 2013 to April 2019. January 2013 was the start of routine fluconazole susceptibility testing on all *Candida* isolates from blood. BJH is a 1368-bed tertiary care academic hospital located in an urban environment with a significant suburban and rural referral base. The study was approved by the Washington University School of Medicine Human Research Protection Office, with a waiver of informed consent.

Cohort Construction

All hospitalized patients aged ≥18 years with *Candida* spp isolated from at least 1 blood culture while admitted were included in the study. The first positive blood culture with isolation of a *Candida* spp during the study time frame was defined as the index blood culture. Data were extracted electronically from the BJH Medical Informatics database and by medical record review (A. M. R.), as previously described [14–17]. Data collected electronically from the index admission included demographics, comorbidities, procedures, vital signs, and laboratory and microbiology results. Medications from inpatient encounters ordered within 1 year preceding the index blood culture were also collected electronically.

Predisposing factors for candidemia were explored with descriptive statistics. Laboratory parameters (white blood cell count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, platelets, and creatinine) and the most extreme vital signs (highest temperature, highest heart rate, lowest blood pressure) measured during the 24 hours preceding the index blood culture were collected. Neutropenia was defined as an absolute neutrophil count ≤1000 cells/μL in the preceding 30 days based on exploration of the data and ascertainment of the inflection point. Microbiology data included positive bacterial blood cultures collected within 1 year prior to the date of collection of the index *Candida* blood culture. Blood cultures with common bacterial skin contaminants other than coagulase-negative staphylococci were excluded using the National Health Safety Network (NHSN) organism list [18]. Criteria for BSI due to coagulase-negative staphylococci required at least 2 positive blood cultures with the same species within a 3-day window, unless only 1 blood culture was performed, as described in the NHSN BSI laboratory event definition [19].

Comorbidities documented within 1 year prior to and during the index admission were identified by International Classification of Diseases, Ninth Revision or Tenth Revision diagnosis codes using the Elixhauser algorithm [20]. Conditions associated with infections by *Candida* spp were identified as previously described [14–17]. Surgical procedures performed within 1 year prior to index admission were identified using NHSN categories [21]. Malignancies were classified using the Clinical Classifications Software system [22]. Other risk factors associated with candidemia were included: presence of central venous catheter and/or dialysis catheter, indwelling urinary catheter, and mechanical ventilation identified using infection control data within 48 hours prior to index blood culture; total parenteral nutrition, pancreatitis, Crohn disease or abdominal fistulas, immunodeficiency, chemotherapy, and myelodysplastic syndrome (MDS) within 1 year prior to index blood culture; and history of bone marrow transplant (BMT)/stem cell transplant (SCT) or solid organ transplant. The complete list of variables is available in Supplementary Table 1 and codes are provided in Supplementary Table 3.

Outcomes

The primary outcome was fluc-R, determined using Sensititre™ YeastOne™ YO9 AST Plates, with breakpoints defined for each *Candida* species based on Clinical and Laboratory Standards Institute performance standards for antifungal testing (M60) [23]. Only isolates classified as resistant were included in the fluc-R group, with susceptible-dose dependent being classified as susceptible. For *Candida krusei* we assumed intrinsic resistance, and for rare species that do not have cutoffs described in M60, we used the susceptibility criteria for *C albicans*.

Statistical Analysis

We performed bivariate analyses to evaluate the association of predisposing factors, comorbidities, medication use, and laboratory values with the development of fluc-R *Candida* BSI. For descriptive statistics, we used χ^2 or Fisher exact tests for categorical variables and Mann-Whitney U tests for continuous variables, as the variables were not normally distributed.

Criteria for variables to be included in initial multivariable analysis included clinical plausibility as determined by physician expertise or variables with $P < .2$ in bivariate analysis. Backward stepwise regression was used to explore the initial model with a variable retention threshold of $P < .1$. Clinical plausibility and overall model performance were prioritized over P values of individual variables. All continuous variables were assessed for modeling using restricted cubic splines. Multicollinearity was assessed using variance inflation factors and the variable with greater clinical plausibility was selected among collinear variables.

Bootstrap validation with 500 repetitions and backward stepwise elimination was performed to test individual variable stability and estimate confidence intervals (CIs). We generated a receiver operating characteristic curve to assess discrimination

using the final set of predictor variables, with calculation of the optimism-corrected c-statistic, and used graphs of observed versus expected values to assess calibration across the probability spectrum [24]. A high cutoff sensitivity of 90.3% was selected to maximize identification of patients at risk for fluc-R *Candida* BSI, and we then obtained the specificity, positive predictive value (PPV), and negative predictive value (NPV) for our model. We used the model to calculate NPV values for lower or higher hypothetical prevalences of fluc-R in other settings based on previously published data (Supplementary Figure 1).

Statistical analysis was performed using SAS version 9.4 Software (SAS Institute, Cary, North Carolina), and all tests were 2-tailed with $P < .05$ considered significant.

RESULTS

Demographics and Risk Factors

A total of 539 hospitalized adults with *Candida* BSI were identified during the study period. The prevalence of fluc-R *Candida* isolates in our cohort was 13.4% (72/539). Age, sex, and race distributions and many comorbidities were present at similar percentages between the 2 groups (Table 1). The median age of all patients was 58 years (interquartile range, 46–66 years); 43.5% were female, and 28.3% were of non–White race.

Patients with fluc-R *Candida* BSI were significantly more likely to have hematological malignancy (56.9% vs 17.9%), MDS (18% vs 3%), immunodeficiency (76.3% vs 52.6%), coagulopathy (73.6% vs 56.9%), depression (55.5% vs 43%),

Table 1. Comparison of Characteristics, Comorbidities, and Potential Risk Factors Between Patients With Fluconazole-Resistant and -Susceptible Candidemia

Variables	Fluconazole-Susceptible (n = 467)	Fluconazole-Resistant (n = 72)	P Value
Age, y, median (IQR)	58 (44–67)	55 (47–61)	.145
Sex, female	199 (42.6)	32 (44.4)	.770
Race, non-White	141 (30.2)	19 (26.4)	.511
Comorbidities			
Pulmonary circulation disorders	118 (25.2)	11 (15.2)	.064
Paralysis	57 (12.2)	4 (5.5)	.097
Diabetes mellitus	208 (44.5)	32 (44.4)	.987
Chronic kidney disease	182 (38.9)	23 (31.9)	.252
Liver disease	123 (26.3)	16 (22.2)	.457
Coagulopathy	266 (56.9)	53 (73.6)	.007
Lymphoma	39 (8.3)	11 (15.2)	.059
Metastatic cancer	69 (14.7)	11 (15.2)	.911
Deficiency anemia	293 (62.7)	51 (70.8)	.183
Drug abuse	81 (17.3)	6 (8.3)	.053
Depression	201 (43)	40 (55.5)	.046
Other potential predisposing factors			
Bone marrow or stem cell transplant	49 (10.5)	31 (43)	<.001
Solid organ transplant	26 (5.5)	3 (4.1)	.623
Myelodysplastic syndrome	14 (3)	13 (18)	<.001
Neutropenia (ANC ≤1000 cells/μL)	78 (16.7)	33 (45.8)	<.001
Hematologic malignancy	84 (17.9)	41 (56.9)	<.001
Solid organ malignancy	158 (33.8)	32 (44.4)	.079
Chemotherapy	81 (17.3)	37 (51.3)	<.001
Immunodeficiency	246 (52.6)	55 (76.3)	.002
Abdominal surgery	86 (18.4)	10 (13.8)	.350
Bacterial bloodstream infection	143 (31)	38 (52.7)	.002
Central venous catheter	191 (40.9)	34 (47.2)	.311
Dialysis catheter	57 (12.2)	5 (6.9)	.192
Foley catheter	145 (31)	26 (36.1)	.390
Medications received within 1 y prior to index *Candida* blood culture			
Azoles	59 (12.6)	39 (54.1)	<.001
Other antifungals	155 (33.1)	44 (61.1)	<.001
Antibiotics	409 (87.5)	69 (95.8)	.039
Antivirals (anti-herpes)	101 (21.6)	37 (51.3)	<.001
Dapsone	4 (0.8)	11 (15.2)	<.001
Total parenteral nutrition	264 (56.5)	43 (59.7)	.610

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ANC, absolute neutrophil count; IQR, interquartile range.

bacterial BSI (52.7% vs 31%), neutropenia (45.8% vs 16.7%), and a history of BMT/SCT (43% vs 10.5%). Patients with fluc-R *Candida* BSI were also more likely to have received chemotherapy (51.3% vs 17.3%) and antimicrobials in the previous year leading up to the index blood culture, including multiple antibiotics, azoles, other antifungals, and antivirals (Table 1). Patients with fluc-R *Candida* BSI were marginally less likely to be coded for drug abuse (8.3% vs 17.3%; *P* = .053).

Clinical Predictive Model

In bivariate analysis, 24 variables with clinical plausibility and/or *P* < .2 were evaluated for inclusion in the multivariable logistic regression model (Table 1). The final prediction model consisted of 5 variables: older age, with higher risk between 40 and 45 years of age and subsequent gradual decline in risk compared to the youngest persons (Figure 1); receipt of azoles (odds ratio [OR], 5.42 [95% CI, 2.90–10.1]), MDS (OR, 3.09 [95% CI, 1.13–8.44]), and bacterial BSI (OR, 2.02 [95% CI, 1.13–3.63]) within 1 year prior to index blood culture; and history of BMT/SCT (OR, 2.81 [95% CI, 1.41–5.63]) (Table 2). All of the variables in the final prediction model were retained in >50% of bootstrapped samples (Supplementary Table 2). The observed versus expected probability plot shows good calibration of the model with overprediction of the probability of fluc-R in the lower probability range where most of the patients are present in the sample, and slight underprediction at very high

probabilities of fluc-R (Figure 2). The uncorrected c-statistic was 0.788 (Figure 3) and the optimism-corrected c-statistic was 0.771. The selected cutoff sensitivity value of 90.3% as well as specificity, PPV, and NPV of the model are presented in Table 3. For the prevalence in our cohort of 13.4% and selected sensitivity of 90.3%, the model has a high NPV of 95.7%, equal to the probability of a patient to have fluc-S *Candida* BSI. Adapting for lower baseline prevalence that can be found in community-based hospitals from 1% to 7%, the NPV increases to 99% and 97.8%, respectively, and for hospitals with higher prevalence of 19% and selected sensitivity of 90.3% the NPV would be 93%.

DISCUSSION

Timely and effective antifungal therapy is critical in the management of candidemia to minimize morbidity and mortality.

Table 2. Multivariable Logistic Regression Analysis of Risk Factors for Fluconazole Resistance in Patients With Candidemia

Variables	Adjusted OR (95% CI)
Bone marrow or stem cell transplant	2.81 (1.41–5.63)
Myelodysplastic syndrome	3.09 (1.13–8.44)
Bacterial bloodstream infection	2.02 (1.13–3.63)
Prior azole use	5.42 (2.90–10.1)

Adjustment for age was performed using a cubic spline.

Abbreviations: CI, confidence interval; OR, odds ratio.
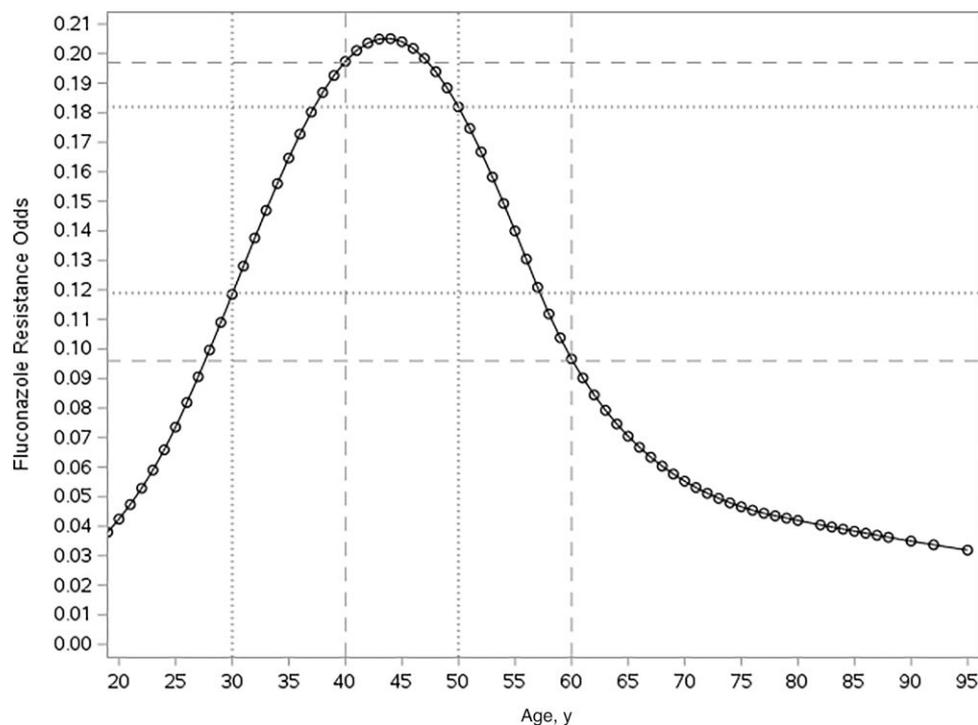
Figure 1. Association between age (variable fixed at their means) and odds of developing fluconazole resistance. Age is presented as a continuous variable using restricted cubic splines with 4 knots.
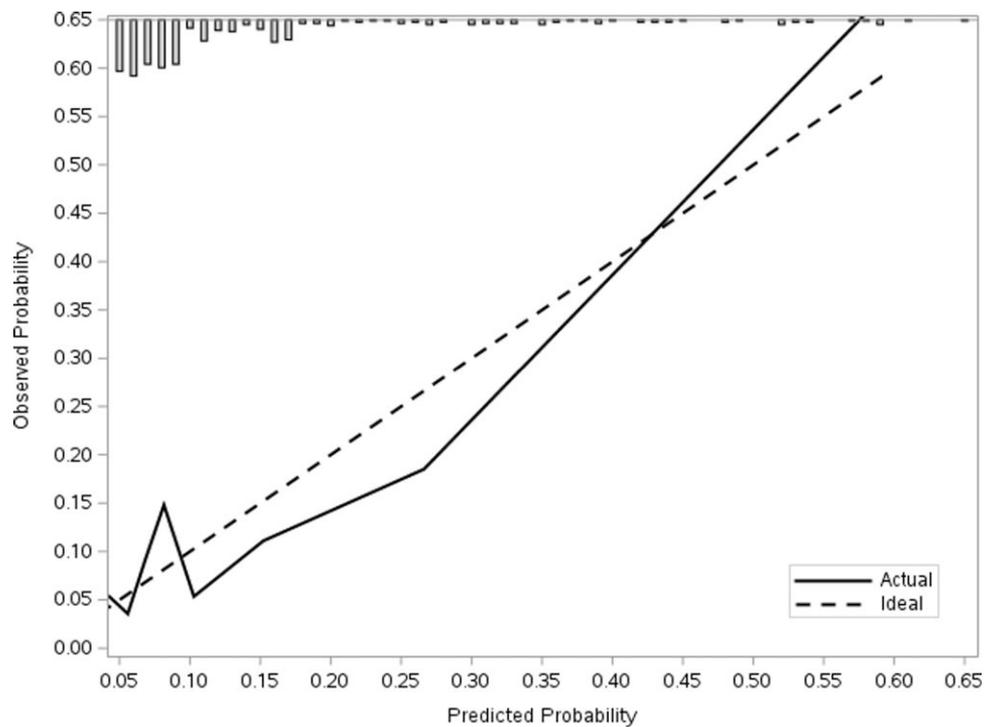
Figure 2. Graph comparing observed versus expected probability of fluconazole resistance. Bars included on the top parameter of the graph indicate the number of individuals with the specific predicted probabilities, illustrating the distribution of predicted probabilities in the cohort.
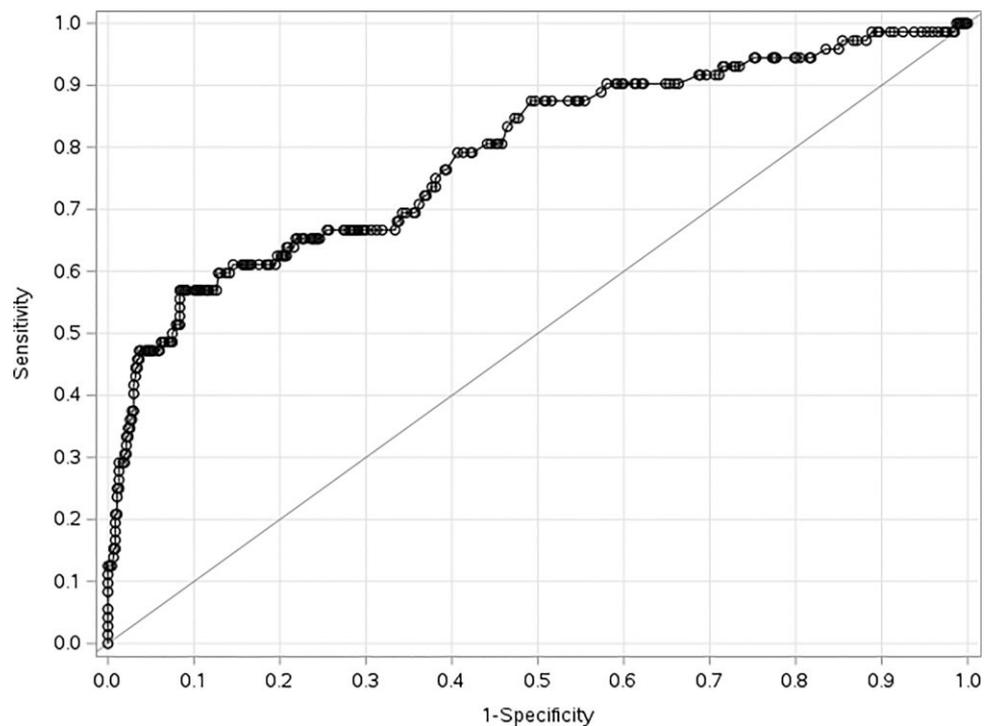
Figure 3. Receiver operating characteristic curve for logistic regression predicting fluconazole-resistant candidemia. The model uncorrected c-statistic is 0.788.

Table 3. Performance Indicators of Clinical Predictive Model for Fluconazole-Resistant Candidemia With Prevalence of 13.4%

Indicator	%
Selected sensitivity	90.3
Specificity	33.7
Positive predictive value	17.3
Negative predictive value	95.7

Fluconazole is an attractive primary or early step-down antifungal regimen when *Candida* isolates are susceptible due to low cost, oral formulations, and decreased healthcare burden (eg, potential for earlier discharge, no nursing care for long-term intravenous access). Unfortunately, there are few data to assist clinicians with identification of patients who would be appropriate for early fluconazole therapy. In this study, we created and internally validated a CPM to estimate the risk of fluc-R *Candida* BSI using readily available clinical parameters—older age, exposure to azoles, MDS, prior bacterial BSI, and history of BMT/SCT. Our model allows clinicians to identify patients at low risk for fluc-R *Candida* BSI who would be candidates for initial fluconazole or safe de-escalation of therapy without awaiting susceptibility testing results. This approach avoids prolonged use of echinocandins and the increased healthcare costs associated with long-term intravenous therapy.

Antifungal resistance is an increasing problem with *Candida* spp, making them difficult to treat. In a period of 6 years (2013–2019) at our institution, we found that almost 14% of all *Candida* BSIs were fluc-R, roughly double the prevalence reported in recent and previous large surveillance reports [7–10], but not as high as some centers [13]. In 4 surveillance studies completed between 1995 and 2017 in different US states, authors reported prevalence of 6%–7% of fluc-R among thousands of cases of candidemia [7–10]. However, resistance rates varied by state, from <1% to 11% [10], while reports from higher level of care centers found reduced susceptibility to fluconazole in up to 19% of isolates [13]. During the time period of these surveillance studies, there were no clear trends and no overall increase in resistance rates [7, 10]. However, an increase in resistance of approximately 10% was noted over the study period between 2012 and 2016 for specific species, including *C parapsilosis* and *C glabrata* [5, 10].

Species identification alone is insufficient to predict antifungal susceptibility patterns; thus, *Candida* spp identification was not included in the model. In addition, initial therapy is usually started once yeast is identified in blood cultures and the species is still unknown. Reliance on species attributes can lead clinicians to avoid fluconazole in many cases where it could be effective [13]. Species historically considered to be fully susceptible to fluconazole, such as *C albicans*, *C tropicalis*, and *C parapsilosis*, have been reported to comprise up to 48% of fluc-R isolates causing *Candida* BSI [13]. In contrast 49%

of *C glabrata* isolates, which tends to have higher resistance, were fully susceptible to fluconazole, and only *C krusei* species had the expected high fluc-R, though it rarely causes BSI in patients without hematological malignancies [13, 14]. Overall, resistance appears to be concentrated in tertiary care hospitals, likely associated with higher-acuity patients with immunocompromising conditions. The high number of BMT recipients and malignancies such as MDS in our cohort potentially explains the relatively high proportion of resistance observed at our institution compared to others studies.

Several risk factors we found associated with fluc-R *Candida* BSI have been reported in previous studies. In particular, prior azole exposure has been consistently identified as an important risk factor for fluc-R *Candida* BSI [11, 13, 25–27]. Similar to the association of widespread antibiotic use and subsequent development of multidrug-resistant bacterial pathogens, it is likely that exposure to azole antifungals would cause selective pressure and increase the likelihood of developing infection with fluc-R *Candida* spp. In patients with hematologic malignancy, recent studies of candidemia describe a shift in epidemiology toward non-*albicans Candida* spp, particularly *C glabrata* and *C krusei*, which have higher prevalence of resistance to fluconazole [14, 25, 26]. Regardless of *Candida* species, the risk of fluc-R appears to increase with suboptimal doses [28], and up to 3-fold higher risk has been described with prolonged azole use [26]. This evidence supports the guideline recommendation to avoid fluconazole as first-line therapy in patients with prior azole exposure [3].

Prior bacterial BSI was also strongly associated with fluc-R, which has been linked to use of broad-spectrum antibiotics due to several potential mechanisms. Similar to multidrug-resistant bacterial organisms, *Candida* spp frequently colonize the gut and are exposed to similar selection pressure. Antibiotic exposure not only can promote colonization by and emergence of multidrug-resistant organisms as well as development of candidemia [29–31], but has also been associated with a 2-fold higher risk of fluc-R [32], which was identical to the increased risk observed in our study. Antibiotics with anaerobic coverage have been described to have some degree of antifungal activity and promote intestinal colonization by fluc-R *Candida* spp [32]. In addition, expression of efflux pump–encoding genes can be induced by some antibacterials that can directly modulate azole resistance [32].

BMT or SCT recipients and MDS were independent risk factors for fluc-R *Candida* BSI, as reported in other studies [33, 34]. Infections due to fluc-R non-*albicans* species such as *C krusei* have a higher propensity to emerge in these settings where prior azole exposure is common, as in BMT/SCT recipients due to long-term prophylaxis [6, 14]. A potential explanation for the increased likelihood of fluc-R in BMT recipients and patients with MDS in our study is that these immunosuppressive conditions pose an additional risk besides prior azole

exposure, likely due to associated neutropenia. In our analysis, hematologic and solid organ malignancy, neutropenia, and immunodeficiency, which are highly correlated with BMT/SCT and MDS, were significant in bivariate analysis but did not meet criteria for retention in the multivariable model. Hematologic malignancy and neutropenia have been described as independent risk factors in some studies with smaller sample sizes [25, 35].

Few studies in the literature describe CPMs to estimate risk of fluc-R, but these predictive models have several limitations. Ostrosky-Zeichner et al found several risk factors, including time to initiation of fluconazole, *C glabrata* or *C krusei* infection, hematologic malignancy, and other antifungal use, to be independently associated with fluconazole failure in candidemia, which was defined as switching/adding other antifungals, persistently positive blood cultures, or death [27]. Some of these risk factors could potentially be associated with fluc-R; however, since the outcome was fluconazole failure, this model cannot predict fluc-R. Another CPM to estimate the risk of fluc-R candidemia developed by Cuervo et al used multicenter surveillance data from 29 hospitals in Spain and was externally validated in 3 other countries [11]. The overall prevalence of fluc-R determined by old Clinical and Laboratory Standards Institute breakpoints was 21% in the derivation cohort and 19% in the validation cohort, which is higher than the approximately 13% in our population. Risk factors associated with fluc-R were similar to ours, including transplant recipient status and prior azole therapy. Hospitalization in units with high prevalence of fluc-R strains was also identified as a risk factor; however, this particular variable limits the generalizability of the model as not all hospitals perform routine surveillance cultures to estimate prevalence of fluc-R in certain units. The cohort was dichotomized into low and high risk for fluc-R candidemia with a cutoff value of ≥2 producing a sensitivity of 82%, specificity of 66%, NPV of 93%, and PPV of 40% in the derivation cohort. Our model prioritized a high sensitivity cutoff resulting in a higher NPV of 95% to identify patients who are truly at low risk of fluc-R candidemia and can be safely initiated or transitioned to fluconazole.

Our study is limited by a retrospective cohort analysis. Although the database was built to maximize comprehensiveness, potential data omissions and coding errors could have occurred leading to misclassification bias of predictor variables. Although we included medications recorded for all inpatient encounters during the study period, we were unable to include outpatient medications as we did not have outpatient drug information. Finally, our study was limited to a single tertiary academic center in the midwestern United States. As the geographic distribution of *Candida* species and local fluconazole resistance rates can vary, the generalizability of our study may be diminished. Our work needs to be repeated and validated in other cohorts.

In conclusion, we created a CPM as a potential tool to identify patients at low risk of fluc-R *Candida* BSI based on easily identifiable risk factors. Utilization of our model could aid clinicians in the selection of optimal antifungal therapy before susceptibility results, if available, are known. Identification of patients at low risk of fluc-R *Candida* BSI using our model would support the initial use of fluconazole, thereby reducing the need for prolonged use of echinocandins. External validation of our CPM in other centers is needed to validate our findings and further expand the generalizability of our study results to diverse clinical settings and evaluate utility in other populations.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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