AAC Journals.ASM.org

Impact of Prior Inappropriate Fluconazole Dosing on Isolation of Fluconazole-Nonsusceptible *Candida* Species in Hospitalized Patients with Candidemia

Dhara N. Shah,[a,b] Raymond Yau,[b] Todd M. Lasco,[b] Jaye Weston,[c] Miguel Salazar,[b] Hannah R. Palmer,[b] and Kevin W. Garey[a,b]

University of Houston College of Pharmacy[a] and St. Luke's Episcopal Hospital,[b] Houston, and Baptist Health System, San Antonio,[c] Texas, USA

Prior use of fluconazole is a modifiable risk factor for the isolation of fluconazole-nonsusceptible *Candida* species. Optimization of the use of fluconazole by appropriate dose or duration may be able to minimize the risk of resistance. The objective of this study was to evaluate the effects of prior fluconazole therapy, including the dose and duration, on fluconazole susceptibility among *Candida* species isolated from hospitalized patients with candidemia. A retrospective cohort study of hospitalized patients with a first occurrence of nosocomial candidemia, from 2006 to 2009, was carried out. The relationships between the initial dose and duration of prior fluconazole therapy and the isolation of fluconazole-nonsusceptible *Candida* species were assessed. An initial fluconazole dose greater than 2 mg/kg and less than 6 mg/kg of body weight was considered suboptimal. A total of 177 patients were identified, of whom 133 patients aged 61 ± 16 years (56% male, 51% Caucasian, 51% with an APACHE II score of ≥15) had candidemia more than 2 days after the hospital admission day. Nine of 107 (8%) patients with fluconazole-susceptible *Candida* species and 9 of 26 (35%) patients with fluconazole-nonsusceptible *Candida* species had prior fluconazole exposure (risk ratio [RR], 3.03; 95% confidence interval [95% CI], 1.57 to 5.86; *P*, 0.0022). Preexposure with an initial dose of fluconazole greater than 2 mg/kg and less than 6 mg/kg occurred in 3 of 9 (33%) and 8 of 9 (89%) patients with fluconazole-susceptible and fluconazole-nonsusceptible *Candida* species, respectively (*P*, 0.0498). We conclude that patients with candidemia due to fluconazole-nonsusceptible *Candida* species were more likely to have received prior fluconazole therapy. Suboptimal initial dosing of prior fluconazole therapy was associated with candidemia with fluconazole-nonsusceptible *Candida* species.

Anti-infective drug exposure is an important factor in the development and emergence of drug-nonsusceptible isolates (20). In patients with *Candida* bloodstream infections, prior antifungal therapy is an independent risk factor for fluconazole-nonsusceptible *Candida* isolates, including *Candida krusei*, *C. glabrata*, *C. albicans*, *C. tropicalis*, and *C. parapsilosis* (13, 23). Specifically, prior fluconazole therapy has been associated with candidemia due to fluconazole-nonsusceptible *Candida* isolates (7, 11, 21). The Infectious Diseases Society of America (IDSA) guidelines recommend an echinocandin antifungal over fluconazole for patients with a history of prior azole therapy due to a higher likelihood of isolation of fluconazole-nonsusceptible *Candida* species (15). Many patients do not receive the IDSA-recommended dose of fluconazole, 6 to 12 mg/kg of body weight/day (6). This suboptimal fluconazole exposure in relation to the MIC has been shown to be a risk factor for mortality (14). For bacterial species, an inverted-U relationship has been described in which a resistant subpopulation increases initially and then declines with increasing exposure above the MIC of the organism (22). *In vitro* studies have demonstrated that a suboptimal fluconazole dosing regimen leads to an increased rate of resistance in *Candida* species in a pattern resembling this inverted-U relationship (1). Using an *in vitro* model, Andes et al. demonstrated that resistance development in a previously susceptible *Candida albicans* population was highly dependent on the exposure of the population to sub-MIC concentrations of fluconazole (1). However, clinical data supporting fluconazole optimization and the development of resistance are scarce. Although previous use of fluconazole has been recognized as a modifiable risk factor, optimization of the use of fluconazole by adjusting either the dose or the duration may be able to minimize the risk of resistance.

The objective of this study was to evaluate an impact of prior fluconazole therapy on fluconazole susceptibility among *Candida* species responsible for the first occurrence of candidemia among hospitalized patients, with a specific focus on the dose and duration of prior fluconazole therapy. The three specific aims of the study were to assess hospitalized patients with candidemia for the susceptibility patterns of *Candida* species; to determine to what extent preexposure to antifungal therapy may be a risk factor for candidemia with fluconazole-nonsusceptible *Candida* species; and to evaluate prior fluconazole dosing and duration for hospitalized patients with candidemia.

(This work was presented in part at the 21st ECCMID/27th ICC meeting in Milan, Italy, 2011.)

MATERIALS AND METHODS

Patient population, study period, and location. This was a retrospective study of hospitalized patients with bloodstream infections due to *Candida* species (candidemia) at a large university-affiliated hospital in Houston, TX. The methodology for this study was adapted from a previously published study assessing the use of antifungal susceptibility testing for hospitalized patients (19). For this study, all patients with candidemia between 2006 and 2009 were evaluated for inclusion and exclusion criteria. Hospitalized patients ≥18 years of age with their first documented case of

Received 4 January 2012 Returned for modification 16 February 2012
Accepted 4 March 2012
Published ahead of print 12 March 2012
Address correspondence to Kevin W. Garey, kgarey@uh.edu.

doi:10.1128/AAC.00019-12

nosocomial candidemia treated with either fluconazole or an echinocandin were included. Nosocomial candidemia was defined as collection of the *Candida* species from the blood more than 48 h after hospital admission. Patients with no antifungal susceptibility report and/or incomplete data were excluded. This study was approved by the Institutional Review Board at St. Luke's Episcopal Hospital (SLEH) and the University of Houston.

Data collection. Data collected from an online medical chart included demographics; medical history; microbiological data, such as pertinent dates related to blood culture (day of sample collection, day on which the culture was found positive, and day of the final susceptibility report), *Candida* species, and MICs; utilization of central venous catheters, total parenteral nutrition, hemodialysis, and broad-spectrum antibiotics during the preexposure time; and antifungal utilization, such as the type of antifungal agent, and start and stop dates. Both the online medical chart and the scanned paper chart were used to obtain various parameters needed to calculate APACHE II scores.

Antifungal susceptibility testing and study definitions. As part of normal clinical practice, the clinical microbiology laboratory utilized Vitek 2 for the identification of *Candida* species and the broth microdilution method (Sensititre) for antifungal susceptibility testing for all *Candida* bloodstream isolates. Susceptibility testing was not repeated on subsequent identical *Candida* species isolated in the next 7 days. The MICs were determined at 24 h according to CLSI Antifungal Testing Subcommittee recommendations. CLSI recommendations were used during the study period to define fluconazole-susceptible (fluconazole MIC, ≤8 μg/ml) or nonsusceptible (fluconazole MIC, >8 μg/ml) *Candida* species (16).

The fluconazole preexposure time was defined as the time from the initiation of fluconazole during the current hospitalization to the day on which the blood sample positive for a *Candida* species was collected. Prior antifungal therapy was defined as the receipt of one or more doses of fluconazole or an echinocandin during the hospitalization but prior to the blood sample collection day. Both the initial dose (in milligrams per kilogram), defined as the first dose received, and the total dose (in milligrams per kilogram), defined as the cumulative dose of prior fluconazole received, were assessed for patients with prior fluconazole therapy. The total duration (in days) of prior fluconazole therapy was also evaluated.

To assess for an inverted-U relationship between prior fluconazole exposure and the isolation of nonsusceptible *Candida* isolates, fluconazole dosing was divided into low-dose, medium-dose, and high-dose groups. Low-dose fluconazole was defined as a dose of ≤2 mg/kg/day (corresponding to a dose lower than any currently recommended for any indication). Medium-dose fluconazole was defined as a dose of >2 mg/kg/day and <6 mg/kg/day (corresponding to a dose higher than that recommended for urinary tract infections and less than that recommended for systemic *Candida* infections). High-dose fluconazole was defined as a fluconazole dose of ≥6 mg/kg/day (corresponding to the recommended dose for systemic *Candida* infections). Medium-dose fluconazole was considered suboptimal dosing, relevant to resistance development, in this study.

Stratification and statistical analysis. Data were recorded on paper data collection report forms, input into a spreadsheet format (Microsoft Excel 2007), and stored using a relational database (Microsoft Access 2007). Stata/IC 11 and SAS, version 9.2, were used for statistical analysis. In order to evaluate risk factors, patients were stratified on the basis of candidemia with fluconazole-susceptible or fluconazole-nonsusceptible *Candida* species. The chi-square test was used for categorical data, and the Student *t* test was used for continuous variables. Nonparametric statistics were used where appropriate. The risk ratio (RR), 95% confidence interval (95% CI), and *P* values were determined. Results from the univariate analysis were further evaluated using multivariate logistic regression analysis, including any confounders identified. A *P* value of <0.05 was considered significant.

TABLE 1 Baseline characteristics, hospitalization variables, and association with isolation of fluconazole-susceptible versus fluconazole-nonsusceptible isolates from 133 patients with candidemia

Baseline characteristic	Value[a] for patients with: Fluconazole-susceptible isolates (n = 107)	Fluconazole-nonsusceptible isolates (n = 26)	P
Age, ≥65 yr	46 (43)	9 (35)	0.437
Gender			0.0558
Female	51 (48)	7 (27)	
Male	56 (52)	19 (73)	
Race			0.6932
Caucasian	53 (50)	14 (54)	
African-American	33 (31)	7 (27)	
Hispanic	14 (13)	4 (15)	
Other	7 (6)	1 (4)	
Medical history			
Diabetes	39 (36)	7 (27)	0.3597
Hypertension	52 (49)	13 (50)	0.9659
Hyperlipidemia	20 (19)	5 (19)	1.000
Chronic kidney disease	24 (22)	7 (27)	0.6269
Cancer	20 (19)	5 (19)	1.000
Transplant	5 (5)	2 (8)	0.6223
Congestive heart failure	25 (23)	10 (38)	0.1169
Myocardial infarction	25 (23)	6 (23)	0.9752
Liver disorder	17 (16)	3 (12)	0.7634
Gastrointestinal disorder	25 (23)	5 (19)	0.6510
Central venous catheter	93 (87)	25 (96)	0.1817
Total parenteral nutrition	47 (44)	16 (62)	0.1067
Hemodialysis	31 (29)	11 (42)	0.1895
Broad-spectrum antibiotics	107 (100)	26 (100)	1.000
Location			0.9497
Intensive-care unit	61 (57)	15 (58)	
Ward	46 (43)	11 (42)	
Mean length of stay (days) ± SD prior to candidemia	42 ± 34	64 ± 47	0.0072
APACHE II score			0.3590
<15	51 (48)	15 (58)	
≥15	56 (52)	11 (42)	
Prior antifungal therapy			
Fluconazole	9 (8)	9 (35)	0.0022
Echinocandins	10 (9)	4 (15)	0.4735

[a] Given as the number (percentage) of patients except where otherwise indicated.

RESULTS

Study population. A total of 177 hospitalized patients with the first documented occurrence of candidemia were identified from 2006 to 2009; of these, 44 patients were excluded due to onset of candidemia within 2 days of hospital admission. Of 133 patients with nosocomial candidemia, 107 (80%) had fluconazole-susceptible and 26 (20%) had fluconazole-nonsusceptible *Candida* species. Baseline characteristics and risk factors assessed for candidemia patients with fluconazole-susceptible versus fluconazole-nonsusceptible *Candida* species are listed in Table 1.

TABLE 2 Susceptibility patterns of *Candida* species[a]

Candida species (no. of isolates)[b]	Fluconazole-susceptible isolates			Fluconazole-nonsusceptible isolates		
	No. (%)	MIC (μg/ml)		No. (%)	MIC (μg/ml)	
		Range	50%		Range	50%
C. albicans (65)	64 (98)	0.12–1	0.5	1 (2)	256	256
C. glabrata (26)	9 (35)	0.12–8	8	17 (65)	16–256	16
C. parapsilosis (19)	17 (89)	0.5–4	1	2 (11)	32	32
C. tropicalis (16)	15 (94)	0.06–4	2	1 (6)	64	64
C. krusei (5)	0 (0)	NA[c]	NA	5 (100)	32–128	64
Other species (2)	2 (100)	0.25–1	NA	0 (0)	NA	NA

[a] Susceptibility breakpoints were determined by using the CLSI guidelines recommended at the time of the study (16).
[b] A total of 133 *Candida* species were tested.
[c] NA, not applicable.

Susceptibility patterns of *Candida* species. *C. albicans* was isolated from 65 of 133 patients (49%); 98% of these isolates were susceptible to fluconazole (Table 2). The 26 fluconazole-nonsusceptible *Candida* isolates included *C. glabrata* ($n = 17$ [65%]), *C. krusei* ($n = 5$ [19%]), C. *parapsilosis* ($n = 2$ [8%]), *C. tropicalis* ($n = 1$ [4%]), and *C. albicans* ($n = 1$ [4%]) isolates.

Preexposure to antifungal therapy as a risk factor for the isolation of fluconazole-nonsusceptible isolates. Eighteen of 133 patients (14%) were preexposed to fluconazole prior to the first episode of candidemia. Nine patients (8%) in the fluconazole-susceptible group and 9 patients (35%) in the fluconazole-nonsusceptible group received prior fluconazole therapy. Preexposure to fluconazole was associated with the isolation of fluconazole-nonsusceptible *Candida* species (RR, 3.03; 95% CI, 1.57 to 5.86; *P*, 0.0022). Other variables associated with the isolation of fluconazole-nonsusceptible *Candida* species included the length of stay (in days) prior to the day of collection (*P*, 0.0072) and male gender (RR, 2.1; 95% CI, 0.94 to 4.65; *P*, 0.0558). These three variables were included in the multivariate logistic regression analysis. After controlling for these other variables, prior fluconazole therapy was independently associated with fluconazole-nonsusceptible *Candida* species (odds ratio [OR], 4.92; 95% CI, 1.62 to 14.92; *P*, 0.005).

Initial dosing regimens of prior fluconazole therapy as a risk factor for the isolation of fluconazole-nonsusceptible isolates. Of the 9 patients with fluconazole preexposure and with fluconazole-susceptible isolates, 2 patients (22%) received initial low-dose fluconazole, 3 patients (33%) received initial medium-dose fluconazole, and 4 patients (44%) received initial high-dose fluconazole (Fig. 1). Of the 9 patients with fluconazole preexposure and with fluconazole-nonsusceptible isolates, 1 patient (11%) received initial low-dose fluconazole and 8 patients (89%) received initial medium-dose fluconazole; none of these patients received initial high-dose fluconazole (Fig. 1). Seventeen of 115 patients (15%) who were not preexposed to fluconazole had a subsequent fluconazole-nonsusceptible isolate, compared to 1 of 3 patients (33%) preexposed to initial low-dose fluconazole, 8 of 11 patients (73%) preexposed to medium-dose fluconazole, and 0 of 4 patients preexposed to high-dose fluconazole (*P*, <0.001). In an analysis of only those patients who received prior fluconazole therapy, initial suboptimal dosing was associated with the isolation of fluconazole-nonsusceptible isolates (RR, 5.09; *P*, 0.0498). After controlling for gender and time of hospitalization prior to candidemia, initial suboptimal fluconazole dosing was associated with an increased risk of isolation of fluconazole-nonsusceptible isolates (OR, 22.0; 95% CI, 1.4 to 351.5; *P*, 0.029). By using a forward, stepwise logistic regression model and entering prior fluconazole and prior optimized fluconazole as potential variables, prior initial suboptimal fluconazole exposure was identified as a significant predictor of the isolation of a fluconazole-nonsusceptible isolate.

Duration of prior fluconazole therapy as a risk factor for the isolation of fluconazole-nonsusceptible isolates. Patients with fluconazole-nonsusceptible candidemia averaged 2.4 ± 3.9 days of fluconazole preexposure, compared to 0.6 ± 2.1 days of fluconazole preexposure for patients with fluconazole-susceptible candidemia ($P < 0.001$). However, among patients who had received prior fluconazole therapy, the average numbers of days of fluconazole preexposure were similar for those with fluconazole-nonsusceptible (6.8 ± 3.6 days) and fluconazole-susceptible (6.9 ± 3.6 days) isolates. By using a forward, stepwise logistic regression model and entering prior optimized fluconazole and days of prior fluconazole preexposure as potential variables, prior suboptimized fluconazole was identified as a significant predictor of the isolation of a fluconazole-nonsusceptible isolate.

DISCUSSION

The 2009 IDSA candidemia guidelines recommend evaluating recent exposure to azoles when selecting either fluconazole or an echinocandin for the empirical management of candidemia in nonneutropenic patients (15). An echinocandin is recommended as initial empirical therapy for patients with recent exposure to azoles, due to potential concerns about the isolation of fluconazole-nonsusceptible *Candida* species. Earlier studies that assessed the relationship between fluconazole and nonsusceptible *Candida* species focused on risk variables associated with specific *Candida* species (4, 10, 17, 18). More-recent studies evaluated risk factors for fluconazole-nonsusceptible *Candida* isolates (7, 11, 21). Exposure to any antifungal was identified as an independent variable associated with reduced fluconazole susceptibility among various *Candida* species, including *C. albicans*, *C. tropicalis*, and *C. parapsilosis* (13). Prior exposure to fluconazole was identified as an independent risk factor for *C. glabrata* candidemia (23), including

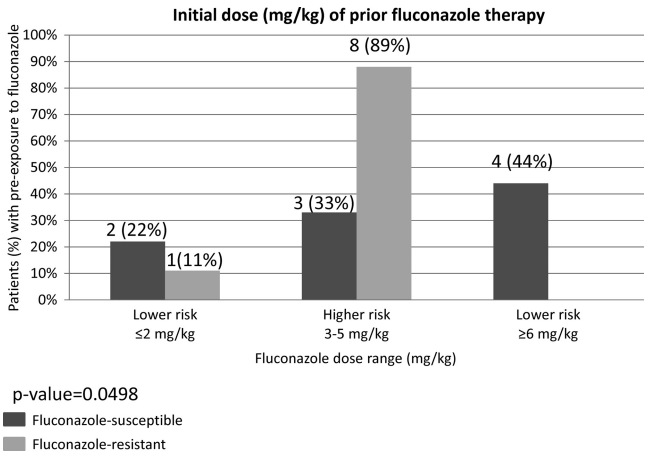

FIG 1 Initial doses (in milligrams per kilogram) during prior fluconazole therapy for patients with subsequent fluconazole-susceptible versus fluconazole-nonsusceptible candidemia.

fluconazole-resistant *C. glabrata* candidemia (9), and candidemia due to fluconazole-nonsusceptible *Candida* isolates (11). Prior fluconazole received at any dose was an independent risk factor for fluconazole-nonsusceptible *Candida* isolates, including *C. glabrata*, *C. krusei*, and *C. tropicalis* (7). In our study, the association between prior antifungal therapy, including the initial dose and duration of prior fluconazole therapy, and the isolation of fluconazole-nonsusceptible *Candida* species responsible for the first occurrence of candidemia was assessed. In this study, 20% of 133 patients had candidemia with fluconazole-nonsusceptible *Candida* isolates. *C. albicans*, *C. tropicalis*, and *C. parapsilosis* accounted for 16% of fluconazole-nonsusceptible *Candida* isolates among patients with the first occurrence of candidemia, as has been reported previously (12, 13). Prior fluconazole therapy was independently associated with fluconazole-nonsusceptible *Candida* species. Prior therapy with an echinocandin was also assessed to determine its potential association with fluconazole-nonsusceptible *Candida* species. However, there was no statistically significant difference in prior echinocandin therapy between candidemia patients with fluconazole-susceptible versus fluconazole-nonsusceptible *Candida* species.

Among 18 candidemia patients who received prior fluconazole therapy, 14 patients (78%) received less than 6 mg/kg/day of fluconazole, and the majority received a dose greater than 2 mg/kg and less than 6 mg/kg. An inverted-U-shaped curve was applied in our study to determine whether there was an association between fluconazole dosing and the likelihood of resistance, based on the ability of this curve to display a relationship between dose intensity and the suppression of subpopulations of resistant isolates, as previously demonstrated in models assessing various Gram-negative pathogens (22). Compared to patients with fluconazole-susceptible candidemia, more candidemia patients with fluconazole-nonsusceptible *Candida* isolates had received a suboptimal dose of fluconazole. These findings provide clinical evidence supporting previous *in vitro* research by Andes et al. (1, 2) In those studies, suboptimal fluconazole dosing regimens leading to extended sub-MIC concentrations were associated with the development of resistance. More-frequent dosing (i.e., split dosing of a total daily dose) and a higher fluconazole AUC (area under the concentration-time curve)/MIC ratio deterred the development of isogenic resistant subpopulations. In our retrospective study, all patients received once-daily fluconazole dosing, and thus, the impact of dosing frequency on the emergence of fluconazole resistance could not be assessed. Suboptimal dosing for candidemia (<6 mg/kg) has been reported for 55% of patients given fluconazole for the treatment of candidemia (6). Various studies have demonstrated the importance of optimizing fluconazole dosing to achieve favorable outcomes, including reduced mortality (3, 5, 8, 14). This study extends those findings by demonstrating that appropriate fluconazole dosing may also be associated with a reduced likelihood of subsequent nonsusceptible *Candida* isolates in the same patient. One pertinent clinical implication of our study is that appropriate fluconazole dosing may also be vital to minimizing the development of fluconazole-resistant *Candida* species. Further *in vivo* and clinical research is warranted to establish a firm relationship between suboptimal weight-based fluconazole dosing and the likelihood of promoting the development of fluconazole-resistant *Candida* species.

This study has several strengths, including a large patient population with the first occurrence of candidemia initially treated with fluconazole or an echinocandin, as recommended by the IDSA guidelines. In order to consistently account for prior antifungal therapy, only patients whose candidemia occurred more than 2 days after hospital admission were included. The retrospective design of the study limited our ability to obtain variables such as the indication for prior antifungal therapy. However, data regarding pertinent baseline characteristics and known risk factors for candidemia were obtained and analyzed. Despite the fairly large sample size, the number of patients who received prior fluconazole therapy and subsequently had a nonsusceptible isolate was quite small. For this reason, the study was underpowered to identify certain variables, such as the duration of prior fluconazole therapy, as a potential risk factor. Also, the initial *Candida* species that were exposed to fluconazole were not available for study. Thus, it was not possible to correlate fluconazole exposure with the MICs for the initial isolates. Despite these limitations, this study provides evidence that optimal dosing of fluconazole may prevent the emergence of fluconazole-resistant *Candida* species. These data build on previous findings that a fluconazole dose greater than or equal to 6 mg/kg should be given to any patient with a suspected or proven systemic *Candida* infection.

Conclusion. Fluconazole-nonsusceptible *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glabrata* isolates from patients with candidemia were identified. Patients with fluconazole-nonsusceptible *Candida* species were more likely to have received prior fluconazole therapy. Prior fluconazole therapy was independently associated with the isolation of fluconazole-nonsusceptible *Candida* species. Suboptimal initial fluconazole dosing during prior antifungal therapy for candidemia was associated with the subsequent isolation of fluconazole-nonsusceptible *Candida* species from the bloodstream of the same patient.

ACKNOWLEDGMENTS

This study was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck & Co., Inc. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck & Co., Inc.

Kevin W. Garey is a recipient of a research grant from the Investigator-Initiated Studies Program of Merck & Co., Inc. All other authors have nothing to disclose.

REFERENCES

1. **Andes D, et al.** 2006. Impact of antimicrobial dosing regimen on evolution of drug resistance in vivo: fluconazole and *Candida albicans*. Antimicrob. Agents Chemother. **50**:2374–2383.
2. **Andes D, Lepak A, Nett J, Lincoln L, Marchillo K.** 2006. In vivo fluconazole pharmacodynamics and resistance development in a previously susceptible *Candida albicans* population examined by microbiologic and transcriptional profiling. Antimicrob. Agents Chemother. **50**:2384–2394.
3. **Antoniadou A, et al.** 2003. Candidemia in a tertiary care cancer center: in vitro susceptibility and its association with outcome of initial antifungal therapy. Medicine (Baltimore) **82**:309–321.
4. **Chow JK, et al.** 2008. Factors associated with candidemia caused by non-*albicans Candida* species versus *Candida albicans* in the intensive care unit. Clin. Infect. Dis. **46**:1206–1213.
5. **Clancy CJ, Yu VL, Morris AJ, Snydman DR, Nguyen MH.** 2005. Fluconazole MIC and the fluconazole dose/MIC ratio correlate with therapeutic response among patients with candidemia. Antimicrob. Agents Chemother. **49**:3171–3177.
6. **Garey KW, et al.** 2007. Inadequacy of fluconazole dosing in patients with candidemia based on Infectious Diseases Society of America (IDSA) guidelines. Pharmacoepidemiol. Drug Saf. **16**:919–927.
7. **Garnacho-Montero J, et al.** 2010. Risk factors for fluconazole-resistant candidemia. Antimicrob. Agents Chemother. **54**:3149–3154.

8. **Graninger W, Presteril E, Schneeweiss B, Teleky B, Georgopoulos A.** 1993. Treatment of *Candida albicans* fungaemia with fluconazole. J. Infect. **26**:133–146.
9. **Lee M, et al.** 1999. A randomized controlled trial of an enhanced patient compliance program for *Helicobacter pylori* therapy. Arch. Intern. Med. **159**:2312–2316.
10. **Lin MY, et al.** 2005. Prior antimicrobial therapy and risk for hospital-acquired *Candida glabrata* and *Candida krusei* fungemia: a case-case-control study. Antimicrob. Agents Chemother. **49**:4555–4560.
11. **Lortholary O, et al.** 2011. Recent exposure to caspofungin or fluconazole influences the epidemiology of candidemia: a prospective multicenter study involving 2,441 patients. Antimicrob. Agents Chemother. **55**:532–538.
12. **Messer SA, Moet GJ, Kirby JT, Jones RN.** 2009. Activity of contemporary antifungal agents, including the novel echinocandin anidulafungin, tested against *Candida* spp., *Cryptococcus* spp., and *Aspergillus* spp.: report from the SENTRY Antimicrobial Surveillance Program (2006 to 2007). J. Clin. Microbiol. **47**:1942–1946.
13. **Oxman DA, et al.** 2010. Candidaemia associated with decreased in vitro fluconazole susceptibility: is *Candida* speciation predictive of the susceptibility pattern? J. Antimicrob. Chemother. **65**:1460–1465.
14. **Pai MP, Turpin RS, Garey KW.** 2007. Association of fluconazole area under the concentration-time curve/MIC and dose/MIC ratios with mortality in nonneutropenic patients with candidemia. Antimicrob. Agents Chemother. **51**:35–39.
15. **Pappas PG, et al.** 2009. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin. Infect. Dis. **48**:503–535.
16. **Pfaller MA, Diekema DJ, Sheehan DJ.** 2006. Interpretive breakpoints for fluconazole and *Candida* revisited: a blueprint for the future of antifungal susceptibility testing. Clin. Microbiol. Rev. **19**:435–447.
17. **Playford EG, et al.** 2008. Candidemia in nonneutropenic critically ill patients: risk factors for non-*albicans Candida* spp. Crit. Care Med. **36**: 2034–2039.
18. **Rodriguez D, et al.** 2010. Predictors of candidaemia caused by non-*albicans Candida* species: results of a population-based surveillance in Barcelona, Spain. Clin. Microbiol. Infect. **16**:1676–1682.
19. **Shah DN, et al.** 2011. Evaluation of antifungal therapy in patients with candidaemia based on susceptibility testing results: implications for antimicrobial stewardship programmes. J. Antimicrob. Chemother. **66**:2146–2151.
20. **Singh R, Tam VH.** 2011. Optimizing dosage to prevent emergence of resistance—lessons from in vitro models. Curr. Opin. Pharmacol. **11**:453–456.
21. **Slavin MA, et al.** 2010. Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. J. Antimicrob. Chemother. **65**: 1042–1051.
22. **Tam VH, Louie A, Deziel MR, Liu W, Drusano GL.** 2007. The relationship between quinolone exposures and resistance amplification is characterized by an inverted U: a new paradigm for optimizing pharmacodynamics to counterselect resistance. Antimicrob. Agents Chemother. **51**: 744–747.
23. **Tapia GG, et al.** 21 July 2011. A scoring model of factors associated with *Candida glabrata* candidemia among critically ill patients. Mycoses. [Epub ahead of print.] doi:10.1111/j.1439-0507.2011.02069.x.