

# Risk Factors for Fluconazole-Resistant *Candida glabrata* Bloodstream Infections

Ingi Lee, MD, MSCE; Neil O. Fishman, MD; Theoklis E. Zaoutis, MD, MSCE; Knashawn H. Morales, ScD; Mark G. Weiner, MD; Marie Synnestevedt, PhD; Irving Nachamkin, DrPH, MPH; Ebbing Lautenbach, MD, MPH, MSCE

**Background:** Bloodstream infections (BSIs) caused by *Candida glabrata* have increased substantially. *Candida glabrata* is often associated with resistance to fluconazole therapy. However, to our knowledge, risk factors for fluconazole-resistant *C glabrata* BSIs have not been studied.

**Methods:** A case-case-control study was conducted at 3 hospitals from January 1, 2003, to May 31, 2007. The 2 case groups included patients with fluconazole-resistant *C glabrata* BSIs (minimum inhibitory concentration  $\geq 16$   $\mu\text{g/mL}$ ) and patients with fluconazole-susceptible *C glabrata* BSIs (minimum inhibitory concentration  $\leq 8$   $\mu\text{g/mL}$ ). Hospitalized patients without *C glabrata* BSIs were randomly selected for inclusion in the control group and were frequency matched to cases on the basis of time at risk. Two case-control studies were performed using this shared control group. The primary risk factor of interest, previous fluconazole use, was evaluated at multivariate analyses, adjusting for

demographic data, comorbid conditions, and antimicrobial exposures.

**Results:** We included 76 patients with fluconazole-resistant *C glabrata* BSIs, 68 patients with fluconazole-susceptible *C glabrata* BSIs, and 512 control patients. Previous fluconazole use (adjusted odds ratio [95% confidence interval], 2.3 [1.3-4.2]) and linezolid use (4.6 [2.2-9.3]) were independent risk factors for fluconazole-resistant *C glabrata* BSIs; previous cefepime use (2.2 [1.2-3.9]) and metronidazole use (2.0 [1.1-3.5]) were independent risk factors for fluconazole-susceptible *C glabrata* BSIs.

**Conclusions:** Previous fluconazole use is a significant risk factor for health care-associated fluconazole-resistant *C glabrata* BSIs. Future studies will be needed to evaluate the effect of decreasing fluconazole use on rates of fluconazole-resistant *C glabrata* BSIs.

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**C**ANDIDA SPECIES ARE THE fourth leading cause of health care-associated bloodstream infections (BSIs) and are associated with significant morbidity and mortality.<sup>1-3</sup> In the United States, there has been a notable shift in the epidemiology of *Candida* BSIs. Bloodstream infections caused by *Candida albicans* have dramatically decreased, and there has been a concomitant increase in certain non-*C albicans* species, in particular, *Candida glabrata*.<sup>4-7</sup>

Historically, fluconazole has been the treatment of choice for *Candida*-related BSIs. However, unlike BSIs caused by *C albicans*, which are almost always fluconazole-susceptible, *C glabrata* BSIs are often associated with fluconazole resistance. The emergence of fluconazole-resistant *C glabrata* BSIs has had important implications because therapy requires higher doses of fluconazole or the use of other antifungal agents such as echinocandins or polyenes.<sup>8</sup>

Fluconazole use has been hypothesized as an important risk factor in the emergence of *C glabrata* infections. Resistance could be induced either by promot-

ing the development of 1 or more resistance mechanisms including upregulating efflux pumps of the adenosine triphosphate-binding cassette transporter family or by altering patient endogenous flora, enabling colonization and subsequent infection with fluconazole-resistant *C glabrata*.<sup>9,10</sup> Although biological plausibility exists, previous studies have reported conflicting results.<sup>11-15</sup> One limitation of those studies is the absence of susceptibility testing to differentiate fluconazole-resistant from fluconazole-susceptible *C glabrata* even though resistance is the main concern with *C glabrata*. We therefore conducted this case-case-control study, which, to our knowledge, is the first to evaluate independent risk factors for BSIs caused by fluconazole-resistant *C glabrata*.

## METHODS

### STUDY DESIGN AND SETTING

This study was conducted at 3 hospitals in the University of Pennsylvania Health System: the Hospital of the University of Pennsylvania, a 625-bed academic tertiary- and quaternary-care medical center; Penn Presbyterian Medi-

Author Affiliations are listed at the end of this article.

cal Center, a 324-bed urban community hospital; and Pennsylvania Hospital, a 481-bed urban community hospital.

We used a case-case-control study design in which 2 parallel case-control studies were conducted using a shared control group.<sup>16</sup> The first case-control study compared patients with fluconazole-resistant *C glabrata* BSIs with a random sample of uninfected control subjects. The second case-control study compared patients with fluconazole-susceptible *C glabrata* BSIs with the same control group.

## STUDY POPULATION

Case subjects were identified through the Hospital of the University of Pennsylvania Clinical Microbiology Laboratory, which began susceptibility testing of all *C glabrata* bloodstream isolates from the 3 involved hospitals in January 1, 2003. *Candida glabrata* was identified by macroscopic and microscopic morphologic features in addition to a positive reaction using the Rapid Assimilation of Trehalose Test (Hardy Diagnostics, Santa Maria, California).<sup>17</sup> Fluconazole susceptibility was performed using Sensititre YeastOne (TREK Diagnostic Systems, Inc, Cleveland, Ohio) in accord with criteria from the Clinical Laboratory Standards Institute.<sup>18</sup> Patients in whom *C glabrata* bloodstream isolates were detected between January 1, 2003, and May 31, 2007, with minimum inhibitory concentration (MIC) of 16 µg/mL or greater were eligible for inclusion in the fluconazole-resistant *C glabrata* case group. Patients with isolates with MIC of 8 µg/mL or less were eligible for the fluconazole-susceptible *C glabrata* case group.<sup>18</sup> Dose-dependent susceptible isolates (MIC of 16-32 µg/mL), which have reduced fluconazole susceptibility and are, therefore, treated with higher fluconazole doses or different antifungal agents than are used to treat *C albicans* or fluconazole-susceptible *C glabrata* BSIs, were included in the fluconazole-resistant *C glabrata* case group.

Inclusion was limited to health care-associated BSIs, defined as *C glabrata* BSIs that developed after at least 48 hours of hospitalization or within 48 hours in patients who fulfilled at least 1 of the following criteria: (1) receipt within the previous 30 days of intravenous treatment, home health care services, or outpatient hemodialysis or (2) residence for at least 2 of the previous 90 days in a hospital, nursing home, or long-term care facility.<sup>19</sup> Each patient was included only once, and only the initial episode of *C glabrata* BSI was reviewed. Patients admitted with outpatient blood cultures positive for *C glabrata* were excluded.

Hospitalized patients without *C glabrata* BSIs were eligible for inclusion in the control group. Control subjects were selected using a computer-generated random-number table and were frequency matched to case subjects by quartiles on the basis of time at risk. Time at risk was defined as the number of days from admission to a blood culture positive for *C glabrata* in the case groups and the number of days from admission to discharge in the control group. The number of control subjects selected was approximately 4-fold the total number of case subjects.

## DATA COLLECTION

Data were abstracted from the Pennsylvania Integrated Clinical and Administrative Research Database, which includes demographic, pharmacy, laboratory, and billing information for more than 800 000 patients with more than 31 000 admissions. This database has been successfully used in studies of antimicrobial resistance.<sup>20,21</sup>

The following data were collected for all subjects: age, sex, race/ethnicity, hospital, time at risk, and comorbid conditions including cancer, cirrhosis, neutropenia (white blood cell count ≤1000/µL or *International Classification of Diseases, Ninth Revision* code), human immunodeficiency virus infection, solid-

organ transplantation, hematopoietic stem cell transplantation, and end-stage renal disease requiring dialysis.

The following variables were collected if they occurred within 30 days preceding a blood culture positive for *C glabrata* in the case groups or the date of discharge in the control group: receipt of chemotherapy, immunosuppression, antibiotic therapy, or total parenteral nutrition, and stay in the intensive care unit. The following antimicrobial agents were assessed individually<sup>22</sup>: amikacin, amoxicillin, amoxicillin-clavulanate, amphotericin, ampicillin, ampicillin-sulbactam, azithromycin, aztreonam, caspofungin, cephalixin, ceftazidime, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, fluconazole, gentamicin, imipenem, kanamycin, levofloxacin, linezolid, meropenem, metronidazole, nafcillin, ofloxacin, penicillin, piperacillin, piperacillin-tazobactam, quinupristin-dalfopristin, tobramycin, trimethoprim-sulfamethoxazole, vancomycin, and voriconazole.

## STATISTICAL ANALYSIS

Bivariate analyses were conducted for each case-control study to identify potential risk factors for fluconazole-resistant and fluconazole-susceptible *C glabrata* BSIs. The  $\chi^2$  or Fisher exact test was used for categorical variables, and the *t* test or Wilcoxon rank sum test was used for continuous variables. The primary association of interest (ie, previous fluconazole use and fluconazole-resistant *C glabrata* BSIs) was stratified by hospital, year of hospitalization, oncologic status, and receipt of chemotherapy.

Adjusted odds ratios (ORs) were calculated using multiple logistic regression. The first multivariate model identified independent risk factors for fluconazole-resistant *C glabrata* BSIs, and the second model evaluated independent risk factors for fluconazole-susceptible *C glabrata* BSIs. Both models included fluconazole as the primary risk factor of interest. Variables with *P* values ≤.20 at bivariate analyses were included separately in multivariate modeling and maintained if their inclusion changed the OR for the primary risk factor of interest by 15% or greater.<sup>23</sup> We qualitatively compared the adjusted OR of the 2 models to identify risk factors unique to fluconazole-resistant vs fluconazole-susceptible *C glabrata* BSIs. Subgroup analysis of the first multivariate model, in which the fluconazole-resistant *C glabrata* case group was limited to isolates with an MIC of 64 µg/mL or higher, was also performed. All statistical calculations were performed using commercially available software (STATA version 10.0; Stata Corp LP, College Station, Texas).

## RESULTS

We identified 76 patients with fluconazole-resistant *C glabrata* BSIs and 68 patients with fluconazole-susceptible *C glabrata* BSIs. The control group included 512 patients without *C glabrata* BSIs. Of patients with *C glabrata* BSIs, half were from the Hospital of the University of Pennsylvania, where 45% of the isolates were fluconazole-resistant and one-fourth each were from Pennsylvania Presbyterian Medical Center and Pennsylvania Hospital, where 60% to 62% of isolates were fluconazole-resistant.

Results at bivariate analyses are given in **Table 1** and **Table 2**. Patients with fluconazole-resistant *C glabrata* BSIs were more likely to have previously used fluconazole (unadjusted OR [95% CI], 4.6 [2.6-8.0]; *P* < .001), less likely to have been hospitalized at the Hospital of the University of Pennsylvania (0.6 [0.3-0.9]; *P* = .02), and had significantly longer median time at risk (23 vs 17 days;

**Table 1. Unadjusted Risk Factors for Fluconazole-Resistant *Candida glabrata* Bloodstream Infections**

Variable <sup>a</sup>	No. (%)		OR (95% CI)	P Value
	Fluconazole-Resistant <i>C glabrata</i> Case Group (n=76)	Control Group (n=512)		
Age, median (interquartile range), y	63 (55-74)	60 (46-74)	...	.07
Male sex	31 (40.8)	268 (52.3)	0.6 (0.4-1.1)	.06
HUP	34 (44.7)	303 (59.2)	0.6 (0.3-0.9)	.02
Time at risk, median (interquartile range), d	23 (12-44)	17 (9-27)	...	.003
Cirrhosis	5 (6.6)	16 (3.1)	2.2 (0.6-6.5)	.17
Dialysis	4 (5.3)	10 (2.0)	2.8 (0.6-10.0)	.09
TPN	5 (6.6)	6 (1.2)	5.9 (1.4-23.9)	.008
Therapy				
Amphotericin	5 (6.6)	11 (2.2)	3.2 (0.8-10.4)	.04
Ampicillin	1 (1.3)	27 (5.3)	0.2 (0.006-1.5)	.16
Ampicillin-sulbactam	15 (19.7)	47 (9.2)	2.4 (1.2-4.7)	.005
Caspofungin	3 (4.0)	9 (1.8)	2.3 (0.4-9.5)	.19
Cefazolin	6 (7.9)	19 (3.7)	2.2 (0.7-6.0)	.12
Cefepime	38 (50.0)	125 (24.4)	3.1 (1.8-5.2)	<.001
Fluconazole	31 (40.8)	67 (13.1)	4.6 (2.6-8.0)	<.001
Gentamicin	20 (26.3)	86 (16.8)	1.8 (1.0-3.2)	.04
Imipenem	3 (4.0)	3 (0.6)	7.0 (0.9-52.7)	.03
Levofloxacin	27 (35.5)	115 (22.5)	1.9 (1.1-3.3)	.01
Linezolid	22 (29.0)	23 (4.5)	8.7 (4.3-17.4)	<.001
Meropenem	5 (6.6)	17 (3.3)	2.0 (0.6-6.0)	.19
Metronidazole	43 (56.6)	164 (32.0)	2.8 (1.6-4.7)	<.001
Piperacillin-tazobactam	14 (18.4)	52 (10.2)	2.0 (1.0-3.9)	.03
Vancomycin	49 (64.5)	199 (38.9)	2.9 (1.7-4.9)	<.001

Abbreviations: CI, confidence interval; HUP, Hospital of the University of Pennsylvania; OR, odds ratio; TPN, total parenteral nutrition; ellipses, ORs unavailable for continuous variables.

<sup>a</sup>Only those variables with *P* values less than or equal to .20 are included. The following variables were also assessed: race/ethnicity, human immunodeficiency virus, malignancy, neutropenia, solid-organ transplantation, hematopoietic stem cell transplantation, chemotherapy, intensive care unit stay, and therapy with amikacin, amoxicillin, amoxicillin-clavulanate, azithromycin, aztreonam, ceftazidime, ceftriaxone, cephalexin, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, kanamycin, nafcillin, ofloxacin, penicillin, piperacillin, quinupristin-dalfopristin, tobramycin, trimethoprim-sulfamethoxazole, and voriconazole.

**Table 2. Unadjusted Risk Factors for Fluconazole-Susceptible *Candida glabrata* Bloodstream Infections**

Variable <sup>a</sup>	No. (%)		OR (95% CI)	P Value
	Fluconazole-Susceptible <i>C glabrata</i> Case Group (n=68)	Control Group (n=512)		
Time at risk, median (interquartile range), d	15 (5-24)	17 (9-27)	...	.13
Malignant neoplasm	8 (11.8)	93 (18.2)	0.6 (0.2-1.3)	.19
Cirrhosis	5 (7.4)	16 (3.1)	2.5 (0.7-7.3)	.09
Therapy				
Cefepime	34 (50.0)	125 (24.4)	3.1 (1.8-5.4)	<.001
Fluconazole	16 (23.5)	67 (13.1)	2.0 (1.0-3.9)	.02
Imipenem	2 (2.9)	3 (0.6)	5.1 (0.4-45.5)	.11
Dialysis	3 (4.4)	10 (2.0)	2.3 (0.4-9.3)	.19
Immunosuppression	21 (30.9)	98 (19.1)	1.9 (1.0-3.4)	.02
Linezolid	7 (10.3)	23 (4.5)	2.4 (0.8-6.2)	.07
Metronidazole	39 (57.4)	164 (32.0)	2.9 (1.7-5.0)	<.001
TMP-SMZ	3 (4.4)	59 (11.5)	0.4 (0.07-1.1)	.07
TPN	4 (5.9)	6 (1.2)	5.3 (1.1-22.8)	.02
Vancomycin	39 (57.4)	199 (38.9)	2.1 (1.2-3.7)	.004

Abbreviations: CI, confidence interval; OR, odds ratio; TMP-SMZ, trimethoprim-sulfamethoxazole; TPN, total parenteral nutrition; ellipses, ORs unavailable for continuous variables.

<sup>a</sup>Only those variables with *P* values less than or equal to .20 are included. The following variables were also assessed: age, sex, race/ethnicity, hospital, human immunodeficiency virus, neutropenia, solid-organ transplantation, hematopoietic stem cell transplantation, chemotherapy, intensive care unit stay, and therapy with amikacin, amoxicillin, amoxicillin-clavulanate, amphotericin, ampicillin, ampicillin-sulbactam, azithromycin, aztreonam, caspofungin, cefazolin, ceftazidime, ceftriaxone, cephalexin, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, gentamicin, kanamycin, levofloxacin, meropenem, nafcillin, ofloxacin, penicillin, piperacillin, piperacillin-tazobactam, quinupristin-dalfopristin, tobramycin, and voriconazole.

*P* = .003). Previous fluconazole use was also significantly associated with fluconazole-susceptible *C glabrata* BSIs (unadjusted OR [95% CI], 2.0 [1.0-3.9]; *P* = .02). There was no effect modification by year, hospital, oncologic status,

or chemotherapy status found in either of the case-control studies.

At multivariate analyses, previous fluconazole use (adjusted OR, 2.3 [1.3-4.2]; *P* = .007) and linezolid use (4.6

**Table 3. Adjusted Risk Factors for *Candida glabrata* Bloodstream Infections**

Variable	Adjusted OR (95% CI); P Value <sup>a</sup>	
	Fluconazole-Resistant <i>C glabrata</i> Case Group	Fluconazole-Susceptible <i>C glabrata</i> Case Group
Time at risk	1.0 (1.0-1.0); .16	...
Therapy		
Cefepime	1.6 (0.9-2.9); .09	2.2 (1.2-3.9); .007
Fluconazole	2.3 (1.3-4.2); .007	1.2 (0.6-2.4); .53
Linezolid	4.6 (2.2-9.3); <.001	...
Metronidazole	1.5 (0.8-2.6); .18	2.0 (1.1-3.5); .02
Vancomycin	1.3 (0.7-2.4); .35	1.3 (0.7-2.3); .34

Abbreviations: CI, confidence interval; OR, odds ratio; ellipses, variable not included in the multivariate model.

<sup>a</sup>Both case groups were independently compared with the control group.

[2.2-9.3];  $P < .001$ ) were independent risk factors for fluconazole-resistant *C glabrata* BSIs (Table 3). In the subgroup analysis, in which fluconazole-resistant *C glabrata* was limited to those isolates with MIC greater than or equal to 64  $\mu\text{g/mL}$  ( $n = 19$ ), previous fluconazole use (5.2 [1.8-15.6];  $P = .003$ ), linezolid use (6 [1.4-14.5];  $P = .01$ ), and time at risk (1.02 [1.01-1.04];  $P = .009$ ) were independent risk factors. Previous cefepime use (adjusted OR [95% CI], 2.2 [1.2-3.9];  $P = .007$ ) and metronidazole use (2.0 [1.1-3.5];  $P = .02$ ) were independent risk factors for fluconazole-susceptible *C glabrata* BSIs (Table 3).

#### COMMENT

To our knowledge, the present study is the first to evaluate independent risk factors for fluconazole-resistant *C glabrata* BSIs. We found that previous fluconazole use and linezolid use were independent risk factors for fluconazole-resistant *C glabrata* BSIs. Previous cefepime use and metronidazole use were independent risk factors for fluconazole-susceptible *C glabrata* BSIs.

Previous fluconazole use could promote either de novo resistance by 1 or more mechanisms including upregulating efflux pumps or resistance by changing a patient's endogenous flora, enabling colonization and infection with fluconazole-resistant *C glabrata*.<sup>9,10</sup> Our results are similar to those of 2 previous studies in patients with cancer that identified previous fluconazole use as a risk factor for invasive *C glabrata* infections (OR, 5-11).<sup>11,12</sup> However, subsequent studies that broadened the study population to include the general inpatient population did not find this association. Several ecologic studies did not enable identification of significant increases in *C glabrata* BSIs despite significant increases in fluconazole use.<sup>13,14</sup> A case-case-control study by Lin et al<sup>15</sup> found that previous fluconazole use was not a risk factor for *C glabrata* and *Candida krusei* BSIs at bivariate or multivariate analyses. Malani et al<sup>24</sup> reported no difference in fluconazole-resistance rates between patients with and without previous fluconazole exposure. Limitations of the study by Malani et al, however, include that multivariate analysis was not performed and that the study may not have been powered to detect this difference.

The difference between the present study and previous studies in general inpatient populations may be related to case group selection. Although previous studies focused on *C glabrata* because of its association with fluconazole resistance, susceptibility testing was typically absent. Both patients with fluconazole-resistant and fluconazole-susceptible isolates were included in the case group. This may have decreased the ability to detect risk factors for fluconazole-resistant *C glabrata*, particularly given the results of this study, which found that previous fluconazole use was significantly associated with fluconazole-resistant *C glabrata* BSIs but not with fluconazole-susceptible *C glabrata* BSIs. High rates of fluconazole use in patients with cancer, however, may have resulted in higher rates of resistance in this population, enabling the investigators to find a strong association.

Linezolid use was also identified as an independent risk factor for fluconazole-resistant *C glabrata* BSIs. Linezolid has broad gram-positive coverage that could alter skin and possibly gastrointestinal flora such as *Enterococcus* species, enabling colonization and subsequent infection with fluconazole-resistant *C glabrata*. Lin et al<sup>15</sup> found vancomycin, another antibiotic with broad gram-positive coverage, to be an independent risk factor for *C glabrata* and *C krusei* BSIs.

Cefepime use and metronidazole use were found to be independent risk factors for fluconazole-susceptible *C glabrata* BSIs. Lin et al<sup>15</sup> identified piperacillin-tazobactam, an antimicrobial agent with both gram-negative and anaerobic coverage, as a significant risk factor for *C glabrata* and *C krusei* BSIs. Animal models have suggested that *C glabrata* may have fewer virulence factors.<sup>25,26</sup> If *C glabrata* is less pathogenic than *C albicans*, *C glabrata* may require selection pressure from antecedent antibiotic use for colonization and infection. Previous studies have also suggested that *Candida* infections can occur via horizontal transfer, and this mode of transmission may be particularly important in *C glabrata* infections, the incidence of which increases with age.<sup>27,28</sup>

There are several potential limitations of the present study. Misclassification of risk factors is possible because data were not collected prospectively (ie, the database may be missing comorbid conditions not identified via *International Classification of Diseases, Ninth Revision*, coding and medications prescribed outside of the University of Pennsylvania Health System). However, the percentage of missing data is unlikely to be dissimilar between groups, and this nondifferential misclassification would bias results toward null. In addition, the study was conducted in 3 hospitals in the same city. Geographic and hospital-associated differences in the susceptibility patterns of *C glabrata* have been previously demonstrated.<sup>2,29</sup>

To our knowledge, the present study is the first to evaluate independent risk factors for fluconazole-resistant *C glabrata* BSIs and to identify previous fluconazole use as a significant risk factor for resistance in the general inpatient population. Future studies will be needed to identify the effect of decreasing fluconazole use on the rates of fluconazole-resistant *C glabrata* BSIs.

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Author Affiliations: Divisions of Infectious Diseases,

(Drs Lee, Fishman, and Lautenbach), and General Internal Medicine (Dr Weiner), Department of Medicine, Departments of Biostatistics and Epidemiology (Dr Morales) and Pathology and Laboratory Medicine (Dr Nachamkin), Centers for Clinical Epidemiology and Biostatistics (Drs Lee, Fishman, Zaoutis, Morales, Weiner, and Lautenbach) and Education and Research on Therapeutics (Drs Lee, Fishman, Zaoutis, Nachamkin, and Lautenbach), and Office of Human Research (Dr Synnestvedt), University of Pennsylvania School of Medicine, Philadelphia; and Division of Infectious Diseases, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia (Dr Zaoutis).

**Correspondence:** Ingi Lee, MD, MSCE, Division of Infectious Diseases, Department of Medicine, Hospital of the University of Pennsylvania, 3400 Spruce St, Third Floor, Silverstein Bldg, Ste E, Philadelphia, PA 19104 (ingi.lee@uphs.upenn.edu).

**Author Contributions:** Dr Lee had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Lee, Fishman, Zaoutis, and Lautenbach. *Acquisition of data:* Lee, Weiner, Synnestvedt, and Nachamkin. *Analysis and interpretation of data:* Lee, Morales, and Lautenbach. *Drafting of the manuscript:* Lee and Lautenbach. *Critical revision of the manuscript for important intellectual content:* Lee, Fishman, Zaoutis, Morales, Weiner, Synnestvedt, Nachamkin, and Lautenbach. *Statistical analysis:* Lee, Morales, and Lautenbach. *Obtained funding:* Lee. *Administrative, technical, and material support:* Lee, Weiner, Synnestvedt, and Nachamkin. *Study supervision:* Fishman, Zaoutis, and Lautenbach.

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## REFERENCES

- Rentz AM, Halpern M, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. *Clin Infect Dis*. 1998;27(4):781-788.
- Pfaller MA, Diekema D. Epidemiology of invasive candidiasis: a persistent public health problem [published corrections appear in *Clin Infect Dis*. 2004; 39(7): 1093 and 2005;40(7):1077]. *Clin Microbiol Rev*. 2007;20(1):133-163.
- Wisplinghoff H, Bischoff T, Tallent S, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals. [published corrections appeared in *Clin Infect Dis*. 2004;39(7):1093 and 2005;40(7):1077]. *Clin Infect Dis*. 2004;39(3): 309-317.
- Rangel-Frausto MS, Wiblin T, Blumberg H, et al. National Epidemiology of Mycoses Survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units and six neonatal intensive care units. *Clin Infect Dis*. 1999;29(2):253-258.
- Baddley JW, Smith A, Moser S, Pappas P. Trends in frequency and susceptibilities of *Candida glabrata* bloodstream isolates at a university hospital. *Diagn Microbiol Infect Dis*. 2001;39(3):199-201.
- Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA*. 1994; 271(20):1598-1601.
- Trick WE, Fridkin S, Edwards J, Hajjeh R, Gaynes R; National Nosocomial Infections Surveillance System Hospitals. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989-1999. *Clin Infect Dis*. 2002;35(5):627-630.
- Pappas PG, Rex J, Sobel J, et al; Infectious Diseases Society of America. Guidelines for treatment of candidiasis. *Clin Infect Dis*. 2004;38(2):161-189.
- Sanguinetti M, Posteraro B, Fiori B, Ranno S, Torelli R, Fadda G. Mechanisms of azole resistance in clinical isolates of *Candida glabrata* collected during a hospital survey of antifungal resistance. *Antimicrob Agents Chemother*. 2005;49(2):668-679.
- Kontoyiannis DP, Lewis R. Antifungal drug resistance of pathogenic fungi. *Lancet*. 2002;359(9312):1135-1144.
- Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. *Clin Infect Dis*. 1997;24(6):1122-1128.
- Bodey GP, Mardani M, Hanna H, et al. The epidemiology of *Candida glabrata* and *Candida albicans* fungemia in immunocompromised patients with cancer. *Am J Med*. 2002;112(5):380-385.
- Asmundsdóttir LR, Erlendsdóttir H, Gottfredsson M. Increasing incidence of candidemia. *J Clin Microbiol*. 2002;40(9):3489-3492.
- Marchetti O, Bille J, Fluckiger U, et al; Fungal Infection Network of Switzerland. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991-2000. *Clin Infect Dis*. 2004;38(3):311-320.
- Lin MY, Carmeli Y, Zumsteg J, et al. Prior antimicrobial therapy and risk for hospital-acquired *Candida glabrata* and *Candida krusei* fungemia: a case-case-control study. *Antimicrob Agents Chemother*. 2005;49(11):4555-4560.
- Kaye KS, Harris A, Samore M, Carmeli Y. The case-case-control study design: addressing the limitations of risk factor studies for antimicrobial resistance. *Infect Control Hosp Epidemiol*. 2005;26(4):346-351.
- Larone D. *Medically Important Fungi: A Guide to Identification*. 4th ed. Washington, DC: ASM Press; 2002.
- National Committee for Clinical Laboratory Standards. *Methods for Antifungal Disk Diffusion Susceptibility Testing of Yeasts: Approved Guideline, M44-A*. Wayne, PA: National Committee for Clinical Laboratory Standards; 2004.
- McDonald JR, Friedman ND, Stout JE, Sexton DJ, Kaye KS. Risk factors for ineffective therapy in patients with bloodstream infections. *Arch Intern Med*. 2005; 165(3):308-313.
- Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fishman NO. Imipenem resistance among *Pseudomonas aeruginosa* isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. *Infect Control Hosp Epidemiol*. 2006;27(9):893-900.
- Gasink L, Fishman N, Weiner M, Nachamkin I, Bilker W, Lautenbach E. Fluoroquinolone-resistant *Pseudomonas aeruginosa*: assessment of risk factors and clinical impact. *Am J Med*. 2006;119(6):526.e19-526.e25.
- MacAdam H, Zaoutis TE, Gasink LB, Bilker WB, Lautenbach E. Investigating the association between antibiotic use and antibiotic resistance. *Int J Antimicrob Agents*. 2006;28(4):325-332.
- Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation [published correction appears in *Am J Epidemiol*. 1989;130(5):1066]. *Am J Epidemiol*. 1989;129(1):125-137.
- Malani A, Hmoud J, Chiu L, Carver PL, Bielaczyc A, Kauffman C. *Candida glabrata* fungemia. *Clin Infect Dis*. 2005;41(7):975-981.
- Fidel PL Jr, Vazquez JA, Sobel JD. *Candida glabrata*: review of epidemiology, pathogenesis, and clinical disease with comparison to *C. albicans*. *Clin Microbiol Rev*. 1999; 12(1):80-96.
- Fidel PL Jr, Cutright JL, Tait L, Sobel JD. A murine model of *Candida glabrata* vaginitis. *J Infect Dis*. 1996;173(2):425-431.
- Vazquez JA, Dembry LM, Sanchez V, et al. Nosocomial *Candida glabrata* colonization: an epidemiologic study. *J Clin Microbiol*. 1998;36(2):421-426.
- Pfaller MA, Diekema DJ. Role of sentinel surveillance of candidemia: trends in species distribution and antifungal susceptibility. *J Clin Microbiol*. 2002;40(10):3551-3557.
- Pfaller MA, Diekema DJ. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*. *Clin Microbiol Infect*. 2004;10(suppl 1):11-23.