J Antimicrob Chemother 2012; **67**: 707–714
doi:10.1093/jac/dkr511 Advance Access publication 18 December 2011

Journal of Antimicrobial Chemotherapy

Timing of susceptibility-based antifungal drug administration in patients with *Candida* bloodstream infection: correlation with outcomes

Shellee A. Grim[1,2]*, Karen Berger[1]†, Christine Teng[3], Sandeep Gupta[4], Jennifer E. Layden[2], William M. Janda[5] and Nina M. Clark[2]

[1]Department of Pharmacy Practice, University of Illinois at Chicago, 833 S. Wood Street Room 164 (M/C 886), Chicago, IL 60612, USA; [2]Section of Infectious Diseases, Department of Internal Medicine, University of Illinois at Chicago, 808 S. Wood Street Room 888 (M/C 735), Chicago, IL 60612, USA; [3]Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, S4A-01-07, Singapore 117543; [4]Community Health Network, 7250 Clearvista Drive, Suite 120, Indianapolis, IN 46256, USA; [5]Department of Pathology, University of Illinois at Chicago, 840 S. Wood Street, Suite 130 CSN (M/C 847), Chicago, IL 60612, USA

*Corresponding author. Tel: +1-312-413-4098; Fax: +1-312-413-1657; E-mail: sgrim@uic.edu
†Present address: New York Presbyterian Hospital, Department of Pharmacy, 525 E. 68th Street, Room K-04, New York, NY 10065, USA.

Received 21 June 2011; returned 17 July 2011; revised 31 October 2011; accepted 10 November 2011

Objectives: We sought to determine the impact of timing of appropriate antifungal therapy, as assessed by susceptibility results, on patient survival.

Methods: Patients ≥16 years of age with first episodes of candidaemia during 2001–09 were included. Clinical data were collected retrospectively, including time to appropriate antifungal therapy and patient survival.

Results: The study population included 446 patients [243 (54%) female, mean age 53 years] with candidaemia, 380 (85%) of whom had antifungal susceptibility data. *Candida albicans* was the most common pathogen (221, 50%) followed by *Candida glabrata* (99, 22%), *Candida parapsilosis* (59, 13%), *Candida tropicalis* (48, 11%) and *Candida krusei* (6, 1%). Appropriate antifungal therapy consisted of fluconazole (177, 40%), an echinocandin (125, 28%), amphotericin B (41, 9%) and voriconazole (6, 1%); 97 (22%) failed to receive appropriate antifungal therapy. The 30 day mortality was 34% (151/446) and there was no clear relationship between time from positive culture to receipt of appropriate antifungal therapy and 30 day survival. On multivariable Cox regression, increased APACHE II score [hazard ratio (HR) 1.11, 95% CI 1.09–1.13, $P<0.001$], cirrhosis (HR 2.15, 95% CI 1.48–3.13, $P<0.001$) and HIV infection (HR 2.03, 95% CI 1.11–3.72, $P=0.02$) were independent predictors of mortality. A secondary analysis requiring patients in the early treatment group to have received ≥24 h of effective antifungal therapy did show a significant mortality benefit to receiving antifungal treatment within 72 h of a positive blood culture being drawn (30 day mortality for early treatment: 27% versus 40%, $P=0.004$; HR for mortality with delayed treatment on multivariable analysis: 1.41, 95% CI 1.01–1.98, $P=0.045$).

Conclusions: *Candida* bloodstream infection is associated with high mortality, despite timely receipt of appropriate antifungal therapy.

Keywords: candidaemia, mortality, survival, initiation

Introduction

Candida is the fourth most common causative pathogen of nosocomial bloodstream infection (BSI) after coagulase-negative staphylococci, *Staphylococcus aureus* and *Enterococcus* species,[1] and invasive candidiasis is associated with high mortality.[2–4] Furthermore, invasive fungal infections are responsible for an increasing proportion of infection-related deaths in the USA.[5]

Timely therapy of BSI is of critical importance and inadequate initial therapy adversely impacts hospital mortality.[6,7] Furthermore, fungal BSIs are associated with higher rates of inadequate initial antimicrobial treatment than bacterial BSIs[6] and carry high mortality rates.[2–4] The importance of early treatment of candidaemia has been suggested by some investigators.[8,9] However, there are limited data definitively demonstrating that early therapy for candidaemia benefits patients. The results of studies addressing this question are conflicting[8–17] and most

of these studies have not employed *in vitro* antifungal susceptibility results to assess the appropriateness of therapy.[8–11,15–17] The purpose of the present study is to investigate the impact of the timing of appropriate antifungal therapy, as assessed by antifungal drug susceptibility results, on mortality among patients with *Candida* BSI.

Methods

This study was conducted at an urban academic medical centre with 489 beds, including 52 adult critical care beds, active abdominal solid organ and stem cell transplant programmes, and a cancer centre. All patients ≥16 years of age with *Candida* bloodstream infection (*Candida* BSI) from January 2001 to December 2009 were identified by the Clinical Microbiology Laboratory. Only the first episode of candidaemia was included for patients with multiple episodes during the study period. Data collection was performed retrospectively to obtain the following information: demographics; comorbidities; severity of illness based on Acute Physiology and Chronic Health Evaluation (APACHE) II scores (the most aberrant values within 24 h prior to the collection of blood samples indicating candidaemia were obtained); presence of mechanical ventilation; time of collection of the first positive blood culture for *Candida*; time of initiation of first appropriate antifungal therapy; initial and follow-up blood culture results; microbiological response to antifungal therapy; and mortality. The difference between the time of collection of the first positive blood culture for *Candida* and receipt of the first appropriate antifungal therapy was defined as the time to appropriate antifungal therapy. Data on the receipt of corticosteroids were collected and the use of high-dose steroids was defined as ≥15 mg prednisone equivalents daily. Patients who received appropriate antifungal therapy for ≥24 h prior to initial BSI culture were excluded from the analysis. The receipt of inappropriate antifungal therapy for ≥24 h prior to the initial BSI culture was not a criterion for study exclusion.

Blood cultures were ordered at the discretion of the primary medical team, based on the presence of signs and/or symptoms of BSI. Blood samples were obtained by nursing or phlebotomy personnel following skin and/or catheter sterilization. Blood samples were inoculated into one aerobic and one anaerobic bottle, and processed using the BacT/ALERT® 3D (bioMérieux, Inc., Durham, NC, USA) automated microbial detection system. Organism identification was made using the Vitek® 2 Yeast Biochemical Card (bioMérieux, Inc.). The API® 20C AUX Yeast Identification Kit (bioMérieux, Inc.) was utilized for organisms that failed identification by the primary method. The appropriateness of antifungal therapy was based on antifungal susceptibility testing, which became routine at our institution for fluconazole, itraconazole and flucytosine in 2003, for voriconazole, posaconazole and amphotericin B in 2007, and for the echinocandins in 2008. Antifungal susceptibilities were determined with the Sensititre® YeastOne® panel (Trek Diagnostic Systems, Inc., Cleveland, OH, USA). For fluconazole-susceptible *Candida* isolates (MIC ≤8 mg/L), a minimum daily dose of 400 mg was considered appropriate. For fluconazole-susceptible dose-dependent (SDD; MIC 16–32 mg/L) isolates, a minimum daily dose of 800 mg was considered appropriate.[18] For patients with a calculated creatinine clearance[19] <50 mL/min, a daily dose of fluconazole of 50% of the normal dose was considered appropriate based on standard dosing adjustments made in renal dysfunction.[20]

The appropriateness of dosing of other antifungals was defined as follows:[21] ≥0.5 mg/kg of amphotericin B deoxycholate once daily; ≥3 mg/kg of lipid formulations of amphotericin B once daily; 70 mg of caspofungin (formulary echinocandin through March 2008) ×1 dose followed by 50 mg once daily (or 35 mg once daily for patients with significant liver impairment); 100 mg of micafungin (formulary echinocandin beginning April 2008) once daily; and 6 mg/kg of voriconazole twice daily ×2 doses followed by ≥3 mg/kg twice daily. In the absence of antifungal susceptibility testing, the following criteria were used to assess the appropriateness of therapy: 400 mg of fluconazole daily was deemed appropriate for the treatment of BSI caused by *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis* and *Candida lusitaniae*; ≥800 mg of fluconazole daily was defined as appropriate for the treatment of *Candida glabrata*; amphotericin B was considered inappropriate for the treatment of BSI caused by *C. lusitaniae*; fluconazole was considered inappropriate for the treatment of *Candida krusei*; the echinocandins were assessed as appropriate for the treatment of all *Candida* species; voriconazole and posaconazole were considered appropriate for all non-*glabrata* *Candida* species; and patients receiving voriconazole or posaconazole for *C. glabrata* infection in the absence of antifungal susceptibility testing were excluded from analysis (Table 1).

Microbiological response was defined as culture-confirmed resolution of infection within 7 days of initiation of appropriate antifungal therapy sustained for ≥6 weeks after the original culture date. Persistent *Candida* BSI was defined as >7 days of candidaemia caused by the initial organism(s) after initiation of appropriate antifungal therapy. Microbiological failure was defined as persistent, recurrent or new BSI due to *Candida* within 6 weeks of the first positive culture. Patients were followed for outcomes after onset of *Candida* BSI. The time to death or loss to follow-up within 30 days after infection was recorded.

The χ^2 test was performed to assess for differences in 30 day mortality based on receipt and timing of appropriate antifungal therapy. A Kaplan–Meier curve was constructed to illustrate the relationship

Table 1. Appropriate antifungal therapy

Appropriate therapy	*n*=349
fluconazole	177
400 mg/day[a]	
800 mg/day[b]	
echinocandin (for all *Candida* species)	125
caspofungin 70 mg ×1 then 50 mg daily	
micafungin 100 mg daily	
amphotericin B (for all *Candida* species except for *C. lusitaniae*)	41
≥0.5 mg/kg/day amphotericin B deoxycholate	
≥3 mg/kg/day lipid formulation of amphotericin B	
voriconazole (for all *Candida* species except for *C. glabrata*)	6
6 mg/kg every 12 h ×2 doses then ≥3 mg/kg twice daily	
posaconazole (for all *Candida* species except for *C. glabrata*)	0
Inappropriate therapy	*n*=97
no antifungal therapy	55
insufficient fluconazole	42
<400 mg/day for fluconazole-susceptible isolates	21
<800 mg/day for fluconazole-SDD isolates	11
<800 mg/day for *C. glabrata* without susceptibilities	3
fluconazole-resistant isolate	5
infection caused by *C. krusei*	2
amphotericin B for *C. lusitaniae*	0
Unable to assess appropriateness	*n*=1
voriconazole for *C. glabrata* without antifungal susceptibilities	1
posaconazole for *C. glabrata* without antifungal susceptibilities	0

[a]For infection caused by fluconazole-susceptible isolates or by *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. lusitaniae* without susceptibilities.
[b]For infection caused by fluconazole-SDD isolates or by *C. glabrata* without susceptibilities.

between the receipt and timing of appropriate antifungal therapy on survival; the log-rank test was used to assess for statistical differences between groups. Univariable Cox regression was performed to determine the patient and infection characteristics associated with 30 day survival. The proportional hazards assumption was tested graphically and with the creation of time-dependent variables. Clinically plausible variables with a *P* value of ≤0.2 were entered into a multivariable Cox regression model. Statistical analyses were performed with PASW Statistics v. 17.0 (SPSS, Chicago, IL, USA). Institutional review board approval was obtained.

Results

There were 453 patients with first episodes of *Candida* BSI during the study period. Six patients received ≥24 h of appropriate antifungal therapy prior to first *Candida* BSI culture and were excluded. One additional patient was excluded because the appropriateness of antifungal therapy could not be determined based on a priori definitions; the patient received voriconazole for *C. glabrata* BSI without voriconazole susceptibility testing. The study sample therefore included 446 patients with a mean age of 53 years; 243 (54%) were female and 229 (51%) were black (Table 2). The number of first episodes of *Candida* BSI averaged 49 per year; there were no discernible trends in the number of infections per year. The most common comorbidities were diabetes mellitus (131, 29%), solid tumour (120, 27%) and cirrhosis (72, 16%), and 249 (56%) of patients were in the intensive care unit (ICU) at the time of *Candida* BSI. The mean and median APACHE II scores were 18.9 and 17.0, respectively. *C. albicans* was the most common pathogen (221, 50%), followed by *C. glabrata* (99, 22%), *C. parapsilosis* (59, 13%), *C. tropicalis* (48, 11%) and *C. krusei* (6, 1%). Antifungal susceptibilities were reported for 380/446 (85%) patients. Appropriate antifungal therapy consisted of fluconazole (177, 40%), caspofungin or micafungin (125, 28%), amphotericin B (41, 9%) and voriconazole (6, 1%). A relatively high percentage of patients (97, 22%) did not receive appropriate initial antifungal therapy; 55 patients (12%) failed to receive any antifungal therapy and 42 patients (9%) received insufficient doses of fluconazole (21 received <400 mg/day for a fluconazole-susceptible isolate, 11 received <800 mg/day for a fluconazole-SDD isolate, 3 received <800 mg for *C. glabrata* without susceptibilities, 5 received fluconazole for a fluconazole-resistant isolate and 2 received fluconazole for BSI caused by *C. krusei*; Table 1).

The 30 day mortality was compared based on the time to initiation of appropriate antifungal therapy (Figure 1). The overall mortality was 34% (151/446), with the highest mortality (45%, 44/97) among the 97 patients who failed to receive appropriate antifungal therapy (data not shown). Though still considerable, mortality was significantly lower for those who received appropriate antifungal therapy (~30%). There was a slight trend toward lower 30 day mortality for patients who received appropriate antifungal therapy within 72 h of the collection of a positive blood culture, but the difference was not statistically significant (32% versus 36%, $P=0.11$). We also analysed the survival of the two groups over time according to the timing of appropriate antifungal therapy. A Kaplan–Meier 30 day survival curve for these data is illustrated in Figure 2(a). There was no significant difference in survival between the patients who received appropriate antifungal therapy within 72 h or beyond 72 h from the initial positive culture being drawn ($P=0.18$), but again there was a trend toward lower survival over time among the latter group.

Univariable Cox regression analysis (Table 3) of all patients with *Candida* BSI ($n=446$) demonstrated that a number of variables were associated with increased mortality risk, including increased age, immunosuppression (e.g. HIV infection, cirrhosis and high-dose steroid therapy), critical illness (e.g. ICU residence at the time of *Candida* BSI, mechanical ventilation, renal dysfunction and increased APACHE II score) and pathogen factors (e.g. BSI caused by *C. glabrata* and BSI caused by a fluconazole-non-susceptible isolate). Microbiological response to treatment could not be assessed in 89 patients, but of the remaining 357 patients, 51 (14%) had microbiological failure (22 persistent and 29 new or recurrent BSI). Notably, the microbiological clearance of infection was protective against mortality. The receipt of appropriate antifungal therapy >72 h after the collection of a positive blood culture was associated with a hazard ratio (HR) of 1.24 (95% CI 0.90–1.71, $P=0.19$). On multivariable Cox regression analysis (Table 4), an increased APACHE II score (HR 1.11, 95% CI 1.09–1.13, $P<0.001$), cirrhosis (HR 2.15, 95% CI 1.48–3.13, $P<0.001$) and HIV infection (HR 2.03, 95% CI 1.11–3.72, $P=0.02$) were independent predictors of mortality controlling for age, serum creatinine ≥2.0 mg/dL and receipt of appropriate antifungal therapy >72 h after collection of a positive blood culture. When controlling for these other clinical characteristics, the timing of appropriate antifungal therapy was not associated with survival after *Candida* BSI. There was also no association between timing of appropriate antifungal therapy and microbiological resolution of *Candida* BSI, including persistent infection.

Because it was possible that patients who died before receiving 24 h of appropriate antifungal therapy may not have benefitted from this therapy even if treatment was administered in a timely manner, a secondary analysis was performed to account for this possibility. There were 18 patients who died prior to receiving 24 h of appropriate antifungal therapy, 14 of whom received appropriate therapy within 72 h of collection of first positive blood culture. These 14 patients were therefore reclassified as having not received timely appropriate therapy given the short duration of antifungal treatment before death (i.e. they were reclassified in the >72 h group). In this analysis, the 30 day mortality was significantly lower among patients who received appropriate antifungal therapy within 72 h of a positive culture being drawn (27% versus 40%, $P=0.004$) and the Kaplan–Meier curve revealed a significant difference in survival between the two groups (Figure 2b; $P=0.001$). In addition, on univariable (HR 1.75, 95% CI 1.26–2.43, $P=0.001$) and multivariable (HR 1.41, 95% CI 1.01–1.98, $P=0.045$) analyses, delayed receipt of antifungals was associated with decreased survival. An analysis was also performed excluding the 18 patients who died before receiving 24 h of appropriate antifungal therapy and the 30 day mortality remained significantly lower among patients who received appropriate antifungal therapy within 72 h of a positive culture being drawn (28% versus 37%, $P=0.047$).

Discussion

These data represent the largest study conducted to date assessing the importance of the timing of appropriate antifungal

Table 2. Characteristics of patients with *Candida* BSI ($n=446$)

	Antifungal timing			
Characteristic	≤72 h, $n=231$	>72 h, $n=215$	total $n=446$	*P* value
Age, mean (range)	52.0 (16–92)	54.3 (17–93)	53 (16–93)	0.14
Male, *n* (%)	107 (46)	96 (45)	203 (46)	0.72
Race, *n* (%)				0.02
black	112 (49)	117 (54)	229 (51)	
Caucasian	71 (31)	50 (23)	121 (27)	
Hispanic	38 (16)	40 (19)	78 (18)	
other	10 (4)	8 (4)	18 (4)	
Year of *Candida* BSI, *n* (%)				0.39
2001	21 (9)	30 (14)	51 (11)	
2002	24 (10)	20 (9)	44 (10)	
2003	19 (8)	28 (13)	47 (11)	
2004	31 (13)	25 (12)	56 (13)	
2005	20 (9)	19 (9)	39 (9)	
2006	33 (14)	24 (11)	57 (13)	
2007	27 (12)	30 (14)	57 (13)	
2008	36 (16)	24 (11)	60 (14)	
2009	20 (9)	15 (7)	35 (8)	
Underlying condition, *n* (%)				
haematological malignancy	15 (7)	12 (6)	27 (6)	0.69
solid tumour	63 (27)	57 (27)	120 (27)	0.86
allogeneic stem cell transplant	3 (1)	2 (1)	5 (1)	0.71
solid organ transplant	21 (9)	20 (9)	41 (9)	0.94
HIV infection	12 (5)	10 (5)	22 (5)	0.79
cirrhosis	36 (16)	36 (17)	72 (16)	0.74
diabetes mellitus	65 (28)	66 (31)	131 (29)	0.55
Clinical features/risk factors				
antibiotics within previous 2 weeks, *n* (%)	216 (94)	200 (93)	416 (93)	0.84
ICU, *n* (%)	128 (55)	121 (56)	249 (56)	0.85
mechanical ventilation, *n* (%)	85 (37)	83 (39)	168 (38)	0.69
total parenteral nutrition, *n* (%)	87 (38)	65 (30)	152 (34)	0.10
neutropenia, *n* (%)	13 (6)	6 (3)	19 (4)	0.14
renal replacement therapy, *n* (%)	58 (25)	61 (28)	119 (27)	0.44
serum creatinine ≥2.0 mg/dL, *n* (%)	75 (33)	97 (45)	172 (39)	0.01
low-dose steroids, *n* (%)	16 (7)	15 (7)	31 (7)	0.98
high-dose steroids, *n* (%)	53 (23)	42 (20)	95 (21)	0.38
surgery within previous 2 weeks, *n* (%)	55 (24)	49 (23)	104 (23)	0.80
APACHE II score, mean (range)	18.3 (3–45)	19.5 (1–50)	18.9 (1–50)	0.15
Candida species, *n* (%)				<0.001
C. albicans	135 (58)	88 (41)	221 (50)	
C. glabrata	30 (13)	69 (32)	99 (22)	
C. parapsilosis	31 (13)	28 (13)	59 (13)	
C. tropicalis	25 (11)	23 (11)	48 (11)	
C. krusei	2 (1)	4 (2)	6 (1)	
C. lusitaniae	1 (0.4)	2 (1)	3 (1)	
other *Candida* species	9 (4)	1 (0.5)	10 (2)	
Appropriate antifungal therapy, *n* (%)				0.28
fluconazole	125 (54)	52 (24)	177 (40)	
echinocandin	79 (34)	46 (21)	125 (28)	
amphotericin B	24 (10)	17 (8)	41 (9)	
voriconazole	3 (1)	3 (1)	6 (1)	
none	0	97 (45)	97 (22)	

therapy for survival after *Candida* BSI and one of only four similar studies[12–14] incorporating *in vitro* susceptibility results to assess the appropriateness of therapy. In our primary analysis, we could not demonstrate a significant association between the receipt of early appropriate antifungal therapy and outcomes, including mortality, microbiological response and persistent infection. However, we also took into account the fact that some patients, although they received antifungal treatment in a timely manner, may not have had an adequate duration of treatment to affect outcome. When we reclassified or excluded patients who died very soon after receiving appropriate therapy, we did find a significant mortality benefit to initiating antifungal therapy within 72 h of obtaining a positive blood culture.

Our results differ in some respects from those of previous investigators. In 2005 and 2006, two studies demonstrated a clear relationship between delaying the initiation of antifungal therapy and mortality. The first of these by Morrell *et al.*[8] concluded that in a retrospective analysis of 157 candidaemic patients, the administration of antifungal treatment ≥12 h after the collection of the first blood culture positive for *Candida* was an independent risk factor for hospital mortality (adjusted odds ratio 2.09, 95% CI 1.53–2.84, $P=0.018$). A major limitation of this study was that only nine patients received antifungal treatment within 12 h of having a blood culture positive for *Candida* obtained, limiting the ability to draw firm conclusions regarding the results due to the small sample size. The mortality rates for patients who received therapy at 12–24, 24–48 and >48 h after a positive blood culture were similar and were in the range of overall mortality of our study (32% versus 34%, respectively). Furthermore, routine antifungal susceptibility testing was not performed on *Candida* isolates and, thus, the appropriateness of therapy could not be assessed.

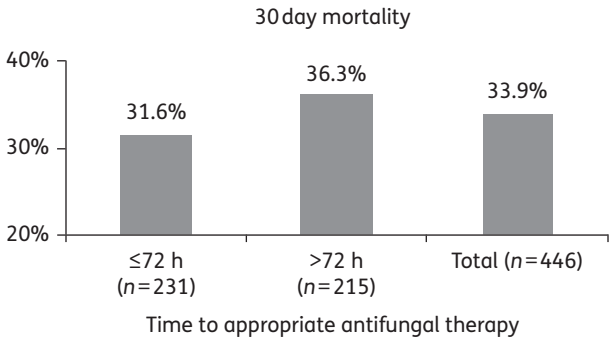

Figure 1. The 30 day mortality based on the time to initiation of appropriate antifungal therapy. $P=0.11$ between ≤72 and >72 h.

A second retrospective cohort study examined the mortality associated with the timing of fluconazole therapy in 230 patients with candidaemia at four medical centres.[9] Mortality rates were lowest for patients beginning fluconazole on the day the first positive blood culture was drawn and rates rose progressively with time to initiation of fluconazole. Earlier initiation of fluconazole was also associated with a decreased length of ICU stay. An important limitation of this study, as in that by Morrell *et al.*,[8] is the lack of antifungal susceptibility testing to assess the appropriateness of therapy. In addition, the study did not examine the effects of newer antifungal agents that are being increasingly used for invasive *Candida* infections.[21]

The results of subsequent studies on this topic have yielded conflicting results. Two smaller studies[15,17] have supported the conclusions of Morrell *et al.*[8] and Garey *et al.*[9] Patel *et al.*[15] described increased mortality among 31 patients with *Candida*-associated septic shock when appropriate antifungal therapy was not received within 15 h of blood sample collection.

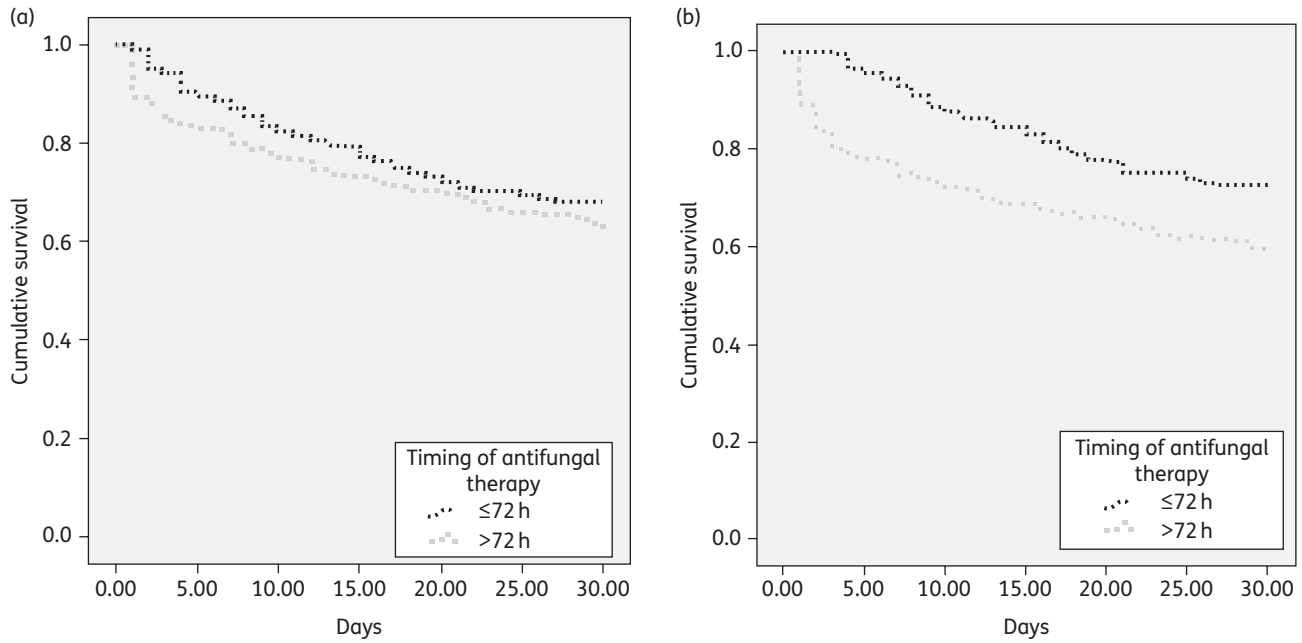

Figure 2. (a) Kaplan–Meier survival curves based on the time to initiation of appropriate antifungal therapy. $P=0.18$ between ≤72 and >72 h. (b) Kaplan–Meier survival curves based on the time to initiation of appropriate antifungal therapy, with patients who received <24 h of appropriate therapy classified in the >72 h group (see text). $P=0.001$ between ≤72 and >72 h.

Table 3. Univariable Cox regression: patient survival ($n=446$)

Characteristic	β	SE	HR	95% CI	*P* value
Antifungal timing, >72 h (reference category=≤72 h)	0.22	0.16	1.24	0.90–1.71	0.19
Age by year	0.02	0.01	1.02	1.01–1.03	0.001
Male gender	0.26	0.16	1.30	0.95–1.79	0.11
Race (reference category=white)					
black	−0.23	0.19	0.80	0.55–1.16	0.24
Hispanic	−0.08	0.24	0.74	0.68–1.72	0.74
Asian	−0.65	0.72	0.52	0.13–2.15	0.37
other	−0.04	0.60	0.96	0.30–3.10	0.95
Culture year					0.65
Underlying condition					
haematological malignancy	0.32	0.30	1.37	0.76–2.47	0.29
solid tumour	−0.02	0.18	0.98	0.69–1.41	0.92
allogeneic stem cell transplant	0.57	0.58	1.77	0.57–5.56	0.33
solid organ transplant	−0.71	0.36	0.49	0.24–1.00	0.051
HIV infection	0.67	0.30	1.95	1.08–3.52	0.03
cirrhosis	1.16	0.18	3.19	2.25–4.52	<0.001
diabetes mellitus	0.02	0.18	1.02	0.72–1.48	0.91
Clinical features/risk factors					
antibiotics within previous 2 weeks	1.32	0.58	3.73	1.19–11.68	0.02
ICU	0.91	0.18	2.47	1.73–3.53	<0.001
mechanical ventilation	0.89	0.16	2.42	1.76–3.34	<0.001
total parenteral nutrition	−0.31	0.18	0.74	0.52–1.04	0.09
neutropenia	0.42	0.34	1.52	0.77–2.98	0.23
renal replacement therapy	0.58	0.17	1.78	1.27–2.48	0.001
serum creatinine ≥2.0 mg/dL	0.83	0.16	2.30	1.67–3.17	<0.001
Steroids (reference category=no steroids)					
low dose	−0.61	0.42	0.55	0.24–1.24	0.15
high dose	0.37	0.18	1.45	1.01–2.08	0.04
surgery within previous 2 weeks	−0.65	0.23	0.52	0.34–0.82	0.004
APACHE II score	0.11	0.00	1.12	1.10–1.14	<0.001
Candida species (reference category=*C. albicans*)					
C. glabrata	0.40	0.19	1.50	1.02–2.19	0.04
C. krusei	0.46	0.59	1.59	0.50–5.05	0.43
other *Candida* species	−0.10	0.21	0.90	0.60–1.35	0.62
Fluconazole susceptibility, non-susceptible (reference category=susceptible)	0.48	0.21	1.61	1.08–2.42	0.02
Antifungal therapy (reference category=fluconazole)					
amphotericin B	0.26	0.30	1.29	0.71–2.45	0.40
echinocandin	0.36	0.21	1.43	0.95–2.15	0.09
voriconazole	−0.43	1.01	0.65	0.09–4.72	0.67
Microbiological cure ($n=357$)	−1.10	0.23	0.33	0.21–0.52	<0.001

SE, standard error of the regression.

From the same institution as Morrell *et al.*,[8] Zilberberg *et al.*[17] studied 90 patients with candidaemia requiring ICU admission. Eighty out of 90 patients failed to received appropriate antifungal therapy within 24 h of infection; in this group the hospital mortality rate was 29% compared with 0% among the 10 patients who received early appropriate therapy ($P=0.059$). Both studies were limited by the lack of availability of routine antifungal susceptibility testing.

Several more recent studies have failed to find an association between the timely receipt of antifungal therapy and mortality after *Candida* BSI.[10–14,16] Taur *et al.*[16] studied 106 patients with cancer and *Candida* BSI, and reported that a longer period

Table 4. Multivariable Cox regression: patient survival ($n=446$)

Characteristic	HR	95% CI	*P* value
APACHE II score	1.11	1.09–1.13	<0.001
Cirrhosis	2.15	1.48–3.13	<0.001
HIV infection	2.03	1.11–3.72	0.02
Age (in years)	1.01	1.00–1.02	0.06
Serum creatinine ≥2.0 mg/dL	0.84	0.58–1.20	0.34
Antifungal timing >72 h (reference category = ≤72 h)	1.10	0.80–1.52	0.57

from the time a positive blood culture was drawn until it became positive ('incubation time') was independently associated with an increased risk of hospital mortality on multivariable analysis. However, the total length of time from when a positive blood culture was drawn to the time of antifungal initiation did not independently affect outcome. From a sample of 96 patients without antifungal susceptibility testing, Fernandez *et al.*[10] reported no difference in the time to antifungal therapy among survivors (61 h) versus non-survivors (59 h) of *Candida* BSI. Hsu *et al.*[11] investigated patients who received an echinocandin for *Candida* BSI; early (≤3 days, $n=107$) versus late (>3 days, $n=62$) initiation of caspofungin for candidaemia was associated with an improved overall response (77% versus 57%, $P=0.006$), but it was not associated with infection-related or all-cause hospital mortality. Parkins *et al.*[14] analysed 199 patients with invasive candidiasis and although appropriate empirical antifungal therapy was protective against hospital mortality, there was no association between timing of antifungal administration and mortality. In this study, antifungal susceptibility testing was available for 89% of the study participants. Klevay *et al.*[12] and Kludze-Forson *et al.*[13] reported antifungal susceptibilities for 100% of their study patients. Klevay *et al.*[12] conducted a matched study of patients with BSI caused by *C. albicans* ($n=54$) or *C. glabrata* ($n=54$), and found that patients with *C. glabrata* were not less likely to receive appropriate antifungal therapy and that there was no association between timing of therapy and 30 day mortality. Similarly, Kludze-Forson *et al.*[13] reported the absence of an association between the timing of appropriate antifungal therapy and hospital mortality among 123 candidaemic patients; increased severity of illness score was the only independent predictor of mortality.

The reason for differing results among various studies investigating the impact of timing of antifungal therapy on outcomes is unknown, but multiple complex factors are likely responsible. Study design details, such as the size of study populations and subgroups, differences in patient comorbidities and illness severity, and variations in the antifungal drugs studied, may have affected the ability to discern the true effect of appropriate early antifungal therapy. With the exception of the study by Patel *et al.*,[15] our study population had the highest mean APACHE II scores. It is possible that results obtained in the studies by Morrell *et al.*[8] and Garey *et al.*[9] may not be as applicable to a more critically ill population of patients. Importantly, we obtained different findings when reclassifying the small subgroup of patients who died before receiving 24 h of effective antifungal therapy as having never received appropriate therapy; in this analysis, the 30 day mortality and survival results are more consistent with the original findings by Morrell *et al.*[8] and Garey *et al.*,[9] showing an impact of earlier antifungal therapy on outcome. None of the previous studies assessing the timing of therapy in candidaemia has performed a similar analysis and this may be an important consideration in any future studies of this type. Lastly, the biggest difference may be the fact that many earlier studies did not employ the routine use of antifungal susceptibility testing to assess the appropriateness of therapy. In any case, it may be that patient comorbidities and critical illness, or pathogen factors, may be just as important if not more important in determining mortality than early administration of antifungal therapy.

The strengths of the current study are its size, use of antifungal susceptibility data, strict criteria for assessing the appropriateness of therapy and the inclusion of detailed information about study patients, including multiple severity-of-illness indicators. However, it is important to recognize that the retrospective design did not allow the capture of all possible data that could have been important in assessing outcomes, such as symptom onset. In addition, the study was conducted at a single centre and therefore may not be directly applicable to other institutions or settings. Lastly, it is assumed in the study design that blood cultures were drawn at the first suspicion of infection, but it is possible that the time to appropriate antifungal therapy was longer for some patients than was assessed if there was a delay in obtaining blood cultures in candidaemic patients. This type of bias could explain higher than expected mortality in patients who appeared to receive early appropriate antifungal therapy. Despite these limitations, our data are consistent with prior studies indicating a high mortality rate among hospitalized patients with candidaemia as well as a particularly high mortality rate among those who never receive appropriate antifungal therapy. Furthermore, we confirmed that BSI due to *C. glabrata* or fluconazole-non-susceptible *Candida* isolates are associated with a higher mortality,[22–25] as are those BSI due to *C. krusei* where fluconazole therapy is administered.[22,26]

In conclusion, among a large group of patients with *Candida* BSI, we did not find a survival benefit to early appropriate antifungal therapy when analysing the study population as a whole, but noted that outcomes could be affected by whether patients had received a certain minimum duration of antifungal therapy. Our results are supported by the inclusion of routine antifungal susceptibility testing to optimally assess the appropriateness of treatments and the fact that the use of newer antifungal medications was included in the analysis. Given the high mortality seen in most studies of candidaemic patients, additional manoeuvres are needed to try to improve outcomes in these patients.

Acknowledgements

This work was presented in part at the Forty-fifth Annual Meeting of the Infectious Diseases Society of America, San Diego, CA, USA, 2007 (Abstract # 1665).

Funding

This work was supported by a grant from Merck & Co., Inc.

Transparency declarations

S. A. G. has received funds for consulting work organized by Pfizer, Inc. and Ortho-McNeil Pharmaceutical, Inc., and has received research grant support from Merck & Co., Inc., Pfizer, Inc., Enzon Pharmaceuticals Inc. and AstellasPharma US, Inc. N. M. C. has received funds for consulting work organized by AstellasPharma US, Inc. and Pfizer, Inc. and speaking for Enzon Pharmaceuticals Inc. and GlaxoSmithKline, and has received research grant support from Merck & Co., Inc., Pfizer, Inc., Enzon Pharmaceuticals Inc. and AstellasPharma US, Inc. All other authors: none to declare.

Author contributions

Study design: S. A. G., W. M. J. and N. M. C. Data collection: S. A. G., K. B., C. T., S. G. and N. M. C. Data analysis: S. A. G., J. E. L. and N. M. C. Manuscript writing/revision: S. A. G., K. B., C. T., S. G., J. E. L., W. M. J. and N. M. C.

References

1 National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990–May 1999, issued June 1999. *Am J Infect Control* 1999; **27**: 520–32.

2 Gudlaugsson O, Gillespie S, Lee K *et al*. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis* 2003; **37**: 1172–7.

3 Sipsas NV, Lewis RE, Tarrand J *et al*. Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001–2007): stable incidence but changing epidemiology of a still frequently lethal infection. *Cancer* 2009; **115**: 4745–52.

4 Walsh TJ, Groll AH. Emerging fungal pathogens: evolving challenges to immunocompromised patients for the twenty-first century. *Transpl Infect Dis* 1999; **1**: 247–61.

5 McNeil MM, Nash SL, Hajjeh RA *et al*. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin Infect Dis* 2001; **33**: 641–7.

6 Ibrahim EH, Sherman G, Ward S *et al*. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; **118**: 146–55.

7 Leibovici L, Shraga I, Drucker M *et al*. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998; **244**: 379–86.

8 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.

9 Garey KW, Rege M, Pai MP *et al*. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006; **43**: 25–31.

10 Fernandez J, Erstad BL, Petty W *et al*. Time to positive culture and identification for *Candida* blood stream infections. *Diagn Microbiol Infect Dis* 2009; **64**: 402–7.

11 Hsu DI, Nguyen M, Nguyen L *et al*. A multicentre study to evaluate the impact of timing of caspofungin administration on outcomes of invasive candidiasis in non-immunocompromised adult patients. *J Antimicrob Chemother* 2010; **65**: 1765–70.

12 Klevay MJ, Ernst EJ, Hollanbaugh JL *et al*. Therapy and outcome of *Candida glabrata* versus *Candida albicans* bloodstream infection. *Diagn Microbiol Infect Dis* 2008; **60**: 273–7.

13 Kludze-Forson M, Eschenauer GA, Kubin CJ *et al*. The impact of delaying the initiation of appropriate antifungal treatment for *Candida* bloodstream infection. *Med Mycol* 2010; **48**: 436–9.

14 Parkins MD, Sabuda DM, Elsayed S *et al*. Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive *Candida* species infections. *J Antimicrob Chemother* 2007; **60**: 613–8.

15 Patel GP, Simon D, Scheetz M *et al*. The effect of time to antifungal therapy on mortality in candidemia associated septic shock. *Amer J Ther* 2009; **16**: 508–11.

16 Taur Y, Cohen N, Dubnow S *et al*. Effect of antifungal therapy timing on mortality in cancer patients with candidemia. *Antimicrob Agents Chemother* 2010; **54**: 184–90.

17 Zilberberg MD, Kollef MH, Arnold H *et al*. Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study. *BMC Infect Dis* 2010; **10**: 150.

18 Pappas PG, Rex JH, Sobel JD *et al*. Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004; **38**: 161–89.

19 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.

20 Pfizer, Inc. *Diflucan Prescribing Information*. New York: Pfizer, Inc., 2010.

21 Pappas PG, Kauffman CA, Andes D *et al*. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503–35.

22 Choi HK, Jeong SJ, Lee HS *et al*. Blood stream infections by *Candida glabrata* and *Candida krusei*: a single-center experience. *Korean J Intern Med* 2009; **24**: 263–9.

23 Dimopoulos G, Ntziora F, Rachiotis G *et al*. *Candida albicans* versus non-*albicans* intensive care unit-acquired bloodstream infections: differences in risk factors and outcome. *Anesth Analg* 2008; **106**: 523–9.

24 Kovacicova G, Krupova Y, Lovaszova M *et al*. Antifungal susceptibility of 262 bloodstream yeast isolates from a mixed cancer and non-cancer patient population: is there a correlation between in-vitro resistance to fluconazole and the outcome of fungemia? *J Infect Chemother* 2000; **6**: 216–21.

25 Slavin MA, Sorrell TC, Marriott D *et al*. Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. *J Antimicrob Chemother* 2010; **65**: 1042–51.

26 Krcmery V Jr, Spanik S, Kunova A *et al*. Nosocomial *Candida krusei* fungemia in cancer patients: report of 10 cases and review. *J Chemother (Florence)* 1999; **11**: 131–6.