Risk Factors for Nosocomial Candiduria Due to *Candida glabrata* and *Candida albicans*

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The aims of this study were to analyze the clinical characteristics and risk factors associated with catheter-associated candiduria due to *Candida glabrata* and due to *Candida albicans* and to compare patients with candiduria due to *C. glabrata* or *C. albicans* (cases) with controls. Controls were a randomly chosen sample of inpatients with Foley catheters for whom urine cultures were negative for *Candida* species. Univariate and multivariate analyses were performed. There were 40 cases of *C. glabrata* candiduria and 289 cases of *C. albicans* candiduria. Factors strongly associated with both *C. albicans* candiduria and *C. glabrata* candiduria were female gender ($P < .05$) and being in the intensive care unit ($P < .01$). Fluconazole use (adjusted odds ratio, 4.37; $P < .01$) and quinolone use (adjusted odds ratio, 3.16; $P < .01$) were specifically associated with *C. glabrata* candiduria but not with *C. albicans* candiduria. In conclusion, patients receiving fluconazole treatment are at risk of developing *C. glabrata* candiduria.

Candida glabrata is an emerging nosocomial pathogen that has a predilection for the urinary tract with a broad spectrum of disease severity [1].

Individual patient characteristics associated with *C. glabrata* candiduria in contrast to those associated with *Candida albicans* candiduria have not been specifically reported in a formalized case-control study design [1]. The aim of our study was to compare the risk factors for candiduria due to *C. albicans* vs. *C. glabrata* by using a single patient sample as the control group.

Methods

Case definition, control definition, and study design. Two retrospective case-control studies were conducted at The Beth Israel Deaconess Medical Center West Campus (Boston). This center is a tertiary care teaching hospital. The first group of cases were patients with nosocomial acquisition of *C. glabrata* candiduria. The second group of cases were patients with nosocomial acquisition of *C. albicans* candiduria.

The microbiology laboratory database was searched to identify all urine cultures positive for *C. albicans* and *C. glabrata* for patients admitted to the center between August 1993 and February 1998. Cases with positive cultures of specimens obtained within the first 48 hours of admission were excluded. Because >98% of urine specimens were obtained from catheterized patients, which is in agreement with the literature [2], it was decided that the most appropriate epidemiological control group would be patients who had Foley catheters. Computer-generated random selection identified 5% of the Foley catheterized patients admitted during the same period for whom urine cultures were negative for *Candida* species as controls. Patients who had been admitted for <48 hours were excluded. The same control group was used for both case-control studies (i.e., same control group for both cases with *C. glabrata* candiduria and cases with *C. albicans* candiduria). The reasoning behind a two case-control study design was to highlight differences and facilitate comparisons among the three groups.

Variables that were explored as possible risk factors included antibiotics and antifungals (the combination of which are referred to as antimicrobials), underlying diseases or comorbid conditions, and stay in the intensive care unit (ICU) during the present hospitalization. For the cases, antimicrobials included as risk factors were antimicrobials given before isolation of *Candida* species, i.e., before the outcome of interest. For controls, any antimicrobials given before the urine culture negative for *Candida* species were included.

Statistical analyses were performed with use of SAS software (SAS Institute, Cary, NC). Univariate analysis was performed separately for each variable. Odds ratios and 95% confidence intervals were calculated for binomial variables; *P* values were calculated by the Fisher's exact test for discrete variables and by the Student's *t* test or Wilcoxon rank-sum test for continuous variables. Variables with a *P* value of <.1 in the univariate analysis were included as final model candidates in a logistic regression model for multivariate analysis. All tests were two-tailed, and a *P* value of <.05 was considered significant in the multivariate model. All multivariate models controlled for length of hospitalization since it was a significant

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Table 1. Risk factors for *Candida glabrata* funguria.

Risk factor	Univariate risk ratio (95% CI)	*P* value	Multivariate risk ratio (95% CI)	*P* value
Antibiotic				
Any antibiotic*	12.67 (3.00–53.55)	<.001	10.64 (2.36–47.97)	<.001
Fluconazole (iv or po)	8.02 (3.08–20.90)	<.001	4.37 (1.32–14.43)	<.01
Quinolones (iv or po)	6.69 (2.94–15.24)	<.001	3.16 (1.14–8.80)	<.01
Penicillins (iv)	3.09 (1.54–6.23)	<.001	NS	
First- or second-generation cephalosporin	1.15 (0.57–2.31)	.70		
Third-generation cephalosporin	1.64 (0.75–3.57)	.21		
Macrolides (iv)	1.58 (0.18–13.67)	.68		
Vancomycin (iv)	5.08 (2.51–10.30)	<.001	NS	
Comorbid condition				
Female	2.92 (1.34–6.37)	<.01	2.93 (1.23–6.99)	.012
Diabetes	3.07 (1.50–6.29)	<.001	3.50 (1.57–7.83)	<.01
HIV infection	0.99 (0.98–1.00)	.61		
ICU admission	3.29 (1.64–6.59)	<.001	3.14 (1.39–7.08)	<.01
Cardiovascular disease	1.35 (0.62–2.96)	.45		
Malignancy	0.68 (0.23–2.00)	.48		
Hepatobiliary disease	2.59 (1.31–5.10)	.005		

NOTE. ICU = intensive care unit.
* When any antibiotic was included in the multivariate model, other antibiotics were not included because of collinearity.

predictor in the univariate analysis and it represents the at-risk period.

Results

During the 4.5-year study period, there were 40 patients with *C. glabrata* candiduria and 289 patients with *C. albicans* candiduria. There was no temporal-spatial clustering of *C. glabrata* funguria. Three hundred five controls were randomly selected from a sample of inpatients with Foley catheters for whom urine cultures were negative for *Candida* species. For cases with *C. glabrata* candiduria, the mean age was 66 years, the mean length of hospitalization before candiduria was 16 days, and the mean number of comorbid conditions was 3.5. In comparison, for cases with *C. albicans*, the mean age was 66 years, the mean length of hospitalization before candiduria was 15 days, and the mean number of comorbid conditions was 3.5. For controls, the mean age was 65 years, the mean length of hospitalization before negative culture was 7 days, and the mean number of comorbid conditions was 2.6.

Results of the univariate and multivariate risk factor analyses for *C. glabrata* candiduria are outlined in table 1. Cases were more likely to be female (OR, 2.93; $P = .012$) and diabetic (OR, 3.50; $P < .01$) and to have been in the ICU (OR, 3.14; $P < .01$) at some time before developing candiduria. Use of any antibiotic (not including antifungals) was a significant risk factor (OR, 10.64; $P < .001$). Analysis of individual classes of antimicrobial agents demonstrated that fluconazole (OR, 4.37; $P < .01$) and quinolones (OR, 3.16; $P < .01$) were risk factors.

Results of the univariate and multivariate risk factor analyses for *C. albicans* candiduria are shown in table 2. Similar to findings for *C. glabrata* candiduria, cases were more likely to be female (OR, 2.54; $P < .001$) and to have been in the ICU (OR, 3.57; $P < .001$), and antibiotic use (not including antifungals) in general was a significant risk factor (OR, 3.87; $P < .001$). In contrast to findings for *C. glabrata* candiduria, cardiovascular disease (OR, 1.61; $P = .04$) and hepatobiliary disease (OR, 1.75; $P < .01$) were also risk factors. Specific antibiotics that were risk factors were penicillins (OR, 2.29; $P < .001$) and vancomycin (OR, 2.12; $P < .01$).

Treatment of candiduria was as follows. Twenty-nine (73%) of 40 patients with *C. glabrata* candiduria received antifungal treatment: 15 (52%) received fluconazole treatment, and 18 (62%) underwent amphotericin B bladder irrigation. Ten patients were treated with more than one antifungal agent. One hundred fifty-six (54%) of 289 patients with *C. albicans* candiduria were treated with antifungal agents: 103 (66%) received fluconazole treatment, and 78 (50%) underwent amphotericin B bladder irrigation. Thirty-eight patients were treated with more than one antifungal agent.

Discussion

In this study, we assessed risk factors for *C. glabrata* candiduria and *C. albicans* candiduria by using a single control group to facilitate comparison. The aims of this study were to confirm the hypothesis that fluconazole use at least partially accounts for the rise in the frequency of *C. glabrata* candiduria and to identify other contributory factors that may prove amenable to modification or be useful for purposes of risk stratification.

We found that diabetes, female gender, and overall antibac-

Table 2. Risk factors for *Candida albicans* funguria.

Risk factor	Univariate risk ratio (95% CI)	*P* value	Multivariate risk ratio (95% CI)	*P* value
Antibiotic				
Any antibiotic*	7.80 (4.81–12.66)	<.001	3.87 (2.24–6.68)	<.001
Fluconazole (iv or po)	2.13 (1.00–4.49)	.05	NS	
Quinolones (iv or po)	1.32 (0.70–2.48)	.39		
Penicillins (iv)	3.68 (2.56–5.29)	<.001	2.29 (1.45–3.60)	<.001
First- or second-generation cephalosporin	1.45 (1.04–2.03)	.03	NS	
Third-generation cephalosporin	4.22 (2.93–6.08)	<.001	NS	
Macrolides (iv)	3.57 (1.29–9.87)	.11		
Vancomycin (iv)	4.77 (3.21–7.03)	<.01	2.12 (1.31–3.40)	<.01
Comorbid condition				
Female	1.46 (1.05–2.04)	.03	2.54 (1.67–3.89)	<.001
Diabetes	1.13 (0.82–1.56)	.47		
HIV infection	0.99 (0.98–1.00)	.17		
ICU admission	5.53 (3.82–8.00)	<.001	3.57 (2.32–5.48)	<.001
Cardiovascular disease	1.37 (0.95–1.99)	.09	1.61 (1.18–2.59)	.04
Malignancy	0.80 (0.50–1.30)	.37		
Hepatobiliary disease	2.34 (1.68–3.24)	<.001	1.75 (1.18–2.59)	<.01

NOTE. ICU = intensive care unit.

* When any antibiotic was included in the multivariate model, other antibiotics were not included because of collinearity.

terial use were significant independent risk factors for both *C. albicans* candiduria and *C. glabrata* candiduria, whereas fluconazole use was associated only with *C. glabrata* candiduria. Unexpectedly, quinolone exposure was another specific risk factor for *C. glabrata* candiduria.

The identification of female gender as a risk factor for candiduria is not unexpected in that female gender is a risk factor for bacterial urinary tract infection [2, 3]. A specific association between quinolone treatment and fungal infection has not been previously noted. The finding could be spurious and needs reevaluation in additional studies. It is possible that differential effects on normal gastrointestinal and vaginal flora by antibacterial agents alter the likelihood of colonization with distinct *Candida* species.

A limitation of this study is that data on duration of indwelling catheters and frequency of catheter exchanges were unavailable. These variables may correlate with the risk of candidal urinary tract infection but are unlikely to be associated with antimicrobial exposure; therefore, these variables are probably not important confounders. We chose to examine risk factors for candiduria because criteria to differentiate colonization from infection are inadequate [4], thus leading to difficulty in assessing the benefit of treatment in multiple studies.

In summary, we demonstrated that the risk factors for *C. albicans* candiduria and *C. glabrata* candiduria differ. In particular, fluconazole use is a significant risk factor for the subsequent isolation of *C. glabrata* from the urine. One remaining question is whether relatively fluconazole-resistant *Candida* species such as *C. glabrata* are simply replacing *C. albicans* (thereby resulting in a stable or decreasing overall incidence of nosocomial fungal infections) or are superimposed on the problem.

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