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Prior Antimicrobial Therapy and Risk for Hospital-Acquired *Candida glabrata* and *Candida krusei* Fungemia: a Case-Case-Control Study

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The incidence of infections caused by *Candida glabrata* and *Candida krusei*, which are generally more resistant to fluconazole than *Candida albicans*, is increasing in hospitalized patients. However, the extent to which prior exposure to specific antimicrobial agents increases the risk of subsequent *C. glabrata* or *C. krusei* candidemia has not been closely studied. A retrospective case-case-control study was performed at a university hospital. From 1998 to 2003, 60 patients were identified with hospital-acquired non-*C. albicans* candidemia (*C. glabrata* or *C. krusei*; case group 1). For comparison, 68 patients with *C. albicans* candidemia (case group 2) and a common control group of 121 patients without candidemia were studied. Models were adjusted for demographic and clinical risk factors, and the risk for candidemia associated with exposure to specific antimicrobial agents was assessed. After adjusting for both nonantimicrobial risk factors and receipt of other antimicrobial agents, piperacillin-tazobactam (odds ratio [OR], 4.15; 95% confidence interval [CI], 1.04 to 16.50) and vancomycin (OR, 6.48; CI, 2.20 to 19.13) were significant risk factors for *C. glabrata* or *C. krusei* candidemia. For *C. albicans* candidemia, no specific antibiotics remained a significant risk after adjusted analysis. Prior fluconazole use was not significantly associated with either *C. albicans* or non-*C. albicans* (*C. glabrata* or *C. krusei*) candidemia. In this single-center study, exposure to antibacterial agents, specifically vancomycin or piperacillin-tazobactam, but not fluconazole, was associated with subsequent hospital-acquired *C. glabrata* or *C. krusei* candidemia. Further studies are needed to prospectively analyze specific antimicrobial risks for nosocomial candidemia across multiple hospital centers.

Yeasts, particularly *Candida albicans*, have been recognized as an important cause of healthcare-associated infection. Candida species are now the fourth most common cause of bloodstream infection among hospitalized patients in the United States (6) and are particularly prevalent pathogens in intensive care units (22). Yeast bloodstream infections are associated with considerable morbidity and mortality, with an attributable risk of death approaching 49% (10, 33). Included in the rising incidence of bloodstream infections caused by yeast is a sharp increase in the proportion caused by candida species other than *C. albicans*, including *Candida glabrata* and *Candida krusei* (18, 29). These species tend to be more resistant to commonly used triazole agents, such as fluconazole (19, 30), and therefore present a particular challenge for clinical management.

Previous investigations have suggested that prior exposure to antifungal agents may be a risk factor for subsequent infection with *C. glabrata* and *C. krusei*. A relationship between fluconazole use and a rise in the prevalence of *C. krusei* was first described by Wingard et al. (37). This association has subsequently been observed at other centers (1, 8, 12, 38). The clinical importance of these observations has been heightened as antifungal prophylaxis is increasingly used for high-risk patient groups, such as those undergoing bone marrow and solid-organ transplantation (27, 40). In addition, fluconazole is commonly selected as the first choice for empirical antifungal therapy for hospitalized patients.

Nevertheless, the relative contribution of specific antimicrobial agents to the subsequent risk for *C. glabrata* or *C. krusei* candidemia remains unclear. Since an increase in prevalence of *C. krusei* predated the use of fluconazole in some institutions (16), fluconazole exposure alone cannot fully explain the reported increase in infections caused by these species. Moreover, previous studies of risk factors for *C. glabrata* or *C. krusei* candidemia may have been limited by methodological considerations, including the use of less than ideal controls (17) and limited consideration of antimicrobial exposure (1, 8, 37). Nevertheless, these studies did consistently identify several predictors of candidemia (*C. albicans* or non-*C. albicans*), including intensive care unit stay, broad-spectrum antibacterial therapy, indwelling catheters, and parenteral feeding (2, 7, 21, 34).

Recent studies have illustrated that the association between prior antimicrobial exposure and subsequent colonization or infection with resistant organisms may be difficult to predict. For example, fluoroquinolone exposure has been identified as a risk factor for methicillin-resistant *Staphylococcus aureus* (32), and expanded-spectrum cephalosporins, metronidazole, and fluroquinolones may be more strongly associated with vancomycin-resistant enterococci than is vancomycin itself (4). In these circumstances, certain antibiotics, rather than promoting de novo resistance, may instead facilitate the acquisition of resistant organisms through alteration of the patient's endogenous colonizing flora.

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In the present study, to best quantify the risk of specific antimicrobial use for subsequent *C. glabrata* or *C. krusei* candidemia, the case-case-control method was used. This design provides an opportunity to compare the risk of infection with mostly azole-resistant candida species (*C. glabrata* and *C. krusei*) versus typically azole-susceptible species (*C. albicans*) with respect to specific antimicrobial agents, including fluconazole.

MATERIALS AND METHODS

Study design. The University of Chicago Hospitals is a 500-bed tertiary care center located on Chicago's South Side that serves a diverse patient population, including a large proportion of African American patients. In addition to routine medical and surgical services, the hospital offers highly specialized care, including solid-organ and bone marrow transplantation.

A retrospective case-case-control design was employed. As described elsewhere, this approach involves the construction of parallel case-control studies with a shared control group, which allows for a more precise estimate of risk (11, 13, 32). The first arm of analysis compared cases of *C. glabrata* or *C. krusei* candidemia with uninfected controls. In the second, subjects with *C. albicans* candidemia served as cases and were again compared to the same uninfected controls.

Patients were eligible for study inclusion if they were admitted for at least 72 h to medicine or surgical services from 1 January 1998 to 31 December 2003, as identified by electronic search of the University of Chicago Hospitals' clinical database. Any patient with blood cultures positive for candida species 30 days prior to admission or within the first 72 h after admission were presumed to have acquired the infection outside the hospitalization period of interest and were therefore excluded. Non-*C. albicans* candida cases were defined as patients with positive blood cultures for either *C. glabrata* or *C. krusei*. *C. albicans* cases were defined as patients with blood cultures positive for *C. albicans*. The control group was composed of randomly selected patients hospitalized for at least 72 h without candidemia. All cases and controls were selected from eligible patients from the study period and were not otherwise matched for time or other characteristics.

Data regarding clinical risk factors were collected from patients' paper and electronic medical records. Four trained clinical abstractors collected the retrospective data, and interreviewer accuracy was verified by comparing redundantly abstracted charts.

Proposed predictors of candidemia included patient demographics, clinical characteristics identified in prior studies as possible risk factors for candidemia, and exposure to antimicrobial agents. Age was expressed as a continuous variable. Dichotomous variables included intensive care unit stay, total parenteral nutrition, intubation, central venous catheter, neutropenia (absolute neutrophil count of less than 1,000/mm^3), abdominal-pelvic surgery, other surgery, diabetes, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, end-stage renal disease, liver disease (cirrhosis, hepatitis B or C), human immunodeficiency virus (HIV), solid-organ transplant, bone marrow transplant, and solid-organ and bone marrow malignancy as well as aggregate variables of "any immune suppression" (HIV, solid-organ or bone marrow transplant, or any immune-modulating medication) and "any malignancy" (solid-organ or hematological malignancy). Risk days were defined as the number of hospital days from admission to the date of the first positive blood culture for case patients or total days in the hospital for control patients.

Individual antimicrobial agents were examined as potential risk factors for candidemia. Additionally, seven aggregate antibiotic classes were analyzed: any fluoroquinolone, any aminoglycoside, any carbapenem, any macrolide, any agent with antianaerobic activity (amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, metronidazole, clindamycin, or any carbapenem), any expanded-spectrum cephalosporin, and any antifungal agents other than fluconazole (amphotericin, voriconazole, itraconazole, caspofungin). All antibiotics were confirmed to have been given before the date of positive blood culture for the case groups. All administered antibiotics were included regardless of duration or dose.

Potential confounding by nonantimicrobial risk factors was addressed by using multivariable logistic regression to generate a propensity score that quantifies each patient's predisposition to candidemia based on nonantimicrobial risk factors. Individual risk factors were initially identified using simple regression models adjusted for days at risk. Those factors preliminarily associated with candidemia ($P \leq 0.10$) were included by stepwise selection in a multivariable logistic regression model to determine the relative contribution of each variable to the final propensity score. The overall propensity score for each subject represents the conditional probability of candidemia based on nonantimicrobial covariates (days at risk, intensive care unit stay, total parenteral nutrition, central venous catheter, intubation, and liver disease). In essence, the propensity score represents a composite risk incorporating the nonantimicrobial covariates for each subject and was used in subsequent models to adjust for potential confounding (3, 23).

Next, with non-*C. albicans* (*C. glabrata* or *C. krusei*) or *C. albicans* candidemia considered separately as outcomes, individual antibiotics were analyzed using simple regression models adjusted for nonantibiotic risk factors using the propensity score. Antibiotics significantly associated with candidemia ($P \leq 0.05$) were then included in multivariable logistic regression models adjusted for the propensity score, again with either non-*C. albicans* or *C. albicans* candidemia as the outcome. Fluconazole was included in the multivariable models regardless of statistical significance. The final multivariable models were tested for overfitting using the Hosmer-Lemeshow test.

SAS software version 8.2 was used for all statistical analysis (SAS Institute, Cary, NC). The study was approved by the Institutional Review Board of the University of Chicago.

RESULTS

Nonantimicrobial risk factors and the propensity score model. Sixty patients with *C. glabrata* or *C. krusei* candidemia were available for analysis (56 with *C. glabrata* and 4 with *C. krusei*). Sixty-eight patients with *C. albicans* candidemia were randomly selected from those eligible for inclusion. One-hundred twenty-one patients without candidemia admitted during the same time period were included as controls.

Nonantimicrobial factors that were associated ($P \leq 0.10$) with any candidemia included intensive care unit stay, total parenteral nutrition, intubation, central venous catheter, diabetes, end-stage renal disease, liver disease, and abdominal surgery (Table 1). These variables, along with number of risk days, were combined in a preliminary multivariable model to determine the propensity score. End-stage renal disease, abdominal surgery, and diabetes, which did not retain statistical significance, were ultimately removed from the final propensity score model, as their inclusion did not significantly alter the effect estimates of the remaining variables. The adjusted odds of covariates included in the final propensity score model are presented in Table 2.

Bivariate analysis of antimicrobial risk factors. The results of analysis of the association between individual antimicrobial agents and subsequent candidemia, adjusted for the propensity score, are presented in Table 3. Vancomycin (odds ratio [OR], 9.48; 95% confidence interval [CI], 3.49 to 25.78), piperacillin-tazobactam (OR, 4.88; CI, 1.43 to 16.70), any aminoglycoside (OR, 4.52; CI, 1.20 to 16.96), any antianaerobic agent (OR, 3.39; CI, 1.37 to 8.43), and any expanded-spectrum cephalosporin (OR, 2.85; CI, 1.04 to 7.75) were each significantly associated with subsequent *C. glabrata* or *C. krusei* candidemia.

For *C. albicans*, ceftazidime (OR, 4.66; 95% CI, 1.11 to 19.49), vancomycin (OR, 4.38; CI, 1.64 to 11.71), any aminoglycoside (OR, 5.72; CI, 1.37 to 23.93), any antianaerobic agent (OR, 2.81; CI, 1.15 to 6.88), and any expanded-spectrum cephalosporin (OR, 3.28; CI, 1.17 to 9.18) were found to be statistically significant risk factors.

Of note, fluconazole was neither significantly predictive nor protective with respect to *C. glabrata* or *C. krusei* candidemia (OR, 2.16; CI, 0.69 to 6.71), nor was it predictive or protective with respect to *C. albicans* candidemia (OR, 1.25; CI, 0.38 to 4.15).

TABLE 1. Demographic and clinical characteristics of the case and control groups

Characteristics	Non-*C. albicans* candida (n = 60)	*Candida albicans* (n = 68)	Combined cases (n = 128)	Control (n = 121)
Demographics				
Male (%)	40	53	47	42
Mean age (yr)	59.9	59.4	59.6	58.7
Non-white race (%)	60	47	56	59
Clinical covariates				
Median risk days	16	13	14[a]	5
Intensive care unit stay (%)	67	78	73[a,c]	30
Total parenteral nutrition (%)	53	47	50[a,c]	2
Intubation (%)	57	57	57[a,c]	12
Central venous catheter (%)	85	85	85[a,c]	28
Neutropenia (%)	17	12	14	4
Diabetes (%)	43	31	37[b,c]	26
Chronic obstructive pulmonary disease (%)	8	7	8	14
Coronary artery disease (%)	30	24	27	30
Congestive heart failure (%)	18	16	17	12
End-stage renal disease (%)	28	13	20[b,c]	7
Liver disease (%)	17	12	14[a,c]	6
Human immunodeficiency virus (HIV) (%)	0	1	1	0
Solid-organ transplant (%)	12	10	11	3
Bone marrow transplant (%)	0	4	2	2
Solid-organ malignancy (%)	23	21	22	26
Bone marrow malignancy (%)	3	10	7	2
Abdominal surgery (%)	32	21	26[b,c]	9
Other surgery (%)	13	21	17	10
Any immune suppression (%)	35	47	41	25
Any malignancy (%)	27	31	29	29

[a] Included in the final propensity score (PS) model.
[b] Removed from the final propensity score (PS) model.
[c] $P \leq 0.10$ when combined cases are compared to controls.

Multivariable adjusted analysis of antimicrobial risk factors. The results of multivariable regression analysis are shown in Tables 4 and 5. Fluconazole was included in each model. For *C. glabrata* or *C. krusei* candidemia, when fluconazole, piperacillin-tazobactam, vancomycin, any expanded-spectrum cephalosporin, and any aminoglycoside were analyzed together and adjusted for the propensity score, only piperacillin-tazobactam (odds ratio, 4.15; 95% confidence interval, 1.04 to 16.50) and vancomycin (odds ratio, 6.48; 95% confidence interval, 2.20 to 19.13) remained statistically significant (Table 4). In contrast, when ceftazidime, fluconazole, vancomycin, any aminoglycoside, and any antianaerobe were considered with *C. albicans* candidemia as the outcome, none of the variables retained their individual significance (Table 5).

TABLE 2. Adjusted odds of covariates included in the propensity score model

Predictor	Odds ratio (95% CI) for any candidemia	P
Days at risk	1.00 (0.97–1.03)	0.94
Intensive care unit stay	1.46 (0.56–3.81)	0.44
Total parenteral nutrition	31.60 (6.86–145.15)	0.00
Intubation	3.30 (1.13–9.67)	0.03
Central venous catheter	5.04 (2.16–11.80)	0.00
Liver disease	4.46 (1.29–15.46)	0.02

DISCUSSION

In this report, we describe a retrospective case-case-control study at a single academic medical center that is, to our knowledge, the first to systematically examine exposure to individual antimicrobial agents and the risk for subsequent healthcare-associated candidemia. Piperacillin-tazobactam and vancomycin were found to be significantly associated with nosocomial *C. glabrata* or *C. krusei* candidemia, even after adjusting for clinical risk factors and other antimicrobial uses. In adjusted analysis, no individual antibiotic was found to be significantly associated with development of *C. albicans* candidemia. Exposure to fluconazole was not found to be a significant risk factor for developing either non-*C. albicans* (*C. glabrata* or *C. krusei*) or *C. albicans* candidemia.

Recognizing that both the sample size and the single-center design of the study may have limited the ability to completely assess the risk for candidemia with every agent examined, the observation of an association between *C. glabrata* or *C. krusei* candidemia and both vancomycin and piperacillin-tazobactam is notable. A role for similar antibacterial agents in promoting candidemia has been described previously. The National Epidemiology of Mycosis Survey reported that among surgical intensive care unit patients, vancomycin and antianaerobic antibiotics were significant risk factors for subsequent candida bloodstream infections in unadjusted analysis (2). The present study extends the consideration of specific antimicrobial risk factors to a more heterogeneous hospital population and al-

TABLE 3. Risk of *C. albicans* and non-*C. albicans* (*C. glabrata* or *C. krusei*) candidemia associated with individual antibiotics, adjusted for the propensity score[a]

Antibiotic(s)[b]	*C. glabrata* or *C. krusei*			*Candida albicans*			Controls
	No. (%)	OR (95% CI)	*P*	No. (%)	OR (95% CI)	*P*	No. (%)
Acyclovir	6 (10)	1.10 (0.24–4.95)	0.90	7 (10)	1.11 (0.25–4.87)	0.89	6 (5)
Amphotericin	3 (5)	1.63 (0.09–28.43)	0.74	4 (6)	4.09 (0.32–52.20)	0.28	1 (1)
Ampicillin	6 (10)	1.13 (0.22–5.72)	0.88	6 (9)	0.40 (0.075–2.12)	0.28	6 (5)
Ampicillin-sulbactam	5 (8)	1.09 (0.22–5.44)	0.91	10 (15)	0.88 (0.21–3.71)	0.86	6 (5)
Azithro	3 (5)	1.17 (0.23–5.90)	0.85	6 (9)	1.11 (0.24–5.05)	0.90	11 (9)
Aztreonam	1 (2)	0.08 (0.01–0.99)	0.05	4 (6)	0.34 (0.05–2.15)	0.25	3 (3)
Cefazolin	5 (8)	0.28 (0.07–1.13)	0.07	14 (21)	0.84 (0.28–2.49)	0.75	17 (14)
Ceftazidime	10 (17)	2.14 (0.52–8.83)	0.29	13 (19)	**4.66 (1.11–19.49)**	**0.04**	4 (3)
Ceftizoxime	11 (18)	1.60 (0.37–6.90)	0.53	10 (15)	0.85 (0.19–3.86)	0.83	7 (6)
Ceftriaxone	13 (22)	2.76 (0.87–8.75)	0.09	15 (22)	2.39 (0.72–7.87)	0.15	12 (10)
Ciprofloxacin	14 (23)	0.95 (0.33–2.75)	0.93	19 (28)	1.48 (0.52–4.23)	0.47	20 (17)
Clindamycin	11 (18)	1.23 (0.38–3.98)	0.73	11 (16)	0.96 (0.28–3.32)	0.94	13 (11)
Fluconazole	18 (30)	2.16 (0.69–6.71)	0.18	14 (21)	1.25 (0.38–4.15)	0.72	9 (7)
Ganciclovir	4 (7)	0.45 (0.07–3.10)	0.42	6 (9)	0.85 (0.16–4.60)	0.85	4 (3)
Gatifloxacin	4 (7)	1.65 (0.24–11.31)	0.61	5 (7)	5.19 (0.80–33.85)	0.09	3 (3)
Gentamicin	9 (15)	4.21 (0.93–19.15)	0.06	14 (21)	4.97 (0.91–27.06)	0.06	3 (3)
Imipenem	8 (13)	2.30 (0.51–10.36)	0.28	7 (10)	1.26 (0.24–6.52)	0.79	4 (3)
Levofloxacin	5 (8)	4.60 (0.56–38.15)	0.16	1 (2)	1.09 (0.05–23.53)	0.96	2 (2)
Metronidazole	19 (32)	2.41 (0.81–7.16)	0.11	24 (35)	2.47 (0.80–7.66)	0.12	11 (9)
Nafcillin	3 (5)	1.04 (0.17–6.44)	0.97	3 (4)	1.89 (0.28–12.64)	0.51	8 (7)
Nystatin	6 (10)	0.99 (0.22–4.48)	0.99	10 (15)	1.81 (0.54–7.50)	0.42	6 (5)
Piperacillin-tazobactam	17 (28)	**4.88 (1.43–16.70)**	**0.01**	16 (24)	2.01 (0.51–7.96)	0.32	5 (4)
Tobramycin	5 (8)	3.00 (0.24–37.14)	0.39	9 (13)	6.79 (0.63–73.00)	0.11	1 (1)
Trimethoprim-sulfamethoxazole	2 (3)	0.17 (0.02–1.22)	0.08	9 (13)	0.76 (0.20–2.88)	0.68	9 (7)
Vancomycin	35 (58)	**9.48 (3.49–25.78)**	**0.00**	34 (50)	**4.38 (1.64–11.71)**	**0.00**	14 (12)
Any fluoroquinolone	20 (33)	1.33 (0.52–3.41)	0.56	23 (34)	1.68 (0.64–4.39)	0.29	25 (21)
Any aminoglycoside	15 (25)	**4.52 (1.20–16.96)**	**0.03**	21 (31)	**5.72 (1.37–23.93)**	**0.02**	4 (3)
Any carbapenem	9 (15)	2.39 (0.54–10.58)	0.25	7 (10)	1.26 (0.24–6.52)	0.79	4 (3)
Any antianaerobic	40 (67)	**3.39 (1.37–8.43)**	**0.01**	48 (71)	**2.81 (1.15–6.88)**	**0.02**	29 (24)
Any expanded-spectrum cephalosporin	20 (33)	**2.85 (1.04–7.75)**	**0.04**	24 (35)	**3.28 (1.17–9.18)**	**0.02**	15 (12)
Any antifungal (other than fluconazole)	4 (7)	1.20 (0.13–11.29)	0.88	5 (7)	2.39 (0.31–18.62)	0.41	2 (2)
Any macrolide	3 (5)	1.01 (0.21–4.85)	0.99	8 (12)	1.07 (0.26–4.39)	0.93	12 (10)

[a] Propensity score adjusts for the following factors significant on primary analysis: days at risk, intensive care unit stay, total parental nutrition, intubation, central venous catheter, and liver disease.
[b] Selected antibiotics with n (total cases and controls) < 5 are not shown. Boldface indicates antibiotics with $P \leq 0.05$.

lows for adjusted analyses considering different candida species as separate outcomes. That each of the two agents may be more closely associated with *C. glabrata* or *C. krusei* candidemia than prior exposure to fluconazole has important clinical implications.

The precise pathophysiologic role that antecedent antibacterial agents could play in promoting in-hospital infection with candida species remains unclear. Ecologic studies have shown that acquisition of nosocomial candida infections likely relies in part on horizontal transmission through indirect patient contact (30, 31). Vancomycin may promote skin colonization by candida species by altering the ecology of the normal skin flora, eradicating colonizing gram-positive organisms and thereby increasing the potential for acquired colonization and subsequent bloodstream infection. Similarly, antibacterial agents with strong antianaerobic activity and high gastrointestinal concentration, such as piperacillin-tazobactam, may preferentially promote colonization of the gastrointestinal tract with candida species. In a study by Samonis et al., it is notable that ticarcillin-clavulanate, but not imipenem-cilastatin, which has a similar antibacterial spectrum but a lower relative gas-

TABLE 4. Adjusted odds of antibiotics and fluconazole associated with *Candida glabrata* or *Candida krusei* bloodstream infection, multivariable model

Predictor[a]	*C. glabrata* or *C. krusei*	
	Odds ratio (95% CI)	*P*
Fluconazole	1.81 (0.48–6.92)	0.38
Piperacillin-tazobactam	**4.15 (1.04–16.50)**	**0.04**
Vancomycin	**6.48 (2.20–19.13)**	**0.001**
Any expanded-spectrum cephalosporin	2.53 (0.83–7.72)	0.10
Any aminoglycoside	1.913 (0.46–8.00)	0.37

[a] Boldface indicates antibiotics with $P \leq 0.05$.

TABLE 5. Adjusted odds of antibiotics and fluconazole associated with *Candida albicans* bloodstream infection, multivariable model

Predictor	*Candida albicans*	
	Odds ratio (95% CI)	*P*
Ceftazidime	1.83 (0.36–9.24)	0.47
Fluconazole	0.89 (0.24–3.35)	0.86
Vancomycin	2.68 (0.89–8.05)	0.08
Any aminoglycoside	2.86 (0.67–4.90)	0.18
Any antianaerobe	1.81 (0.67–4.90)	0.24

trointestinal concentration, promoted candida colonization of the human gastrointestinal tract (24).

If antecedent antibiotics promote candidemia through alteration of endogenous flora, the results of the present study suggest that *C. glabrata* or *C. krusei*, having lower intrinsic pathogenicity and virulence than *C. albicans* (14, 25, 36), may require increased antibiotic selection pressure in order for colonization of the skin and gastrointestinal tract to occur. In contrast, the more ubiquitous and relatively more virulent *C. albicans* may not require such strong selection pressure to establish colonization. This may help explain why specific antibacterials appeared more important for acquisition of *C. glabrata* or *C. krusei* than *C. albicans* candidemia.

An additional important but counterintuitive finding was the lack of association between fluconazole and subsequent *C. glabrata* or *C. krusei* versus *C. albicans* candidemia. While this observation may be attributed to the limited sample size and single-institution nature of the study, the results at least suggest that some antibacterial agents, specifically vancomycin and piperacillin-tazobactam, may be more important than fluconazole in promoting *C. glabrata* or *C. krusei* candidemia. These results appear to contradict the widely held assumption that prior exposure to fluconazole is the single most important predisposing criteria for subsequent non-*C. albicans* candidemia. Though there has been a historical association between fluconazole use and the increased incidence of relatively resistant non-*C. albicans* candida species, the degree to which fluconazole plays a role in the risk to individual patients remains unclear (35). The results of the present study are consistent with prospective, placebo-controlled trials that have shown a limited effect of prophylactic fluconazole on the epidemiology of non-*C. albicans* candidemia in cancer patients (9, 39). Similarly, in several retrospective and prospective trials, HIV-infected patients who received intermittent or long-term dosing of fluconazole for prophylaxis of fungal infections did not experience a clinically significant shift from *C. albicans* to other, more resistant species (20, 26, 28).

That fluconazole was not protective for subsequent *C. albicans* candidemia was also somewhat unexpected. Prior studies have shown that in selected populations, such as bone marrow transplantation patients (9), neutropenic patients with leukemia (15), liver transplant recipients (40), and surgical intensive care unit patients (2), prophylaxis with fluconazole is effective in reducing the incidence of superficial and invasive fungal infections. However, it is likely that a significant proportion of the patients studied here received fluconazole not as prophylaxis but as empirical treatment for deteriorating clinical status. Thus, failure to detect a protective effect may reflect "confounding by indication," in that patients who ultimately develop candidemia are also those most likely to receive empirical fluconazole treatment (5). Such confounding would likely affect both case groups equally.

There are several limitations to the present study. First, data were collected from a single center, resulting in a limited sample size that could be influenced by local outbreaks, specific infection control practices, or regional susceptibility patterns. Second, antibiotic susceptibility testing was not routinely available for yeast isolates during this time period, raising the possibility of misclassification bias. In the study, the assumption was made that *C. glabrata* and *C. krusei* are inherently more resistant to fluconazole than *C. albicans*. However, if the percentage of *C. glabrata* or *C. krusei* candida susceptible to fluconazole approached that of *C. albicans*, the difference in risk estimates associated with fluconazole exposure between the two groups would be biased towards the null. Third, the retrospective nature of this analysis may be susceptible to reviewer bias. To validate interreviewer accuracy, identical charts were intermittently abstracted by multiple reviewers, all of whom were well-trained clinical data analysts.

From a clinical perspective, these results suggest that exposure to certain antibacterial agents may in fact be more closely linked with the subsequent development of *C. glabrata* or *C. krusei* candidemia than receipt of fluconazole. Selection of antimicrobial therapy may need to better account for the influence of such agents on colonization pressures in skin and gastrointestinal environments. Future prospective studies including data from multiple centers that analyze antimicrobial use and subsequent colonization and infection by *C. glabrata* and *C. krusei* will lead to a better understanding of the epidemiology of these increasingly important pathogens.

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REFERENCES

1. **Abi-Said, D., E. Anaissie, O. Uzun, I. Raad, H. Pinzcowski, and S. Vartivarian.** 1997. The epidemiology of hematogenous candidiasis caused by different candida species. Clin. Infect. Dis. **24:**1122–1128.
2. **Blumberg, H. M., W. R. Jarvis, J. M. Soucie, J. E. Edwards, J. E. Patterson, M. A. Pfaller, M. S. Rangel-Frausto, M. G. Rinaldi, L. Saiman, R. T. Wiblin, and R. P. Wenzel.** 2001. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin. Infect. Dis. **33:**177–186.
3. **Carmeli, Y., J. Castro, G. M. Eliopoulos, and M. H. Samore.** 2001. Clinical isolation and resistance patterns of and superinfection with 10 nosocomial pathogens after treatment with ceftriaxone versus ampicillin-sulbactam. Antimicrob. Agents Chemother. **45:**275–279.
4. **Carmeli, Y., G. M. Eliopoulos, and M. H. Samore.** 2002. Antecedent treatment with different antibiotic agents as a risk factor for vancomycin-resistant Enterococcus. Emerg. Infect. Dis. **8:**802–807.
5. **de Koning, J. S., N. S. Klazinga, P. J. Koudstaal, A. Prins, G. J. Borsboom, and J. P. Mackenbach.** 2005. The role of 'confounding by indication' in assessing the effect of quality of care on disease outcomes in general practice: results of a case-control study. BMC Health Serv. Res. **5:**10.
6. **Edmond, M. B., S. E. Wallace, D. K. McClish, M. A. Pfaller, R. N. Jones, and R. P. Wenzel.** 1999. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin. Infect. Dis. **29:**239–244.
7. **Edwards, J. E., Jr., G. P. Bodey, R. A. Bowden, T. Buchner, B. E. de Pauw, S. G. Filler, M. A. Ghannoum, M. Glauser, R. Herbrecht, C. A. Kauffman, S. Kohno, P. Martino, F. Meunier, T. Mori, M. A. Pfaller, J. H. Rex, T. R. Rogers, R. H. Rubin, J. Solomkin, C. Viscoli, T. J. Walsh, and M. White.** 1997. International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections. Clin. Infect. Dis. **25:**43–59.
8. **Gleason, T. G., A. K. May, D. Caparelli, B. M. Farr, and R. G. Sawyer.** 1997. Emerging evidence of selection of fluconazole-tolerant fungi in surgical intensive care units. Arch. Surg. **132:**1197–1202.
9. **Goodman, J. L., D. J. Winston, R. A. Greenfield, P. H. Chandrasekar, B. Fox, H. Kaizer, R. K. Shadduck, T. C. Shea, P. Stiff, D. J. Friedman, et al.** 1992. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N. Engl. J. Med. **326:**845–851.
10. **Gudlaugsson, O., S. Gillespie, K. Lee, J. Vande Berg, J. Hu, S. Messer, L. Herwaldt, M. Pfaller, and D. Diekema.** 2003. Attributable mortality of nosocomial candidemia, revisited. Clin. Infect. Dis. **37:**1172–1177.

11. **Harris, A. D., J. Castro, D. C. Sheppard, Y. Carmeli, and M. H. Samore.** 1999. Risk factors for nosocomial candiduria due to *Candida glabrata* and *Candida albicans*. Clin. Infect. Dis. **29:**926–928.
12. **Hope, W., A. Morton, and D. P. Eisen.** 2002. Increase in prevalence of nosocomial non-*Candida albicans* candidaemia and the association of *Candida krusei* with fluconazole use. J. Hosp. Infect. **50:**56–65.
13. **Kaye, K. S., A. D. Harris, H. Gold, and Y. Carmeli.** 2000. Risk factors for recovery of ampicillin-sulbactam-resistant *Escherichia coli* in hospitalized patients. Antimicrob. Agents Chemother. **44:**1004–1009.
14. **Krcmery, V., and A. J. Barnes.** 2002. Non-albicans *Candida* spp. causing fungaemia: pathogenicity and antifungal resistance. J. Hosp. Infect. **50:**243–260.
15. **Laverdiere, M., C. Rotstein, E. J. Bow, R. S. Roberts, S. Ioannou, D. Carr, and N. Moghaddam.** 2000. Impact of fluconazole prophylaxis on fungal colonization and infection rates in neutropenic patients. The Canadian Fluconazole Study. J. Antimicrob. Chemother. **46:**1001–1008.
16. **Merz, W. G., J. E. Karp, D. Schron, and R. Saral.** 1986. Increased incidence of fungemia caused by *Candida krusei*. J. Clin. Microbiol. **24:**581–584.
17. **Nguyen, M. H., J. E. Peacock, Jr., A. J. Morris, D. C. Tanner, M. L. Nguyen, D. R. Snydman, M. M. Wagener, M. G. Rinaldi, and V. L. Yu.** 1996. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am. J. Med. **100:**617–623.
18. **Pfaller, M. A., D. J. Diekema, R. N. Jones, S. A. Messer, and R. J. Hollis.** 2002. Trends in antifungal susceptibility of *Candida* spp. isolated from pediatric and adult patients with bloodstream infections: SENTRY Antimicrobial Surveillance Program, 1997 to 2000. J. Clin. Microbiol. **40:**852–856.
19. **Pfaller, M. A., S. A. Messer, R. J. Hollis, R. N. Jones, and D. J. Diekema.** 2002. In vitro activities of ravuconazole and voriconazole compared with those of four approved systemic antifungal agents against 6,970 clinical isolates of *Candida* spp. Antimicrob. Agents Chemother. **46:**1723–1727.
20. **Powderly, W. G., D. Finkelstein, J. Feinberg, P. Frame, W. He, C. van der Horst, S. L. Koletar, M. E. Eyster, J. Carey, H. Waskin, et al.** 1995. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. N. Engl. J. Med. **332:**700–705.
21. **Puzniak, L., S. Teutsch, W. Powderly, and L. Polish.** 2004. Has the epidemiology of nosocomial candidemia changed? Infect. Control Hosp. Epidemiol. **25:**628–633.
22. **Richards, M. J., J. R. Edwards, D. H. Culver, and R. P. Gaynes.** 2000. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect. Control Hosp. Epidemiol. **21:**510–515.
23. **Rubin, D. B.** 1997. Estimating causal effects from large data sets using propensity scores. Ann. Intern. Med. **127:**757–763.
24. **Samonis, G., A. Gikas, E. J. Anaissie, G. Vrenzos, S. Maraki, Y. Tselentis, and G. P. Bodey.** 1993. Prospective evaluation of effects of broad-spectrum antibiotics on gastrointestinal yeast colonization of humans. Antimicrob. Agents Chemother. **37:**51–53.
25. **Shakir, B. S., M. V. Martin, and C. J. Smith.** 1983. Relative effectiveness of various yeasts, Candida spp. and *Torulopsis glabrata*, for inducing palatal infection in the Wistar rat. Arch. Oral Biol. **28:**1069–1071.
26. **Singh, N., M. J. Barnish, S. Berman, B. Bender, M. M. Wagener, M. G. Rinaldi, and V. L. Yu.** 1996. Low-dose fluconazole as primary prophylaxis for cryptococcal infection in AIDS patients with CD4 cell counts of < or = 100/mm^3: demonstration of efficacy in a positive, multicenter trial. Clin. Infect. Dis. **23:**1282–1286.
27. **Slavin, M. A., B. Osborne, R. Adams, M. J. Levenstein, H. G. Schoch, A. R. Feldman, J. D. Meyers, and R. A. Bowden.** 1995. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation–a prospective, randomized, double-blind study. J. Infect. Dis. **171:**1545–1552.
28. **Sobel, J. D., H. C. Wiesenfeld, M. Martens, P. Danna, T. M. Hooton, A. Rompalo, M. Sperling, C. Livengood III, B. Horowitz, J. Von Thron, L. Edwards, H. Panzer, and T. C. Chu.** 2004. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N. Engl. J. Med. **351:**876–883.
29. **Trick, W. E., S. K. Fridkin, J. R. Edwards, R. A. Hajjeh, and R. P. Gaynes.** 2002. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin. Infect. Dis. **35:**627–630.
30. **Vazquez, J. A., L. M. Dembry, V. Sanchez, M. A. Vazquez, J. D. Sobel, C. Dmuchowski, and M. J. Zervos.** 1998. Nosocomial *Candida glabrata* colonization: an epidemiologic study. J. Clin. Microbiol. **36:**421–426.
31. **Vazquez, J. A., V. Sanchez, C. Dmuchowski, L. M. Dembry, J. D. Sobel, and M. J. Zervos.** 1993. Nosocomial acquisition of *Candida albicans*: an epidemiologic study. J. Infect. Dis. **168:**195–201.
32. **Weber, S. G., H. S. Gold, D. C. Hooper, A. W. Karchmer, and Y. Carmeli.** 2003. Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized patients. Emerg. Infect. Dis. **9:**1415–1422.
33. **Wenzel, R. P.** 1995. Nosocomial candidemia: risk factors and attributable mortality. Clin. Infect. Dis. **20:**1531–1534.
34. **Wey, S. B., M. Mori, M. A. Pfaller, R. F. Woolson, and R. P. Wenzel.** 1989. Risk factors for hospital-acquired candidemia. A matched case-control study. Arch. Intern. Med. **149:**2349–2353.
35. **White, M. H.** 1997. The contribution of fluconazole to the changing epidemiology of invasive candidal infections. Clin. Infect. Dis. **24:**1129–1130.
36. **Wingard, J. R.** 1995. Importance of *Candida* species other than *C. albicans* as pathogens in oncology patients. Clin. Infect. Dis. **20:**115–125.
37. **Wingard, J. R., W. G. Merz, M. G. Rinaldi, T. R. Johnson, J. E. Karp, and R. Saral.** 1991. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N. Engl. J. Med. **325:**1274–1277.
38. **Wingard, J. R., W. G. Merz, M. G. Rinaldi, C. B. Miller, J. E. Karp, and R. Saral.** 1993. Association of *Torulopsis glabrata* infections with fluconazole prophylaxis in neutropenic bone marrow transplant patients. Antimicrob. Agents Chemother. **37:**1847–1849.
39. **Winston, D. J., P. H. Chandrasekar, H. M. Lazarus, J. L. Goodman, J. L. Silber, H. Horowitz, R. K. Shadduck, C. S. Rosenfeld, W. G. Ho, M. Z. Islam, et al.** 1993. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. Ann. Intern. Med. **118:**495–503.
40. **Winston, D. J., A. Pakrasi, and R. W. Busuttil.** 1999. Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. **131:**729–737.