Antibiotic exposure as a risk factor for fluconazole-resistant Candida spp. bloodstream infection

Running head: fluconazole-resistant candidemia

Ronen Ben-Ami¹, Karen Olshtain-Pops², Michal Krieger³, Ilana Oren⁴, Jihad Bishara⁵, Michael Dan⁶, Yonit Wiener-Well⁷, Miriam Weinberger⁸, Oren Zimhony⁹, Michal Chowers¹⁰, Gabriel Weber¹¹, Israel Potasman¹², Bibiana Chazeran¹³, Imad Kassis⁴, Itamar Shalit⁵, Colin Block², Nathan Keller³, Dimitrios P. Kontoyiannis¹⁴, Michael Giladi¹ for Israeli Candidemia Study Group*
Center, Afula and Ziv Medical Center, Zefat, All in Israel, and MD Anderson Cancer Center, Houston, Texas, USA.

Word count: abstract, 165; text, 2509

Keywords: candidemia, fluconazole, drug resistance, Candida glabrata, antibacterial agents

Corresponding author: Ronen Ben-Ami, M.D., Infectious Disease Unit, Tel Aviv Sourasky Medical Center, 6 Weizman st., Tel Aviv 64239, Israel. Tel: +972-3-6973317. Fax: +972-3-6974996. Email: ronenba@tasmc.health.gov.il
Abstract

Recent exposure to azoles is an important risk factor for infection with fluconazole-resistant Candida spp., but little is known about the role of antibacterial drug exposure in the emergence of drug-resistant Candida. We did a prospective nationwide surveillance study of candidemia in Israel and analyzed the propensity-score adjusted association between antifungal and antibacterial drug exposure and bloodstream infection with C. glabrata and fluconazole-resistant Candida isolates. Four-hundred forty-four episodes of candidemia (450 Candida isolates, 69 [15%] C. glabrata and 38 [8.5%] fluconazole-resistant isolates) from 18 medical centers in Israel were included. C. glabrata bloodstream infection was strongly associated with recent metronidazole exposure (odds ratio, 3.2; \( P < 0.001 \)). Infection with a fluconazole-resistant isolate was associated with exposure to carbapenems, trimethoprim-sulfamethoxazole, clindamycin and colistin (odds ratio, 2.8; \( P = 0.01 \)). The inclusion of antibacterial drug exposure in a multivariable model significantly enhanced the model’s predictive accuracy for fluconazole-resistant Candida bloodstream infection. Our findings may be relevant to the selection of empirical antifungal treatment, and broaden the scope of antibiotic-associated collateral damage.
Introduction

*Candida* species have emerged as frequent causes of nosocomial bloodstream infection (BSI) in association with well-defined risk factors, including prolonged hospitalization, abdominal surgery, antibiotic treatment, neutropenia and central venous catheterization (14). Candidemia is associated with high rates of attributable mortality, prolongation of hospital stay and excessive costs (28). In recent years there has been a shift in the distribution of *Candida* species causing invasive infection, with non-*albicans* species now surpassing *C. albicans* in many institutions (14, 25). Of particular concern is the rising incidence of the azole-nonsusceptible species *C. glabrata* and the inherently fluconazole-resistant species *C. krusei* (11, 25, 27).

Fluconazole is often used as empirical treatment of candidemia. However, given the correlation between the survival rate and the timely initiation of appropriate treatment for candidemia (8), accurate assessment of the risk of fluconazole-resistant *Candida* (FRC) BSI is of prime importance. Patients who were recently treated with an azole drug are at increased risk of infection with FRC (9), and should be treated initially with an echinocandin agent according to current guidelines (18). However, experimental and clinical data support the notion that non-antifungal antimicrobial agents also affect the risk of colonization and infection with FRC (15, 17, 22). Since exposure to antibacterial drugs among at-risk patients far exceeds exposure to antifungal agents, even modest effects of individual antibacterials could translate into significant overall changes in the
susceptibility patterns of Candida spp. Nevertheless, the collateral effects of antibacterial drugs on Candida spp are poorly understood. To address this question, we analyzed prospectively-collected data from a nationwide study of candidemia in Israel and examined the association between exposure to antifungal and antibacterial agents and the risk of infection with FRC.
Methods

Study design
We performed a prospective nationwide study of candidemia in Israel from November 2005 through June 2007. Eighteen medical centers, which together account for 75% of the hospital beds in Israel, were included. All candidemia episodes that occurred in the participating centers during the study period were eligible for inclusion in this study. Clinical data were prospectively entered into standardized data forms by on-site investigators at each of the centers. The Candida spp. clinical isolates underwent preliminary identification and susceptibility testing in each center according to local practices. Subsequently, isolates were transferred together with the corresponding data forms to the central study site where species identification and susceptibility testing were performed as detailed below. Data forms were collected by the study coordinator, reviewed by the principal investigator and entered into a computerized database. The study was approved by the ethics committees of each of the participating centers.

Data collection
On-site data collection included demographics, performance status, Charlson comorbidity index (4), and the presence of any of the following conditions in the month preceding candidemia: surgery, hematopoietic stem cell or solid organ transplantation, cytotoxic chemotherapy, systemic corticosteroid treatment (a
dose equivalent to prednisone 10 mg/d for at least 14 days), neutropenia (absolute neutrophil count <500 cells/μl), indwelling central vascular catheter, urinary bladder catheter, intravenous drug abuse, prematurity, intensive care unit hospitalization, mechanical ventilation, burns or dialysis. In addition, a detailed history of antifungal and antibacterial drug use in the month preceding candidemia was obtained.

**Microbiological testing**

Species identification and susceptibility testing were performed at the central study site. All fungal isolates were maintained in sterile water at -80°C until testing. Prior to testing, each strain was passaged on Sabouraud’s dextrose agar to ensure purity and viability. Candida species were identified using standard microbiology methods, including growth on CHROMagar Candida (CHROMagar, Paris, France) and the Vitek 2 system with use of the YST-ID card (bioMerieux, Durham, NC). Susceptibility to fluconazole was determined using the E-test (AB biodisk, Sweden) method according to the manufacturer’s instructions. Susceptibility results were interpreted according to the recently revised Clinical Laboratory Standards Institute breakpoints for fluconazole (21). Specifically, for all Candida species except C. glabrata and C. krusei, fluconazole MIC breakpoints were: susceptible, ≤2 μg/mL, susceptible dose-dependent, 4-8 μg/mL, and resistant >8 μg/mL. For C. glabrata, the corresponding MIC breakpoints were <8 μg/mL, 16-32 μg/mL, and >32 μg/mL, respectively. C. krusei was considered always resistant to fluconazole. Susceptibility testing was
performed at least in duplicate for each isolate and the highest MIC was reported.

Statistical analyses

To identify predictors of FRC BSI, we first performed bivariable analyses using Chi squared and Fisher’s exact tests for categorical variables and Student’s t test for continuous variables. Variables were then tested in a multivariable logistic regression model. Variables were added individually to the regression model to confirm their association with FRC BSI. Next, the simultaneous effects of variables that were significantly associated with FRC BSI individually were modeled. The significance threshold for retaining variables in the model was $P < 0.05$. Goodness of fit for multivariable models was assessed with the Hosmer Lameshow test, and predictive accuracy was assessed by calculating the area under the receiver operator characteristics (ROC) curve.

The effect of antimicrobial drug exposure was analyzed for each drug separately, as well as for antimicrobial drug categories (β lactams, penicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, macrolides, tetracyclins and triazoles) (Table 2). Exposure to antibacterials with antianaerobic activity (metronidazole, clindamycin, carbapenems, β lactam/β lactamase inhibitor combinations and chloramphenicol) was also analyzed in aggregate.
To limit confounding by non-antibacterial risk factors, we calculated the conditional probability of recent exposure to specific antibacterial drugs based on non-antibacterial risk factors using propensity score analysis (23, 24). Propensity scores were generated using logistic regression with antibacterial drug exposure as the dependent variable. Non-antibacterial covariates were included in the multivariable model by stepwise selection with $P < 0.05$ set as the limit for inclusion in the model. We tested that the balancing property of the propensity score was satisfied by subclassification of the cohort into quintiles based on individual propensity scores. Then, using FRC BSI as the outcome variable, individual antibacterial drugs and drug-classes were analyzed using logistic regression adjusted for the propensity score and the number of days at risk. Calculations were performed with the Stata software package (version 11.1, StataCorp, College Station, TX).
Results

A total of 450 patient-specific Candida spp. bloodstream isolates from 444 patients were included in this study. Patient demographics and clinical risk factors for candidemia are summarized in Table 1. The majority of candidemia episodes (97.8%) were nosocomial; 355 (80%) occurred in hospitalized patients and 79 (17.8%) occurred in outpatients discharged from hospital within the previous 30 days, and were therefore considered healthcare-associated. C. albicans was the most frequent species (198 cases, 44.5%), followed by C. parapsilosis (n=75, 16.8%), C. tropicalis, (n=74, 16.6%), and C. glabrata (n=68, 15.3%).

Antimicrobial drug exposure. Of 444 patients in the study cohort, 410 (92.3%) received treatment with at least one antibacterial agent within 30 days prior to the onset of candidemia. The most common antibacterial agents were β-lactams (88%), vancomycin (44%), aminoglycosides (31%) and metronidazole (29%) (Table 2). Most patients (359, 81%) were exposed to multiple antibacterial drugs, either concomitantly or sequentially. Patients received a median of 3 antibacterial drugs (interquartile range, 2-4) in the month preceding candidemia. Sixty-three patients (14%) received a systemic antifungal agent within 30 days prior to candidemia, most commonly fluconazole (56 patients) or amphotericin B (8 patients).
C. glabrata BSI. There were 68 episodes of C. glabrata BSI. Bivariable analysis identified a positive association of C. glabrata infection with metronidazole exposure and a negative association with aminoglycoside exposure (Table 2). Nonantibiotic predictors of C. glabrata BSI were age ≥65 years, poor performance status, an indwelling urinary bladder catheter, residence at a long term care facility and a Charlson score of ≥1. Neutropenia and the presence of a central venous catheter were negatively associated with C. glabrata infection (Figure 1A).

On multivariable analysis, recent metronidazole exposure remained a significant predictor of C. glabrata infection (adjusted odds ratio [OR] 3.2, 95% confidence interval [CI] 1.7-6.0; \( P < 0.001 \)) together with poor performance status (OR 1.8; \( P = 0.04 \)), neutropenia (OR 0.1; \( P = 0.03 \)) and the presence of a central venous catheter (OR 0.4; \( P = 0.02 \)) (Figure 1A).

Fluconazole-resistant Candida spp. BSI. Fifty-four episodes of candidemia (12.1%) were caused by isolates nonsusceptible to fluconazole: 16 (3.6%) were susceptible dose-dependent and 38 (8.5%) were resistant to fluconazole. The 38 fluconazole-resistant bloodstream isolates were C. krusei (14 of 14 isolates), C. parapsilosis (10/75, 13.3%), C. glabrata (6/68, 8.8%), C. tropicalis (5/74, 6.7%), C. guilliermondii (2/2) and C. farinosa (1/1).
Bivariable analysis revealed a significant association between FRC BSI and exposure to TMP-SMX (OR 4.5, *P*=0.001), carbapenems (OR 2.3, *P*=0.01), clindamycin (OR 3.7, *P*=0.03), and colistin (OR 2.8, *P*=0.02). Exposure to cephalosporins was negatively associated with FRC BSI (OR 0.4, *P*=0.01) (Table 2 and Fig. 1). Exposure to antianaerobic antibiotics was associated with a non-statistically significant trend for FRC BSI (OR 2.1, *P*= 0.09).

As described in the Methods, we constructed a propensity score that predicted a patient’s likelihood of receiving any of the four antibacterial drugs associated with increased risk of FRC BSI. Non-antibacterial covariates ultimately included in the propensity score are shown in Table 3. Importantly, indices of the severity of illness at the time of candidemia (circulatory shock, renal failure and respiratory failure) were not associated with the risk of exposure to one of these antibacterial agents. In the propensity-adjusted multivariable analysis, FRC BSI remained significantly associated with exposure to one of the four antibacterial drug classes (OR 2.8, 95% CI 1.2-6.3 *P*= 0.01), together with neutropenia (OR 3.3, 95% CI 1.5-7.3; *P*= 0.002) and recent fluconazole exposure (OR 4.3, 95% CI 1.5-12.2; *P*= 0.005) (Figure 1).

To assess whether obtaining a history of recent antibacterial drug exposure can enhance the accuracy of predictive models to detect FRC BSI, we determined the incremental effect of antibacterial covariates on the area under the ROC curve. We compared the performance of three models; all included neutropenia.
as a covariate, together with previous fluconazole exposure (model 1), exposure
to antibacterial drugs (carbapenems, trimethoprim-sulfamethoxazole, clindamycin
or colistin; model 2), and exposure to fluconazole and antibacterials (model 3).
The predictive accuracy for FRC BSI, expressed as the area under the ROC
curve, was 0.67, 0.76 and 0.78 for models 1, 2 and 3 respectively, and was
significantly greater for models that included antibacterial exposure (models 2
and 3) than for the model that included only neutropenia and fluconazole
exposure (model 1; \(P = 0.003\); Fig. 2).
Discussion

In this analysis of data from a national candidemia study, we found that recent exposure to antibacterial drugs affected the risk of bloodstream infection with fluconazole-resistant *Candida* isolates. Moreover, inclusion of antibacterial drugs in a multivariable model enhanced the model’s predictive accuracy for fluconazole-resistance compared to a model based on neutropenia and azole exposure alone. These findings suggest that “collateral damage”, a term used to describe the adverse ecological effects of antibacterial drug use (19), extends beyond the selection of drug resistance among bacteria, and that antibiotic pressure may have significant effects on azole resistance in *Candida* spp.

At least four potential mechanisms may underlie the observed associations between antibacterial drug exposure and candidemia. First, by altering resident gut flora, antibacterials may selectively impair colonization-resistance in a way that favors gastrointestinal colonization with drug-resistant *Candida* species. Colonization of the gut with *Candida* spp. is an antecedent to hematogenous dissemination both in immunocompetent and neutropenic individuals (5). Specifically, antibacterial drugs with predominant effects on anaerobic bacteria, such as metronidazole and clindamycin, were shown to promote intestinal colonization by *C. glabrata* in an animal model (22). In another study, the addition of metronidazole to a gastrointestinal decontamination regimen that included ciprofloxacin and fluconazole increased intestinal yeast colonization (26). Second, many antibacterial agents have some degree of antifungal activity (1),
which could explain selective pressure similar to that induced by azole exposure.

Metronidazole is an imidazole derivative with weak in vitro activity against
*Candida* spp. but additive or synergistic fungicidal activity when combined with
amphotericin B (3, 6). TMP-SMX and the polymyxins display in vitro activity
against a variety of fungal organisms, including *Candida* spp. (2, 30). Third, some
antibacterials directly modulate azole resistance by inducing the expression of
efflux pump-encoding genes (13). Lastly, the immunomodulatory effects of
antibacterial drugs might predispose for certain fungal pathogens. For example,
sulfonamides were shown to have both inhibitory and stimulatory effects on the
host response against *Candida* spp. (7, 16), whereas fluoroquinolones had no
effect at therapeutic concentrations (10).

A number of case-control studies have reported exposure to antibacterial drugs
with an antianaerobic spectrum of activity as a risk factor for candidemia (29),
and more specifically for *C. glabrata* BSI (15, 17). Similar to our findings, Lee at
al. reported that metronidazole use was associated with fluconazole-susceptible
*C. glabrata* BSI, but not with fluconazole-resistant *C. glabrata* BSI (15).
Interestingly, 3 of the 5 antibacterial drugs linked with fluconazole-resistant
isolates in our study (metronidazole, clindamycin and carbapenems) have
significant antianaerobic activity.

A striking feature of the current cohort of patients with candidemia is the almost
universal exposure to antibacterial drugs in the preceding month. Moreover, the
majority of patients received multiple classes of antibacterials, either concomitantly or sequentially. These findings underscore the importance of addressing antibacterial burden, which in a hospitalized population frequently constitutes the sum of multiple drug effects.

Limitations of our study are inherent in its observational nature. Exposure to antibacterial drugs may reflect several confounding covariates, such as severity of illness, length of hospitalization and comorbid conditions (confounding by indication). In our patient cohort there was no significant association between the occurrence of FRC BSI or exposure to the antibacterials of interest and severity of illness. We sought to adjust for possible confounders using multivariable analyses and propensity score adjustment. Propensity score matching aims to balance confounding covariates between antibiotic treated and untreated patients. Importantly, we adjusted all risk estimates for the number of days at risk. However, even this methodology cannot correct for unknown confounders.

In addition, it should be noted that the rate of fluconazole resistance in C. glabrata isolates was lower than that reported for most populations (20). Different antibacterial drugs may affect fluconazole resistance in populations where higher C. glabrata resistance rates are observed. Thus, our predictive model should be validated for different patient cohorts. Of note, we used the recently adjusted CLSI clinical breakpoints for fluconazole and Candida susceptibility, which should increase the sensitivity of detecting emerging resistance in common Candida spp. isolates (21). Compared with previous CLSI breakpoints, use of the current
values increased the rate of fluconazole resistance in *Candida* bloodstream isolates from 5.3% to 8.5%, with the most marked increase occurring in *C. parapsilosis* (1.3% to 13.3%).

Unnecessary use of antibiotics is frequent, accounting for as much as 30% of total antimicrobial therapy days, with antianaerobic agents accounting for a third of redundant antibacterial drug use (12). It is now well recognized that antibacterial drugs promote the emergence and dissemination of multidrug resistant nosocomial bacteria in a class-specific manner (19). Selection of fluconazole-resistant invasive *Candida* strains may represent an additional adverse consequence of excessive antibiotic use. Recognizing robust associations between antibacterial drug exposure and FRC BSI should allow the implementation of improved predictive schemes to direct empirical antifungal treatment in high risk patients.
Acknowledgments

This work was funded in part by a grant from Merck Sharp & Dohme Ltd, Israel.

The authors wish to thank Anna Novikov and Nathaniel Albert for excellent technical assistance, and Esther Shabtai for statistical consultation.

Presented in part at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, Massachusetts, USA (Abstract M-1068).

Appendix: Additional Israeli Candidemia Study Group Investigators

Tel Aviv Sourasky Medical Center, Tel Aviv: Ruth Orni-Wasserlauf; Hadassah Medical Center, Jerusalem: Allon Moses, Hila Elinav; Chaim Sheba Medical Center, Tel Hashomer: Galia Rahav, Yasmin Maor, Anna Goldshmidt-Reuven; Rambam Medical Center, Haifa: Renato Finkelstein, Hannah Sprecher; Rabin Medical Center and Schneider Children's Hospital, Petah Tikva: Michal Paul, Itzhak Levi, Zmira Samra, Elad Goldberg; Wolfson Medical Center, Holon: Tamar Gottesman, Orna Schwartz-Harari; Shaare Zedek Medical Center, Jerusalem: Amos Yinon, Orli Megged; Assaf Harofeh Medical Center, Zerifin: Tsilia Lazarovitch; Kaplan Medical Center, Rehovot: Pnina Ciobotaro; Meir Medical Center, Kfar Saba: BatSheva Gottesman; Bnai Zion Medical Center, Haifa: Alona Paz; Emek Medical Center, Afula: Raul Raz, Dan Miron; Soroka Medical Center, Beer Sheva: Klaris Riesenber, Lisa Saidel; Bikur Holim Medical Center, Jerusalem: Efraim Halperin; Hillel Yafe Medical Center, Hadera: David Hassin; Poriya Medical Center, Tiberias: Soboh Soboh.
References


sulphamethoxazole against Candida albicans J Antimicrob Chemother. 10:539-
541.

combination against Candida spp. Rev IberoamMicol. 15:78-80.

new method of classifying prognostic comorbidity in longitudinal studies:

gastrointestinal tract in hematogenous candidiasis: from the laboratory to the

amphotericin B and nitroimidazoles against Candida albicans. Mycoses. 40:187-
192.

mice treated with penicillin-tetracycline or trimethoprim-sulfamethoxazole when
31:691-697.


Table 1. Demographic and clinical features of 444 patients with Candida bloodstream infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Male, N (%)</td>
<td>238 (53.6)</td>
</tr>
<tr>
<td>Sex, Female, N (%)</td>
<td>206 (46.4)</td>
</tr>
<tr>
<td>Age – years, median (interquartile range)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 years, N (%)</td>
<td>52 (11.7)</td>
</tr>
<tr>
<td>&gt; 65 years, N (%)</td>
<td>224 (50.5)</td>
</tr>
<tr>
<td>Residence at a long term care facility, N (%)</td>
<td>48 (10.8)</td>
</tr>
<tr>
<td>Performance status, Independent, N (%)</td>
<td>191 (43.0)</td>
</tr>
<tr>
<td>Performance status, Partially dependent, N (%)</td>
<td>88 (19.8)</td>
</tr>
<tr>
<td>Performance status, Completely dependent, N (%)</td>
<td>89 (20.0)</td>
</tr>
<tr>
<td>Performance status, Unknown, N (%)</td>
<td>76 (17.1)</td>
</tr>
<tr>
<td>Charlson score, median (interquartile range)</td>
<td>3 (1-5)</td>
</tr>
</tbody>
</table>

Exposure to candidemia risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use, N (%)</td>
<td>410 (92.3)</td>
</tr>
<tr>
<td>Central vascular catheter, N (%)</td>
<td>331 (74.5)</td>
</tr>
<tr>
<td>Urinary bladder catheter, N (%)</td>
<td>245 (55.1)</td>
</tr>
<tr>
<td>Parenteral nutritional support, N (%)</td>
<td>147 (33.1)</td>
</tr>
<tr>
<td>Stay at an intensive care unit, N (%)</td>
<td>197 (44.4)</td>
</tr>
<tr>
<td>Mechanical ventilation, N (%)</td>
<td>199 (44.8)</td>
</tr>
</tbody>
</table>
Surgery, N (%) 175 (39.4)
  Abdominal surgery, N (%) 87 (19.6)
  Chest surgery, N (%) 26 (5.9)
  Other surgery, N (%) 92 (20.7)
Cytotoxic chemotherapy, N (%) 82 (18.5)
Neutropenia, N (%) b 54 (12.2)
Dialysis, N (%) 39 (8.7)
Prematurity, N (%) 29 (6.5)
Stem cell transplantation, N (%) 22 (5.0)
Burns, N (%) 11 (2.5)
Systemic corticosteroids, N (%) c 7 (1.6)
Intravenous drug abuse, N (%) 7 (1.6)
Solid organ transplantation, N (%) 4 (0.9)

Severity of illness and outcome
Shock 70 (15.7)
Renal failure 35 (7.8)
Respiratory failure 40 (9.0)
In-hospital death 216 (48.7)

a Within 30 days prior to the onset of candidemia.
b Absolute neutrophil count <500 cells/μl.
Defined as a use of systemic corticosteroid at a dose equivalent to prednisone 10 mg/d for at least 14 days within the month preceding candidemia.
Table 2. Unadjusted bivariate associations between antimicrobial drug exposure and *Candida* spp. infection in 444 patient-specific episodes of bloodstream infection.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>N (%)</th>
<th>C. glabrata</th>
<th>Fluconazole-resistant <em>Candida</em> spp. a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N=68 (15.3%)</td>
<td>N=38 (8.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Odds ratio</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>All antibacterial drugs</td>
<td>410 (92)</td>
<td>1.0 (0.4-2.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>β-lactam b</td>
<td>391 (88)</td>
<td>0.9 (0.5-1.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Penicillin c</td>
<td>262 (59)</td>
<td>0.8 (0.4-1.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>β-lactam/ β-lactamase inhibitor d</td>
<td>200 (44)</td>
<td>1.0 (0.5-1.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>240 (54)</td>
<td>1.3 (0.5-1.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>152 (34)</td>
<td>0.6 (0.3-1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>94 (21)</td>
<td>0.9 (0.4-1.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>130 (29)</td>
<td><strong>2.7 (1.5-4.7)</strong></td>
<td><em>&lt;0.001</em></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>12 (2.7)</td>
<td>1.8 (0.5-6.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>22 (4.9)</td>
<td>0.8 (0.1-3.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Macrolide</td>
<td>33 (7.4)</td>
<td>1.2 (0.4-3.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>196 (44)</td>
<td>0.6 (0.3-1.06)</td>
<td>0.06</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>140 (31)</td>
<td>0.4 (0.2-0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Colistin</td>
<td>31 (6.9)</td>
<td>1.0 (0.4-2.7)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Antianaerobic agents e

<table>
<thead>
<tr>
<th></th>
<th>Count</th>
<th>Mean (Range)</th>
<th>SD</th>
<th>Median (Range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antifungal drugs f</td>
<td>63 (14)</td>
<td>1.0 (0.4-2.2)</td>
<td>0.8</td>
<td>4.8 (2.1-10.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>8 (1.8)</td>
<td>0.7 (0.01-6.2)</td>
<td>0.8</td>
<td>3.7 (0.3-21.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>56 (13)</td>
<td>1.2 (0.5-2.6)</td>
<td>0.6</td>
<td>5.0 (2.2-11.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>3 (0.7)</td>
<td>2.7 (0.04-54)</td>
<td>0.3</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>3 (0.7)</td>
<td>0 (0-7.1)</td>
<td>0.4</td>
<td>5.4 (0.09-106.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Any triazole</td>
<td>61 (14)</td>
<td>1.1 (0.4-2.4)</td>
<td>0.7</td>
<td>5.3 (2.4-11.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

a Fluconazole-resistant strains were C. krusei (n=14), C. parapsilosis (n=10), C. glabrata (n=6), C. tropicalis (n=5), C. guilliermondii (n=2) and C. farinosa (n=1).

b Includes penicillins, cephalosporins, and carbapenems.

c Includes penicillin G, penicillin VK, amoxicillin, ampicillin, and cloxacillin.

d Includes amoxicillin-clavulanic acid, ampicillin-sulbactam and piperacillin-tazobactam.

e Aggregate of antimicrobial agents with antianaerobic activity, includes metronidazole, clindamycin, carbapenems, and β-lactam/β-lactamase inhibitor combinations.

f There were no cases of candidemia in patients with exposure to echinocandins within the previous month.
Not applicable: cannot be calculated because all 3 patients with itraconazole exposure had FRC BSI.

Not shown in the Table are antibacterial agents that were given to small numbers of patients: rifampicin (8 patients), linezolid (6 patients), tetracyclines (5 patients) and nitrofurantoin (2 patients).
Table 3. Risk factors for exposure to a high-risk antibacterial drug \( ^a \) used to calculate the propensity score

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio (95% Confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary bladder catheter</td>
<td>2.2 (1.4-3.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplantation</td>
<td>3.6 (1.3-9.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>Recent azole exposure</td>
<td>2.3 (1.2-4.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Time at risk</td>
<td>1.01 (1.008-1.02)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\( ^a \) High risk antibacterial drugs were trimethoprim-sulfamethoxazole, carbapenems, clindamycin and colistin.
Figure legends

Figure 1. Association of antibiotic and non-antibiotic covariates with C. glabrata, C. krusei and fluconazole-resistant Candida bloodstream infection

Forest plots showing the associations of antibiotic and non-antibiotic covariates with C. glabrata BSI (A), and FRC BSI (B). Individual graphs show significantly associated covariates by bivariable analysis and multivariable analysis. Plots show the odds ratio (marker) and 95% confidence interval (whiskers) for each covariate. Solid markers are used for non-antibacterial covariates and open markers for antibacterial covariates. All covariates refer to exposure within 30 days prior to the onset of candidemia. CVC, central venous catheter; TMP-SMX, trimethoprim-sulfamethoxazole. Antibacterial drug exposure denotes exposure to carbapenems, trimethoprim-sulfamethoxazole, colistin or clindamycin.

Figure 2. Comparative accuracy of predictive models for fluconazole-resistant Candida spp. bloodstream infection

The predictive accuracy, as represented by the area under the receiver-operator characteristics (ROC) plot, is shown for 3 models. FRC BSI is the dependent variable for all models. Covariates for model 1: neutropenia and exposure to fluconazole; model 2: neutropenia and exposure to antibacterial drugs (carbapenems, trimethoprim-sulfamethoxazole, clindamycin or colistin; model 3: neutropenia, exposure to fluconazole and exposure to antibacterials. Area under
the ROC curve was significantly higher for models that included antibacterial covariates (2 and 3) as compared to model 1 ($P=0.003$).