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Clinical and economic outcomes of decreased fluconazole susceptibility in patients with *Candida glabrata* bloodstream infections

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Abstract

Background—The impact of reduced fluconazole susceptibility on clinical and economic outcomes in patients with *Candida glabrata* bloodstream infections (BSI) is unknown.

Methods—A retrospective cohort study was conducted to evaluate 30-day inpatient mortality and postculture hospital charges in patients with *C glabrata* BSI with decreased fluconazole susceptibility (minimum inhibitory concentration [MIC] $\geq 16 \mu\text{g/mL}$) versus fluconazole-susceptible *C glabrata* BSI (MIC $\leq 8 \mu\text{g/mL}$). These analyses were adjusted for demographics, comorbidities, and time at risk. Secondary analyses limited the *C glabrata* group with decreased fluconazole susceptibility to MIC $\geq 64 \mu\text{g/mL}$.

Results—There were 45 (31%) deaths among 144 enrolled patients: 19 deaths (25%) among 76 patients with *C glabrata* BSI with decreased fluconazole susceptibility and 26 deaths (38%) among 68 patients with fluconazole-susceptible *C glabrata* BSI. Decreased fluconazole susceptibility was not independently associated with increased 30-day inpatient mortality (adjusted odds ratio, .60; 95% confidence interval (CI): .26-1.35; $P = 0.22$) or hospital charges (multiplicative change in hospital charges, .93; 95% CI: .60-1.43; $P = 0.73$). Older age was

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associated with increased mortality and increased time at risk was associated with increased hospital charges.

Conclusion—Crude mortality rates remain high in patients with *C glabrata* BSI. However, decreased fluconazole susceptibility was not associated with increased mortality or hospital charges.

Keywords

Candida glabrata; bloodstream infections; mortality; hospital charges

Among patients with health care-associated bloodstream infections (BSI), *Candida* BSI are associated with prolonged hospital stay, hospital charges, and mortality rates.¹⁻³ There has been a significant increase in BSI because of non-*Candida albicans*, particularly *Candida glabrata*, which are often associated with decreased fluconazole susceptibility (fluconazole dose-dependent susceptible [minimum inhibitory concentration (MIC), 16-32 µg/mL] or fluconazole-resistant [MIC ≥ 64 µg/mL] isolates). Several studies suggest that *C glabrata* BSI are associated with increased mortality rates compared with other *Candida* species,⁴⁻⁶ although this finding has been inconsistent across studies.⁷⁻¹⁰ A significant limitation of most prior studies is the lack of susceptibility testing to differentiate fluconazole-susceptible *C glabrata* from *C glabrata* with decreased fluconazole susceptibility. One study exists that compared fluconazole-less-susceptible versus fluconazole-susceptible *C glabrata* BSI and reported no significant difference in mortality rates. However, limitations of this study included a small sample size and the lack of adjustment for potential confounders.¹¹ We therefore performed this study to determine the impact of decreased fluconazole susceptibility on 30-day inpatient mortality and postculture hospital charges in patients with *C glabrata* BSI.

METHODS

Study design and setting

A retrospective cohort study was conducted at 3 hospitals (ie, 1 academic tertiary/quarternary care medical center and 2 urban community hospitals) in the University of Pennsylvania Health System from January 1, 2003, to May 31, 2007.

Study population

The study population included all patients with health care-associated *C glabrata* BSI. Each patient was only included once for their first positive blood culture. Health care-associated infections were defined as those occurring at least 48 hours after hospital admission or within 48 hours of admission in patients who received intravenous treatment as an outpatient or through home health care services or who underwent outpatient hemodialysis, all within 30 days prior to the positive culture, or who resided in a hospital, nursing home, or long-term care facility for ≥ 2 days within the past 90 days.¹²

The exposed group was defined as all patients with health care-associated *C glabrata* BSI with decreased fluconazole susceptibility (MIC ≥ 16 µg/mL). This group included patients with fluconazole dose-dependent susceptible (MIC, 16-32 µg/mL) and fluconazole-resistant (MIC ≥ 64 µg/mL) isolates because these patients should not be treated with traditional doses of fluconazole but rather should be treated with a different antifungal agent (or higher doses of fluconazole if the isolates are fluconazole dose-dependent susceptible). The unexposed group was defined as those with health care-associated fluconazole-susceptible *C glabrata* BSI (MIC ≤ 8 µg/mL). The primary outcomes of interest included 30-day inpatient

mortality and postculture hospital charges. Secondary analyses were performed, limiting fluconazole-resistant *C glabrata* to MIC $\geq$ 64 μ g/mL.

Microbiologic methods

The Hospital of the University of Pennsylvania Clinical Microbiology Laboratory processes blood cultures positive for *C glabrata* from all 3 hospitals. *C glabrata* is identified via morphology and the Rapid Assimilation of Trehalose Test (Hardy Diagnostics, Santa Maria, CA).¹³ Sensititre YeastOne (Trek Diagnostics, Cleveland, OH), a US Food and Drug Administration-approved 24-hour MIC method, was used for susceptibility testing all *C glabrata* bloodstream isolates beginning at the University of Pennsylvania Health System on January 1, 2003.¹⁴

Data collection

Data were primarily collected from the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD). PICARD integrates administrative and clinical information (eg, demographics, diagnoses, pharmacy information, hospital charges) for both inpatient and outpatient activity occurring within the University of Pennsylvania Health System and has been used successfully in prior studies focusing on antimicrobial resistance.^{15,16} The primary outcomes were 30-day inpatient mortality and postculture hospital charges accrued from the date of the first positive blood culture until patient discharge or death. Demographic variables collected included age, sex, and race. Hospitalization characteristics included the hospital to which the patient was admitted, year of hospitalization, and time at risk (ie, time from hospital admission to the first positive blood culture). Comorbidities included diabetes mellitus, human immunodeficiency virus infection, malignancy, neutropenia, solid organ transplantation, hematopoietic stem cell transplantation, cirrhosis, and end-stage renal disease requiring dialysis. We also ascertained events occurring 30 days preceding the positive *C glabrata* blood culture including receipt of total parenteral nutrition, chemotherapy or immunosuppression, and intensive care unit stay. Data variables regarding treatment were extracted from PICARD and patient charts, including the type and dose of empiric antifungal treatment used (ie, fluconazole, voriconazole, caspofungin, amphotericin), the type and dose of definitive antifungal agent used (ie, treatment once susceptibility data were available), and whether appropriate antifungal treatment was initiated within 2 days of the date when the positive blood culture was first obtained. Appropriate antifungal treatment was as defined by the 2004 Infectious Diseases Society of American guideline, which was primarily used during the period this study was conducted. The guideline states that *C glabrata* BSI with MIC $\leq$ 8 μ g/mL may be treated with fluconazole, amphotericin, or echinocandins.¹⁷ *C glabrata* BSI with MIC $\geq$ 16 μ g/mL may be treated with echinocandins, amphotericin, or voriconazole; and *C glabrata* BSI with MIC 16-32 μ g/mL may, in addition to the agents listed above, be treated with higher dose fluconazole 12 mg/kg/day (800 mg/day for a 70 kg person).¹⁷ Although studies have suggested that delayed time to appropriate treatment is associated with worse outcomes,⁵ the guideline does not state within what time frame appropriate treatment should be administered.

Statistical analysis

Bivariable analyses were performed using χ^2 or Fisher exact test for categorical variables and Student *t* test or Wilcoxon rank-sum test for continuous variables to identify potential confounding variables. A *P* value of $< .20$ was considered significant. Hospital type and year of hospitalization were assessed as modifiers of the effects of 30-day inpatient mortality and postculture hospital charges on *C glabrata* with decreased fluconazole susceptibility.

Multivariable logistic regression was performed to evaluate the association between *C glabrata* BSI with decreased fluconazole susceptibility and 30-day inpatient mortality. Multivariable linear regression was performed to evaluate the association between *C glabrata* BSI with decreased fluconazole susceptibility and postculture hospital charges. Postculture hospital charges were log transformed to achieve normality for analyses and reported as a multiplicative effect. Significant variables (ie, demographic variables, hospitalization characteristics, comorbidities, and events occurring 30 days prior to the positive *C glabrata* blood culture) from bivariable analyses were maintained in multivariable modeling if they changed the odds ratio (OR) for the primary association of interest (ie, *C glabrata* with decreased fluconazole susceptibility and 30-day inpatient mortality or hospital charges) by $\geq 15\%$.¹⁸

Secondary analyses were performed by repeating the analyses outlined above but limiting *C glabrata* with decreased fluconazole susceptibility to those with MIC ≥ 64 $\mu\text{g/mL}$. In addition, descriptive and bivariable analyses were performed regarding antifungal treatment. We described the proportion of patients with *C glabrata* with decreased fluconazole susceptibility vs. fluconazole-susceptible *C glabrata* BSI treated with appropriate antifungal agents, and how many were treated ≤ 2 days prior to drawing a positive culture. We also performed analyses to determine whether mortality or hospital charges differed based on antifungal treatment or time to treatment. STATA, version 10.0 (STATA Corp, College Station, TX), was utilized for all biostatistical analyses.

RESULTS

Baseline patient characteristics

A total of 144 patients was enrolled: 76 patients with *C glabrata* with decreased fluconazole susceptibility (MIC ≥ 16 $\mu\text{g/mL}$) and 68 patients with fluconazole-susceptible *C glabrata*. Seventy-seven (54%) patients were female, 68 (47.2%) were white, and the mean age was 61 years (range, 25-94 years). The most common comorbidities included diabetes mellitus in 27 (18.8%) patients and malignancy in 25 (17.4%) patients. Fifty-two (40%) patients had been in the intensive care unit prior to the positive blood culture. There were 19 patients with fluconazole-resistant *C glabrata* (MIC ≥ 64 $\mu\text{g/mL}$) included in secondary analyses.

30-Day inpatient mortality

Forty-five (31%) hospitalized patients died within 30 days of their positive blood culture. There were 19 (25%) deaths in patients with *C glabrata* BSI with decreased fluconazole susceptibility compared with 26 (38%) deaths in patients with fluconazole-susceptible *C glabrata* BSI (unadjusted relative risk, 0.65; 95% confidence interval [CI]: 0.46-1.07; $P = .09$). After adjusting for age and year of hospitalization, there was no significant difference in mortality between patients with *C glabrata* with decreased fluconazole susceptibility and fluconazole-susceptible *C glabrata* BSI (adjusted OR, 0.60; 95% CI: 0.26-1.35; $P = .22$) (Tables 1 and 2), and the effect remained non-significant in secondary analyses. Older age was independently associated with mortality (67.1 years [95% CI: 62.4-71.9 years] vs 58.6 years [95% CI: 55.6-61.7 years], respectively; adjusted OR, 1.04; 95% CI: 1.01-1.07), with a similar effect size seen in secondary analyses.

Postculture hospital charges

After adjusting for the hospital the patient was admitted to, time at risk, malignancy, hematopoietic stem cell transplantation, receipt of chemotherapy, and intensive care unit admission prior to the positive culture, there was no significant difference in hospital charges between patients with *C glabrata* with decreased fluconazole susceptibility and

fluconazole-susceptible *C glabrata* BSI (multiplicative change in hospital charges = 0.93; 95% CI: 0.60-1.43; $P = .73$). Results remained nonsignificant in secondary analyses.

Increased time at risk was independently associated with increased hospital charges in primary and secondary analyses. The average hospital charges increased by a multiple of 1.01 (95% CI: 1.01-1.02; $P = .002$) for a 1-day increase in time at risk, with similar results in secondary analyses.

Antifungal treatment: *C glabrata* with decreased fluconazole susceptibility versus fluconazole-susceptible *C glabrata* BSI

During their hospitalization, 117 (81.3%) patients were treated with an appropriate antifungal agent at the appropriate dose, 15 (10.4%) patients were treated with an inappropriate antifungal agent or dose, and 12 (8.3%) patients were not treated with an antifungal agent. In patients with *C glabrata* BSI with decreased fluconazole susceptibility, 15 (19.7%) patients received an inappropriate antifungal agent or dose, and 5 (6.6%) patients did not receive antifungal treatment. In patients with fluconazole-susceptible *C glabrata* BSI, 0 (0%) patients received an inappropriate antifungal agent or dose, and 7 (10.3%) patients did not receive antifungal treatment.

Of those patients who received appropriate antifungal treatment, there were no significant differences in the types of antifungal agents administered ($P = .26$). In patients with *C glabrata* BSI with decreased fluconazole susceptibility, 11 (24.4%) received higher dose fluconazole, 7 (15.6%) received voriconazole, 9 (20.0%) received caspofungin, and 5 (11.1%) received amphotericin. In patients with fluconazole-susceptible *C glabrata* BSI, 38 (38.4%) received fluconazole, 17 (17.2%) received voriconazole, 24 (24.2%) received caspofungin, and 6 (6.1%) received amphotericin.

When we evaluated time to appropriate treatment, 15 (20%) patients with *C glabrata* BSI with decreased fluconazole susceptibility received appropriate antifungal treatment ≤ 2 days of drawing a positive blood culture versus 41 (60%) patients with fluconazole-susceptible *C glabrata* BSI (unadjusted OR, 0.16; 95% CI: 0.07-0.36; $P < .001$).

30-Day inpatient mortality

Compared with receiving appropriate treatment, not receiving antifungal treatment (unadjusted OR, 2.66; 95% CI: 0.80-8.84; $P = .11$) and treatment with an inappropriate antifungal agent or dose (unadjusted OR, 2.32; 95% CI: 0.78-6.93; $P = .13$) were not associated with mortality. In secondary analyses (where the exposed group was limited to fluconazole-resistant *C glabrata* BSI with MIC ≥ 64 $\mu\text{g/mL}$), not receiving antifungal treatment achieved significance (unadjusted OR, 5.40; 95% CI: 0.98-29.77; $P = .05$). Receiving appropriate antifungal treatment ≤ 2 days of the positive blood culture was not associated with mortality (unadjusted OR, 0.95; 95% CI: 0.58-1.57; $P = .85$) and remained nonsignificant in secondary analyses.

Postculture hospital charges

Not receiving antifungal treatment (multiplicative change in hospital charges = 0.11; 95% CI: 0.05-0.27; $P < .001$) and treatment with an inappropriate antifungal agent or dose (multiplicative change in hospital charges = 0.30; 95% CI: 0.16-0.55; $P < .001$) were associated with decreased hospital charges; and remained significant in secondary analyses.

Receiving appropriate antifungal treatment ≤ 2 days of the positive blood culture was not associated with postculture hospital charges (multiplicative change in hospital charges = 1.01; 95% CI: 0.65-1.57; $P = .97$), and remained nonsignificant in secondary analyses.

DISCUSSION

Crude mortality rates were high in patients with *C glabrata* BSI. Patients with *C glabrata* BSI with decreased fluconazole susceptibility were not associated with increased 30-day inpatient mortality or hospital charges. Older age was independently associated with increased mortality. Increased time at risk was independently associated with increased hospital charges. Patients with *C glabrata* BSI with decreased fluconazole susceptibility were more likely to receive an inappropriate antifungal agent or dose and less likely to receive appropriate antifungal treatment ≤ 2 days of a positive blood culture. No antifungal treatment, treatment with an inappropriate antifungal agent or dose, and initiating appropriate antifungal treatment ≤ 2 days of the positive blood culture were not significantly associated with mortality in primary analyses; however, no antifungal treatment was significantly associated with mortality in secondary analyses. No antifungal treatment and treatment with an inappropriate antifungal agent or dose were associated with decreased hospital charges, whereas initiating appropriate antifungal treatment ≤ 2 days of a positive blood culture was not.

There was a 31% 30-day inpatient mortality in patients with health care-associated *C glabrata* BSI. Similarly, high mortality rates (29%-59%) have previously been reported^{7,8,11,19,20} and may be partly attributable to inappropriate treatment (ie, delays in treatment, treatment with an agent the organism is resistant to, inadequate treatment dose or duration, or no treatment at all). Our study reported 18.7% of patients did not receive antifungal treatment or received an inappropriate antifungal agent or dose. We also found that no antifungal treatment was significantly associated with increased mortality in secondary analyses.

In patients with *C glabrata* BSI, decreased fluconazole susceptibility was not an independent risk factor for mortality. We reported a 21% to 25% mortality in patients with *C glabrata* BSI with decreased fluconazole susceptibility compared with a 38% mortality in patients with fluconazole-susceptible *C glabrata* BSI. The only other study that performed susceptibility testing of *C glabrata* bloodstream isolates reported no significant difference ($P = .48$) in mortality between patients with *C glabrata* BSI with decreased fluconazole susceptibility (50%) and patients with fluconazole-susceptible *C glabrata* BSI (38%). Our results are also similar to studies that did not identify *C glabrata* as an independent risk factor for mortality in patients with *Candida* BSI. Because patients with *C glabrata* BSI with decreased fluconazole susceptibility were more likely to receive an inappropriate antifungal agent or dose and less likely to be started on appropriate antifungal treatment ≤ 2 days after a positive blood culture and because these factors were not associated with increased mortality, we suspect that additional factors may be as important in determining mortality. For example, antibiotic resistance can be associated with decreased fitness and/or virulence in certain bacterial pathogens.^{21,22} Although the differences were not significant, this may potentially explain the lower mortality rates seen in patients with *C glabrata* BSI with decreased fluconazole susceptibility. Further studies will need to evaluate whether antifungal resistance is indeed associated with decreased fitness and/or virulence in fungal pathogens such as *C glabrata*.²³ In addition, although this is the largest study comparing outcomes between patients with *C glabrata* with decreased fluconazole susceptibility versus fluconazole-susceptible *C glabrata* BSI, it is possible that the limited number of outcomes may have decreased the ability to detect a difference.

Although *C glabrata* with decreased fluconazole susceptibility was not an independent risk factor for increased hospital charges, time at risk was. Increased time at risk signifies a longer period of time for patients to undergo potential treatments and procedures and may be associated with higher severity of illness.

There are several potential limitations to our study. The limited number of outcomes may have resulted in decreased power to detect a difference. Second, it is possible that potential confounders were not included. For example, although removing central venous catheters is important in the treatment of *Candida* BSI, we did not collect this information because of concern for data accuracy. At our institution, many central venous catheters were placed by house staff and were therefore not associated with an electronic order that would have been captured in PICARD. Misclassification of *C glabrata* isolates based on the results from the SensitreYeastOne assay compared with the Clinical and Laboratory Standards Institute reference method has been shown in a study by Alexander et al²⁴; however, a study by Pfaller et al reported excellent agreement between these tests.²⁵ Last, our observation period, 30-day inpatient mortality, may not have been sufficient to assess the outcomes of interest.

In summary, our study reported high mortality rates among patients with *C glabrata* BSI. However, decreased fluconazole susceptibility was not independently associated with increased mortality or hospital charges.

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Table 1

Variables associated with 30-day inpatient mortality

Variable	Primary analyses [*]		Secondary analyses [†]	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
<i>Candida glabrata</i> BSI with decreased fluconazole susceptibility	0.60 (0.26-1.35)	.22	0.24 (0.05-1.05)	.06
Age, yr	1.04 (1.01-1.07)	.004	1.03 (1.00-1.06)	.05
Year [‡]				
2004	2.18 (0.65-7.35)	.21	NV [§]	NV [§]
2005	0.91 (0.23-3.61)	.90	NV [§]	NV [§]
2006	1.50 (0.43-5.29)	.53	NV [§]	NV [§]
2007	4.74 (0.74-30.39)	.10	NV [§]	NV [§]
Time at risk, days	NV [§]	NV [§]	1.01 (0.99-1.04)	.21

BSI, bloodstream infection; CI, confidence interval; OR, odds ratio.

^{*} Primary analyses: *C. glabrata* with decreased fluconazole susceptibility defined as MIC ≥ 16 µg/mL.

[†] Secondary analyses: *C. glabrata* with decreased fluconazole susceptibility defined as MIC ≥ 64 µg/mL.

[‡] Comparison group: 2003.

[§] Variable not included in multivariable model.

Table 2

Variables associated with hospital charges

Variable	Primary analyses [*]		Secondary analyses [†]	
	Multiplicative change in hospital charges (95% CI)	P	Multiplicative change in hospital charges (95% CI)	P
<i>Candida glabrata</i> BSI with decreased fluconazole susceptibility	0.93 (0.60-1.43)	.73	1.37 (0.69-2.70)	.36
Hospital: HUP	1.63 (0.92-2.87)	.09	NV [‡]	NV [‡]
Time at risk, days	1.01 (1.01-1.02)	.002	1.01 (1.00-1.02)	.02
Malignancy	0.78 (0.44-1.39)	.40		
Chemotreatment	2.09 (0.16-26.92)	.57	NV [‡]	NV [‡]
H SCT	3.58 (0.11-117.29)	.47	NV [‡]	NV [‡]
ICU	1.17 (0.66-2.07)	.58	NV [‡]	NV [‡]

BSI, bloodstream infection; CI, confidence interval; HSCT, hematopoietic stem cell transplantation; HUP, Hospital of the University of Pennsylvania; ICU, intensive care unit.

^{*} Primary analyses: *C. glabrata* with decreased fluconazole susceptibility defined as MIC $\geq$ 16 μ g/mL.

[†] Secondary analyses: *C. glabrata* with decreased fluconazole susceptibility defined as MIC $\geq$ 64 μ g/mL.

[‡] Variable not included in multivariable model.