MAJOR ARTICLE

Time to Initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-Institutional Study

Kevin W. Garey,[1] Milind Rege,[1] Manjunath P. Pai,[2] Dana E. Mingo,[3] Katie J. Suda,[4] Robin S. Turpin,[5] and David T. Bearden[6]

[1]Department of Clinical Science and Administration, University of Houston College of Pharmacy, Houston, Texas; [2]University of New Mexico College of Pharmacy, Albuquerque; [3]Baptist Memorial Health Care and [4]Department of Pharmacy, University of Tennessee Health Science Center, Memphis; [5]Merck, West Point, Pennsylvania; and [6]Oregon State University College of Pharmacy, Portland

Background. Inadequate antimicrobial treatment is an independent determinant of hospital mortality, and fungal bloodstream infections are among the types of infection with the highest rates of inappropriate initial treatment. Because of significant potential for reducing high mortality rates, we sought to assess the impact of delayed treatment across multiple study sites. The goals our analyses were to establish the frequency and duration of delayed antifungal treatment and to evaluate the relationship between treatment delay and mortality.

Methods. We conducted a retrospective cohort study of patients with candidemia from 4 medical centers who were prescribed fluconazole. Time to initiation of fluconazole therapy was calculated by subtracting the date on which fluconazole therapy was initiated from the culture date of the first blood sample positive for yeast.

Results. A total of 230 patients (51% male; mean age ± standard deviation, 56 ± 17 years) were identified; 192 of these had not been given prior treatment with fluconazole. Patients most commonly had nonsurgical hospital admission (162 patients [70%]) with a central line catheter (193 [84%]), diabetes (68 [30%]), or cancer (54 [24%]). *Candida* species causing infection included *Candida albicans* (129 patients [56%]), *Candida glabrata* (38 [16%]), *Candida parapsilosis* (25 [11%]), or *Candida tropicalis* (15 [7%]). The number of days to the initiation of antifungal treatment was 0 (92 patients [40%]), 1 (38 [17%]), 2 (33 [14%]) or ⩾3 (29 [12%]). Mortality rates were lowest for patients who began therapy on day 0 (14 patients [15%]) followed by patients who began on day 1 (9 [24%]), day 2 (12 [37%]), or day ⩾3 (12 [41%]) ($P = .0009$ for trend). Multivariate logistic regression was used to calculate independent predictors of mortality, which include increased time until fluconazole initiation (odds ratio, 1.42; $P < .05$) and Acute Physiology and Chronic Health Evaluation II score (1-point increments; odds ratio, 1.13; $P < .05$).

Conclusion. A delay in the initiation of fluconazole therapy in hospitalized patients with candidemia significantly impacted mortality. New methods to avoid delays in appropriate antifungal therapy, such as rapid diagnostic tests or identification of unique risk factors, are needed.

Candida species are the fourth most common cause of nosocomial bloodstream infections (BSIs) worldwide [1]. Although a trend toward greater incidence of fungal BSI was noted during the 1990s, this appears to have stabilized, with an annual incidence in the United States of 8 cases per 100,000 population [2–4]. Although adequate antifungal treatment has demonstrated protection against mortality and increased duration of hospitalization, recent studies indicate candidemia-attributable mortality remains 19%–49% [2, 5].

Inadequate antimicrobial treatment is an independent determinant of hospital mortality, and fungal BSIs are among the types of infection with the highest rates of inappropriate initial treatment [6]. Either a lack of or inadequate empirical antifungal treatment is associated with higher overall and attributable mortality rates, as well as a greater duration of hospitalization, compared with timely treatment with an appropriate antifungal [6–8]. One study reports that inadequate treatment actually results in less hospital resource consumption, perhaps because of a higher death rate and

Received 17 January 2006; accepted 13 March 2006; electronically published 16 May 2006.

Reprints or correspondence: Dr. Kevin Garey, Texas Medical Center, University of Houston, 1441 Moursund St., Houston, TX 77030 (kgarey@uh.edu).

Clinical Infectious Diseases 2006; 43:25–31

1058-4838/2006/4301-0004$15.00

death occurring at an earlier age [2]. Although the most common cause of inadequate treatment for fungal BSI is a lack of empirical therapy [6, 9], the specific impact of delayed treatment for patients with candidemia has not been well established. Delaying antifungal therapy appears to be a common practice, and the impact on mortality may be significant [8, 10]. A recent study addressing the effects of delayed treatment found any deferment >12 h to be an independent predictor of hospital mortality [10]. This study used data from 1 medical center, and results may not be generalizable to other settings.

Because there is a significant potential for reducing high mortality rates attributable to candidemia, we sought to assess the impact of delayed treatment across multiple study sites. We performed a retrospective cohort study in 4 geographically distinct university-affiliated health care centers. The goals of our analyses were to establish the frequency and duration of delayed treatment across study sites and to estimate the impact of treatment delay on mortality and length of stay.

PATIENTS, MATERIALS, AND METHODS

Study location and patient population. This study was conducted at 4 general surgical and/or medical University-affiliated hospitals in the United States: St. Luke's Episcopal Hospital (Houston, Texas; 664 hospital beds; 118 intensive care unit [ICU] beds); Baptist Memorial Hospital (Memphis, Tennessee; 633 hospital beds; 60 ICU beds); Albuquerque Regional Medical Center (Albuquerque, New Mexico; 384 hospital beds; 48 ICU beds); and Portland Medical Center (Portland, Oregon; 411 hospital beds; 51 ICU beds). The study period was January 2002–January 2005. All hospitalized patients with a blood culture positive for *Candida* species were eligible for investigation and were included in the study. This study was approved by the institutional review boards at the University of Houston and at each participating institution.

Study design, patient population, and data collection. A retrospective cohort study design was used with a main independent outcome variable of hospital mortality. Secondary outcome variables included length of stay in the ICU and total duration of hospitalization.

All patients hospitalized for at least 48 h with their first documented episode of BSI due to *Candida albicans* or a non-*albicans* species of *Candida* who were prescribed fluconazole were eligible for study entry. Exclusion criteria included patients with previous *Candida* BSIs or patients <18 years old. Hospital guidelines at each institution recommended initial treatment of suspected BSIs with an antistaphylococcal agent along with another agent with activity against gram-negative organisms. Infectious disease specialists were available for consultation at all sites. At each institution, the decision to add empirical fluconazole therapy for patients with suspected nosocomial BSIs was at the discretion of the prescribing physician, but it was recommended for patients at high risk for fungal infections (e.g., patients receiving total parenteral nutrition, with bowel perforation, or with persistent or new signs and symptoms of infections despite receiving antibacterial therapy). Data collected on standardized case report forms included fluconazole therapy start and stop dates, dose, and route; *Candida* species type and date of culture; demographic characteristics, including age, sex, race, and past medical and surgical history; APACHE II scores (ICU patients only); use of corticosteroids; presence of a central venous catheter; total parenteral nutrition administration; requirement for hemodialysis or mechanical ventilation; type of hospital admission (medical or surgical); and location of the patient at the time of culture (ICU or non-ICU). Laboratory information included data to calculate APACHE II scores, serum creatinine values, WBC count, and maximum temperature within the 24 h prior to collection of a blood sample for culture. Outcome variables that were collected included hospital discharge status (survivor or nonsurvivor) and admission and discharge dates from the hospital and ICU.

Definitions. All definitions were selected prospectively during the initial study design. Time to fluconazole therapy was defined as the number of days from the culture of the first blood sample positive for yeast to the administration of fluconazole. Empirical fluconazole therapy was defined as any fluconazole therapy started within 24 h of the time the blood sample was obtained for culture but before the identification of the organism. The onset of symptoms time was defined as the date on which the blood sample was obtained for culture. Inappropriate therapy of candidemia was defined as the initiation of fluconazole therapy with eventual isolation of *Candida krusei,* inadequate fluconazole dosing, or isolation of an organism that was found to be resistant to fluconazole on the basis of in vitro susceptibility tests (if available). Inadequate dosing was defined as <400 mg of fluconazole per day, excluding loading doses, and as appropriate for renal functioning [11, 12].

Blood culture technique. Blood culture technique was similar at all 4 institutions. Blood cultures were ordered at the discretion of the primary physician because of signs and symptoms of possible BSI. Trained nurses or phlebotomists obtained all blood samples after sterile disinfection of a peripheral vein or central venous catheter. All blood samples were inoculated into aerobic media and processed in the clinical microbiology laboratory of each institution using automated culture techniques (Vitek Yeast Identification; bioMérieux Vitek).

Statistical analysis. The primary objective was to compare differences in mortality on the basis of time to initiation of fluconazole therapy. Subanalyses consisted of the influence of initial fluconazole dose and type of *Candida* species on the relationship between mortality and time to initiation of flu-

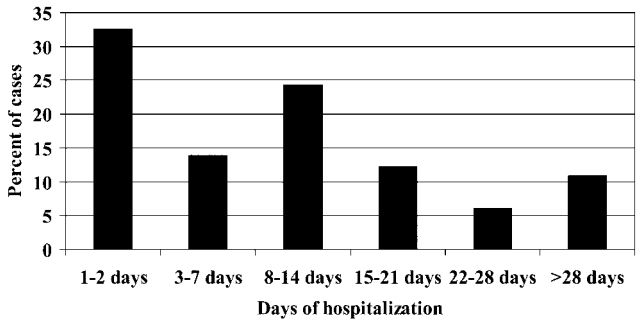

Figure 1. Time, in days, to onset of candidal bloodstream infection after hospital admission in 230 hospitalized patients with candidemia. Patients who had bloodstream infections within 1–2 days after hospital admission were transferred from another hospital.

conazole therapy. The secondary objective was to compare differences in hospitalization duration and length of time in the ICU on the basis of time to initiation of fluconazole therapy. Any patient receiving fluconazole for >24 h before culture date was considered to have breakthrough or persistent candidemia and was analyzed separately [13, 14].

The collected data was first inputted into a relational database (Microsoft Access 2000; Microsoft) and then analyzed using SAS software, version 9.1 (SAS Institute). Values are expressed as mean ± SD for continuous variables and as a percentage of the group from which they were derived for categorical variables. Univariate statistical analysis, followed by multivariate regression, was performed for each analysis. Univariate statistical analysis included the Student's *t* test for normally distributed continuous data and the Mann-Whitney *U* test for non-normally distributed continuous data. Either χ^2 or Fisher's exact tests were used for categorical data.

Mortality differences were assessed using logistic regression, with the primary dependent variable being time to initiation of fluconazole therapy. Other variables associated with mortality ($P < .2$) in the univariate analyses were included in the regression models for the multivariate analysis. A backward elimination strategy was employed with variables, with $P < .1$ kept in the model. Log-transformed length of ICU stay (days) and hospitalization duration (days) were assessed using linear regression. Backward selection processes were used. Variables were checked for confounding, collinearity, and interaction. Confounders and interaction terms were included in the multivariate models if inclusion of the covariate changed the coefficient of any statistically significant variable in the logistic regression model by ⩾10%. All tests were 2-tailed. A *P* value of <.05 was considered statistically significant.

RESULTS

Patient demographic characteristics. The cohort consisted of 230 patients with *Candida* BSIs who were prescribed fluconazole. The mean age ± SD was 56 ± 17 years, and 51% of the patients were male. The most common patient ethnicities were white (52%), African-American (22%), or Hispanic (20%). The most common comorbidities included diabetes (30%), solid-organ cancer (24%), or end-stage renal disease (10%). Variables present on the day blood culture was performed included presence of a central venous catheter (84%), parenteral nutrition administration (29%), mechanical ventilation (23%), and corticosteroid use (15%). Patients were most commonly admitted with a nonsurgical diagnosis (70%), and 41% were in the ICU at the time of *Candida* blood culture.

Candida *isolates and antimicrobial treatment characteristics.* Eighty-three percent of cases occurred during the first 3 weeks of hospitalization (figure 1). Thirty-three percent of cases were isolated during the first 2 days of hospitalization after transfer from another hospital. Isolated organisms included *C. albicans* (56%), *Candida glabrata* (17%), *Candida parapsilosis* (11%), *Candida tropicalis* (7%), *C. krusei* (3%), and other *Candida* species (3%) (table 1). Eight patients (3%) had 2 fungal species isolated from their blood cultures. All mixed cultures contained *C. albicans* with the addition of *C. glabrata* (2 cultures), *C. parapsilosis* (5 cultures), and *C. tropicalis* (1 culture). Mortality ranged from 0%–63% based on type of organism ($P = .0232$ by χ^2 analysis).

Thirty-eight patients (16.5%) were prescribed fluconazole for >24 h before the onset of candidemia and were considered to have breakthrough or persistent infections and analyzed separately. Time to initiation of fluconazole therapy for the remaining 192 patients was day 0 (39.6%), day 1 (16.5%), day 2 (14.4%), or day ⩾3 (12.6%). Fluconazole was considered to be inappropriate for 14 patients either because of isolation of *C. krusei* (6 patients) or isolation of *C. glabrata* with a maintenance fluconazole dose of <400 mg adjusted for renal function (8 patients). A total of 172 patients (75%) received a fluconazole dose ⩾400 mg.

Relationship between hospital mortality and days to initiation of fluconazole. Seventeen (45%) of 38 patients with break-

Table 1. Yeast isolates from patients with candidemia.

Fungal isolate	No. (%) of patients		Mean no. of days ± SD to initiation of fluconazole
	Total	Hospital mortality	
Candida albicans	129 (56)	33 (26)	0.7 ± 1.26
Candida glabrata	38 (17)	17 (45)	0.58 ± 1.41
Candida parapsilosis	25 (11)	0 (0)	0.76 ± 1.16
Candida tropicalis	15 (7)	4 (27)	0.6 ± 1.24
Candida krusei	8 (3)	3 (38)	0.5 ± 1.31
Mixed *Candida* culture	8 (3)	5 (63)	0.5 ± 1.51
Candida lusitaniae	4 (2)	1 (25)	0.25 ± 0.5
Candida rugosa	1 (<1)	0 (0)	0

through or persistent candidemia died. The relationship between the timing of fluconazole administration and hospital mortality for patients receiving fluconazole at the onset of symptoms or later is displayed in figure 2. Mortality was lowest if fluconazole therapy was started on the same day that the culture was performed (day 0) (15.4%) and increased to 23.7% if fluconazole therapy was started on day 1, 36.4% if it was started on day 2, and 41.4% if it was started day ⩾3 ($P = .0009$, by test for trend). In univariate analysis, other variables associated with increased mortality included APACHE II score ($P < .01$), being hospitalized in the ICU ($P < .001$) on the date of onset of symptoms, corticosteroid treatment ($P = .036$), or mechanical ventilation ($P < .001$) (table 2). There was also a significant difference in mortality between different study sites, but in multivariate analyses, study site was not associated with an increased risk of mortality. Other variables associated with increased mortality ($P < .2$ but $P > .05$) included in the multivariate model included requirement for central venous catheter, older age, total parenteral nutrition administration, and WBC count. HIV status was not included in the multivariate model because of the low number of patients (5) with this condition.

A similar analysis was conducted that excluded the 16 patients for whom fluconazole therapy was considered inappropriate to eliminate the potential influence of fluconazole resistance. After exclusion of these resistant organisms, the mortality rate was lowest for patients who began fluconazole therapy at the onset of symptoms of candidemia (14.1%) and increased each day to 23.5% if fluconazole therapy was started on day 1, 36.4% if it was started on day 2, and 42.3% if it was started day ⩾3 ($P < .0006$, by test for trend).

Multivariate analysis. All variables with a P value <.2 in the univariate analysis were included in the multivariate model, along with type of *Candida* species. Time from onset of symptoms to start of fluconazole therapy (days) and APACHE II score (1-point increments) were identified as independent risk factors for hospital mortality. No other variable entered in the model was significant at the $P < .05$ level (table 3).

To assess the effect of fluconazole dose on mortality, the initial starting dose of fluconazole (excluding the loading dose) was entered into a multivariate logistic regression equation. The main dependent variable was hospital mortality and the independent variables included fluconazole dose, time to initiation of fluconazole therapy, and APACHE II score. The starting dose of fluconazole was not an independent predictor of mortality after controlling for these variables ($P > .05$). Similar results were obtained if the data were limited to patients in whom fluconazole therapy was deemed appropriate.

Secondary outcomes. To assess the relationship between time to initiation of fluconazole therapy and length of hospitalization or ICU stay, time to initiation of fluconazole was dichotomized into starting within 1 day of or >1 day after a blood sample was obtained for culture (table 4). Overall duration of hospitalization did not differ significantly regardless of time to initiation of fluconazole therapy or among hospital survivors or nonsurvivors. However, patients who began fluconazole within 1 day of the onset of symptoms had a significantly decreased time in the ICU ($P = .03$). Not surprisingly, hospital survivors also spent fewer days in the ICU ($P = .0002$).

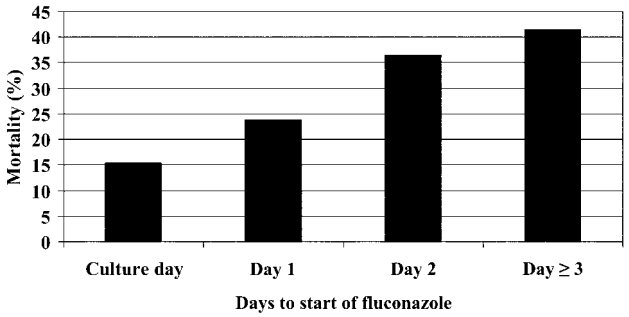

Figure 2. Relationship between hospital mortality and the number of days to initiation of fluconazole therapy. We calculated the days to the start of fluconazole therapy by subtracting the start date of fluconazole therapy from the culture date of the first blood sample positive for yeast ($P = .0009$ for trend, using the Mantel-Haenszel χ^2 test).

In a separate analysis that included only hospital survivors, the mean hospital length of stay ± SD did not differ in patients given therapy within 1 day (27 ± 17 days), compared with patients given fluconazole >1 day after the blood sample was obtained for culture (28 ± 22 days) ($P = .91$). ICU stay was shorter for patients given fluconazole within 1 day (5 ± 9 days), compared with patients given fluconazole >1 day after the blood sample was obtained for culture (9 ± 18 days); however, these results did not reach statistical significance ($P = .614$).

DISCUSSION

Up to 70% of patients with candidemia do not receive empirical antifungal therapy within 24 h of the time the blood sample is obtained for culture. Morrell et al. [10] demonstrated, in a single-institution study, that a delay in antifungal prescribing of ⩾12 h from the time of blood sample collection increased mortality by 2.09-fold. This study confirms and expands on the finding of Morrell and colleagues by showing similar results in a multi-institutional study using a homogenous population that was prescribed fluconazole for the treatment of candidemia. Results of our study demonstrate that mortality increases with each subsequent day that empirical fluconazole therapy is delayed and that earlier initiation of fluconazole therapy is also associated with a decreased length of time in the ICU.

Candidemia is associated with one of the highest rates of mortality of any BSI [9]. Crude mortality rates of 67% were reported for BSI due to *Candida* species, compared with BSI due to *Enterobacter* species (53%), *Pseudomonas aeruginosa*

Table 2. Characteristics of 192 patients with candidemia and their relationship to hospital mortality.

Characteristic	Hospital discharge status		Relative risk (95% CI)	*P*
	Alive	Dead		
Demographic characteristics				
Age, mean years ± SD	55 ± 17	60 ± 17	…	.059
Sex				
Male	77 (55)	26 (55)	0.98 (0.59–1.61)	.934
Female	64 (45)	21 (45)	…	
Race/ethnicity				
White	69 (48)	27 (58)	1.00	.674
Black	37 (25)	9 (0.19)	0.62 (0.27–1.46)	.275
Hispanic	30 (21)	8 (17)	0.68 (0.28–1.67)	.402
Other/unknown	9 (6)	3 (6)	0.85 (0.21–3.39)	.820
Location hospitalized				
Texas	23 (15)	19 (41)	N/A	.002
Tennessee	50 (36)	8 (17)	N/A	
New Mexico	57 (39)	10 (21)	N/A	
Oregon	15 (10)	10 (21)	N/A	
Underlying condition or risk factor				
Diabetes	44 (30)	12 (26)	0.83 (0.47–1.48)	.528
Cancer	35 (23)	12 (28)	1.18 (0.87–1.30)	.552
HIV infection	2 (1)	3 (6)	2.55 (1.19–5.46)	.061
Hemodialysis	12 (8)	6 (13)	1.41 (0.70–2.87)	.360
Surgical admission	42 (29)	15 (32)	1.11 (0.65–1.89)	.701
Variables assessed on date of blood culture				
APACHE II score	15.3 ± 5.9	20.8 ± 8.0	…	<.001
WBC count, mean 10^9 cells/L ± SD	13.1 ± 10.5	16.0 ± 13.1	…	.154
Hospitalized in ICU	41 (28)	33 (70)	3.76 (2.16–6.54)	<.001
Central venous catheter	116 (80)	43 (91)	2.23 (0.86–5.79)	.069
Corticosteroid treatment	14 (10)	10 (21)	1.89 (1.09–5.79)	.036
Total parenteral nutrition	32 (22)	15 (33)	1.50 (0.89–2.53)	.139
Mechanical ventilation	20 (14)	20 (43)	2.82 (1.77–4.47)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit; N/A, not applicable.

(47%), or *Staphylococcus aureus* (24%). Attributable mortality rates of 49% were also shown among patients with candidemia, compared with uninfected control subjects matched for age, sex, date of hospital admission, underlying diseases, length of time at risk, and type of surgical procedure [5]. Previously, Morrell et al. [10] studied a total of 157 consecutive patients with BSI due to *Candida* species who were treated with any antifungal agent over a 3-year period. Nine patients (5.7%) received antifungal therapy within 12 h after a blood sample was obtained for culture, 10 (6.4%) received antifungal therapy within 12–24 h, 86 (54.8%) received antifungal therapy within 24–48 h, and 52 (33.1%) received antifungal therapy after >48 h. After controlling for APACHE II score and prior antibiotic treatment, receipt of an antifungal agent >12 h after the blood sample was obtained for culture was associated with an increased risk of mortality of 2.09-fold ($P = .018$). Mortality was ~30% for all time points after this, although a small increase in mortality was noted with longer delays. Similar results were seen in our study, such that mortality was 15.4% if therapy was started on the same day as the blood sample was obtained, and it increased to 23.7% for day 1, 36.4% for day 2, and 41.4% for therapy begun on day ⩾3. We included only patients given fluconazole in our study to assure a patient population that was as homogenous as possible in terms of antifungal therapy, and this homogeneity may have produced a stronger temporal relationship than that observed in the previous study [10].

Avoiding delays in treatment of patients with candidemia is

Table 3. Multivariate model of independent risk factors for hospital mortality.

Variable	Adjusted OR (95% CI)	*P*
Time from culture date to start of fluconazole therapy, days	1.50 (1.09–2.09)	.0138
APACHE II score, 1-point increments	1.13 (1.08–1.18)	<.001

Table 4. Duration of hospitalization and length of intensive care unit stay in relation to time to initiation of fluconazole and discharge status.

Variable	Initiation of fluconazole treatment		P	Hospital discharge status		P
	Within 1 day	After 1 day		Dead	Alive	
Length of stay in the intensive care unit, days	6 ± 10 (0)	10 ± 17 (3)	.03	12 ± 15 (6)	7 ± 14 (0)	.0002
Duration of hospitalization, days	27 ± 17 (22)	29 ± 26 (21)	.91	30 ± 29 (20)	27 ± 19 (22)	.45

NOTE. Data are mean ± SD (median).

difficult. Although *Candida* species are the fourth most commonly isolated organism in patients with BSI, they account for only 8% of all BSIs [15]. By contrast, gram-positive bacteria, such as coagulase-negative staphylococci, *S. aureus,* and *Enterococcus* species, account for 60% of all BSIs [16]. Also, the majority of risk factors identified for candidemia are also common for multidrug-resistant bacteria and are not helpful in distinguishing patients with bacteremia from those with candidemia [17]. Thus, avoiding delays in treatment of candidemia by increasing empirical antifungal prescribing would likely involve massive empirical overprescribing of antifungal agents for patients without candidemia, along with the increased toxicities and costs associated with such overprescribing. Optimal methods for avoiding delays in antifungal therapy would be more-rapid diagnosis of *Candida* infection or identification of unique risk factors for BSIs due to *Candida* species. A recently published study distinguished risk factors for BSIs due to *Candida* species, compared with methicillin-resistant *S. aureus,* vancomycin-resistant enterococci, or antibiotic-resistant gram-negative organisms [18]. This study identified the presence of a central venous catheter, bowel endoscopy, and underlying malignancy as significant predictors of candidemia, compared with infection with resistant bacterial species. Development of nonculture methods for the rapid diagnosis of candidemia in patients with BSI may also significantly improve the ability to quickly prescribe appropriate antifungal therapy [19, 20]. In this current study, mortality rates continued to increase after identification of the organism if therapy was not started. Taken together, these data would suggest that clinicians should consider the use of empirical antifungal therapy in patients at high risk for candidemia and should initiate antifungal therapy without delay in patients in whom BSI due to *Candida* species has been identified.

Our study has many important limitations. We were unable to assess the reason for the delay in empirical antifungal therapy. However, it is more likely that bias would have worked against the observed association, because one would assume that there would be more urgency to treat patients for whom the suspicion of candidemia was strongest. Second, antifungal susceptibility testing was rarely ordered for these patients; thus, susceptibility of fluconazole was based on the general susceptibility pattern of each *Candida* species. However, the results of our study did not differ when we excluded *Candida* species with known resistance to fluconazole. Third, although we chose to limit our analysis to patients given fluconazole to assure a homogenous treatment population, extrapolation of these results to other antifungal agents will need to be performed.

In conclusion, we demonstrated that a delay in fluconazole prescribing in hospitalized patients with candidemia significantly impacts mortality and length of ICU stay. New methods to avoid delays in appropriate antifungal therapy, such as rapid diagnostic tests or identification of unique risk factors, are needed.

Acknowledgments

Financial support. Merck (grant 1-5-51369).

Potential conflicts of interest. K.W.G. has received past research support from Merck. M.P.P has received research support from Pfizer, Astellas, and Enzon Pharmaceuticals. R.S.T. is an employee of Merck. All other authors: no conflict.

References

1. Pfaller MA, Diekema DJ, Jones RN, et al. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J Clin Microbiol **2001**; 39:3254–9.
2. Morgan J, Meltzer MI, Plikaytis BD, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. Infect Control Hosp Epidemiol **2005**; 26:540–7.
3. Miller LG, Hajjeh RA, Edwards JE Jr. Estimating the cost of nosocomial candidemia in the United States [letter]. Clin Infect Dis **2001**; 32:1110.
4. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. Clin Infect Dis **1998**; 27:781–8.
5. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis **2003**; 37:1172–7.
6. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **2000**; 118:146–55.
7. Ben-Abraham R, Keller N, Teodorovitch N, et al. Predictors of adverse outcome from candidal infection in a tertiary care hospital. J Infect **2004**; 49:317–23.
8. Bouza E, Sousa D, Munoz P, Rodriguez-Creixems M, Fron C, Lechuz JG. Bloodstream infections: a trial of the impact of different methods of reporting positive blood culture results. Clin Infect Dis **2004**; 39: 1161–9.
9. Harbarth S, Ferriere K, Hugonnet S, Ricou B, Suter P, Pittet D. Epi-

demiology and prognostic determinants of bloodstream infections in surgical intensive care. Arch Surg **2002**; 137:1353–9 [discussion, 1359].
10. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother **2005**; 49:3640–5.
11. Takakura S, Fujihara N, Saito T, Kudo T, Iinuma Y, Ichiyama S. Clinical factors associated with fluconazole resistance and short-term survival in patients with *Candida* bloodstream infection. Eur J Clin Microbiol Infect Dis **2004**; 23:380–8.
12. Pappas PG, Rex JH. Therapeutic approach to *Candida sepsis.* Curr Infect Dis Rep **1999**; 1:245–52.
13. Kontoyiannis DP, Reddy BT, Hanna H, Bodey GP, Tarrand J, Raad II. Breakthrough candidemia in patients with cancer differs from de novo candidemia in host factors and *Candida* species but not intensity. Infect Control Hosp Epidemiol **2002**; 23:542–5.
14. Safdar A, Cross EW, Chaturvedi V, Perlin DS, Armstrong D. Prolonged candidemia in patients with cancer. Clin Infect Dis **2002**; 35:778–9.
15. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to *Candida albicans:* frequency of occurrence and antifungal susceptibility in the SCOPE program. Diagn Microbiol Infect Dis **1998**; 31:327–32.
16. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
17. Ostrosky-Zeichner L. New approaches to the risk of *Candida* in the intensive care unit. Curr Opin Infect Dis **2003**; 16:533–7.
18. von Baum H, Ober JF, Wendt C, Wenzel RP, Edmond MB. Antibiotic-resistant bloodstream infections in hospitalized patients: specific risk factors in a high-risk population? Infection **2005**; 33:320–6.
19. Leinberger DM, Schumacher U, Autenrieth IB, Bachmann TT. Development of a DNA microarray for detection and identification of fungal pathogens involved in invasive mycoses. J Clin Microbiol **2005**; 43:4943–53.
20. Bu R, Sathiapalan RK, Ibrahim MM, et al. Monochrome LightCycler PCR assay for detection and quantification of five common species of *Candida* and *Aspergillus.* J Med Microbiol **2005**; 54:243–8.