

Initial management of candidemia at an academic medical center: Evaluation of the IDSA guidelines[☆]

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Abstract

Treatment of candidemia is more complicated because of the changing epidemiology of *Candida* and introduction of newer antifungal agents. Utilization and benefit of practice guidelines and infectious disease consultation for the management of candidemia has not been previously described in the routine clinical setting. We prospectively studied the impact of the Infectious Disease Society of America (IDSA) guidelines for the management of candidemia and infectious disease consultation on clinical outcomes in 119 patients with candidemia at a tertiary care hospital. Medical records were reviewed to capture data concerning use of antifungal agents, management of central venous catheters, and infectious disease consultation. Initial antifungal therapy was consistent with the IDSA guidelines in 76% of patients. Variation from the guidelines was independently associated with higher mortality (24% versus 57%, $P = 0.003$). Infectious disease consultation was independently associated with lower mortality (18% versus 39%, $P < 0.01$). Use of the IDSA guidelines and infectious disease consultation service was found to improve patient outcomes in patients with candidemia at our institution. Further studies should be performed to validate newer guidelines in a clinical setting at other institutions.

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1. Introduction

Candida species are a common cause of nosocomial bloodstream infections with significant associated morbidity, mortality, and increased health-care costs (Edmond et al., 1999; Pittet et al., 1997; Rentz et al., 1998; Wey et al., 1988). Surveillance data from the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) study from 1995 to 2002 indicate that *Candida* is the fourth most common cause of nosocomial bloodstream infection comprising 9% of bloodstream infections (Wisplinghoff et al., 2004). *Candida albicans* remains the single most common *Candida* species isolated, but non-

albicans species are increasing in frequency, and often have varying degrees of antifungal susceptibility, thereby complicating the choice of initial antifungal therapy (Wisplinghoff et al., 2004; Pappas et al., 2003; Trick et al., 2002; Rangel-Frausto et al., 1999; Kao et al., 1999; Viscoli et al., 1999).

Guidelines for the management of candidemia have been recently published by the Infectious Diseases Society of America (IDSA) and focus on management of central venous catheters (CVCs) and specific antifungal therapy (Rex et al., 2000; Pappas et al., 2004). These guidelines are largely based on data from clinical trials and may not necessarily reflect clinical practice. The extent to which the IDSA guidelines for management of candidemia are used in clinical practice is unknown. Clinical outcomes in patients with candidemia whose management is consistent with the IDSA guidelines for candidemia have not been described, particularly with regards to management of CVCs and initial antifungal therapy. Moreover, the

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specific impact of the infectious disease consultant in the care of patients with candidemia has not been prospectively evaluated.

We were interested in assessing the management of candidemia at our institution and comparing actual management practices to those recommended by the treatment guidelines. Specifically, we focused on the management of CVCs, use of antifungal medications, utilization of the infectious diseases consultation service, and clinical outcomes based on adherence to the guidelines available at the time this study was conducted (Rex et al., 2000).

2. Methods

2.1. Study design

We prospectively identified consecutive cases of candidemia in adult patients ≥ 18 years at the University of Alabama at Birmingham from July 2002 to July 2003 by daily review of blood culture data logbooks from the University Hospital microbiology laboratory. Candidemia was defined as the first isolation of *Candida* species from at least 1 culture of peripheral blood or blood cultured through a CVC. Blood cultures were performed using the BacT/ALERT3D method (bioMérieux, Durham, NC), and cultures found to be positive for yeast by Gram stain were plated on Sabouraud's dextrose agar. *Candida* species were identified by morphology on corn meal agar and assimilation profile on API 20C (bioMérieux). Patient chart review was performed and data were prospectively collected and included demographics, APACHE II score at the time the blood culture positive for *Candida* was drawn, and *Candida* species isolated (Knaus et al., 1985). Clinical characteristics of patients at onset of candidemia (day on which initial positive blood culture was drawn) were recorded and included use of immunosuppressive drugs, surgery within the past month, renal insufficiency (Cr ≥ 1.4 mg/dL), diabetes mellitus, neutropenia, HIV infection, receipt of an organ transplant, location in an intensive care unit (ICU), presence of CVC, receipt of at least 1 dose of a systemic antifungal medication within 14 days before current episode of candidemia, use of broad-spectrum antibiotics, and isolation of *Candida* species from other sites. Treatment data were collected and included choice of initial antifungal therapy, management of CVCs, and outcomes. Neutropenia was defined as ≤ 500 neutrophils per mm^3 . In addition, we determined if patients were referred for infectious diseases consultation and if the primary service caring for the patient was a medical or surgical service.

2.2. Clinical outcomes

Patient outcomes included all-cause mortality and resolution of infection at 6 weeks after the first positive culture and were determined by review of medical records of hospitalization or follow-up visits and conversation with

the patient's medical provider in some cases. Resolution of infection was defined as the absence of clinical symptoms or signs attributable to candidemia (fever, hypothermia, leukocytosis, and/or hypotension), with or without documented negative follow-up blood cultures. Mortality was defined as death by any cause within 6 weeks of the first positive culture.

2.3. IDSA guidelines

Initial management of candidemia was assessed in the context of the 2000 IDSA guidelines for the management of candidemia that were available during the study period (Rex et al., 2000). These guidelines recommend (1) removal of existing CVCs when feasible, (2) use of fluconazole or conventional amphotericin B as initial therapy in hemodynamically stable patients, (3) use of conventional amphotericin B in hemodynamically unstable patients or patients who develop candidemia while on azole drugs, and (4) treatment for all patients with candidemia. Recommendations on the use of a lipid preparation of amphotericin B were based on our institutional pharmacy guidelines as follows: lipid preparation of amphotericin B for patients with renal insufficiency as demonstrated by a serum creatinine (Cr) ≥ 2.5 mg/dL or creatinine clearance (CrCl) < 30 mL/min (in nontransplant patients), serum Cr > 2.0 mg/dL (in transplant patients), doubling of serum Cr (≥ 1.2 mg/dL in nontransplant patients), or intolerance to conventional amphotericin B despite appropriate measures. The recommended duration of antifungal therapy is 14 days after the last positive blood culture and resolution of clinical signs or symptoms of infection (Rex et al., 2000). Two physicians (JWB and MP) prospectively reviewed initial antifungal treatment and consistency with the guidelines as defined above.

2.4. Exclusion criteria

Patients were excluded from the study if they were less than 19 years, if they were not hospitalized at the time of blood culture positivity for *Candida*, or if the patient died before blood cultures became positive for *Candida* or before initiation of antifungal treatment. Patients who received caspofungin, voriconazole, or investigational antifungal drugs for the initial treatment of candidemia were excluded from the initial treatment and outcome analyses because of the lack of treatment guidelines for these drugs.

2.5. Statistical methods

Demographic and baseline characteristics are presented using simple descriptive statistics. Student's *t*-test was used to compare the APACHE II scores for those subjects' therapies in agreement with the IDSA guidelines versus those that varied with the guidelines. Fisher exact test was used for univariate categorical factors, and the logistic regression model was used for multivariable analysis.

3. Results

During the study period, we identified 119 adult patients with candidemia. Males comprised 50% of patients, 58% were White, and 41% African American. Mean age was 51.8 years (range 19–85), mean APACHE II score was 16.1 ± 0.71 , and 71% were on medical services at the time blood cultures were drawn. Commonly noted baseline characteristics included presence of CVCs in 109 (92%) patients, use of broad-spectrum antibiotics in 101 (85%) patients, and renal insufficiency in 57 (48%) of 119 patients (Table 1).

3.1. *Candida species*

One hundred twenty-two *Candida* bloodstream isolates were cultured from 119 patients. *C. albicans* was the most common species isolated (41%), followed by *C. parapsilosis* (24%), *C. glabrata* (20%), *C. tropicalis* (8%), *C. krusei* (4%), *C. lusitanae* (2%), and *C. guillieromondi* (1%). Four patients had more than 1 *Candida* species isolated from blood cultures (*C. glabrata* and *C. tropicalis* in 2 patients, *C. albicans* and *C. tropicalis* in 1 patient, and *C. albicans* and *C. parapsilosis* in 1 patient). After institution of therapy, repeat blood cultures were performed in 73% of patients to document clearance of candidemia. Antifungal susceptibility testing was performed on all isolates and reported in a separate article (Baddley et al., 2004). Mortality data were available for 104 (87.4%) of 119 patients. *C. albicans* was associated with higher mortality (32%) than non-*albicans* species (26%, $P = 0.19$). Among non-*albicans* species, mortality was highest with *C. krusei* (40%), followed by *C. tropicalis* (37.5%), *C. parapsilosis* (26%), and *C. glabrata* (22.2%).

Table 1
Baseline patient characteristics ($N = 119$)

Characteristic	
Race	
White	69 (58)
African American	49 (41)
Other	1 (1)
Sex	
Male	59 (50)
Age (years)	51.8 (19–85)
APACHE II score	16.1/16 (0–47)
Medical patients	85 (71)
Surgical patients	34 (29)
Underlying condition or risk factors at time positive blood culture was drawn	
CVCs present	109 (92)
Broad-spectrum antibiotics	101 (85)
Renal insufficiency	57 (48)
Presence in ICU	57 (48)
Immunosuppression	41 (34)
Total parental nutrition	37 (31)
Surgery	35 (29)
Diabetes mellitus	35 (29)
Systemic antifungal therapy	31 (26)
Neutropenia	16 (13)

Values are given as n (%), mean [range], or mean/median [range].

Table 2
Initial antifungal therapy

Antifungal agent	
Fluconazole	90 (75)
Amphotericin B	13 (11)
Lipid amphotericin B preparation	6 (5)
Voriconazole	1 (1)
Caspofungin	1 (1)
None	8 (7)

Values are given as n (%).

3.2. Antifungal therapy

The choice of initial antifungal therapy among 119 patients is shown in Table 2. Fluconazole was the initial choice in 90 (75%) patients, amphotericin B in 13 (11%) patients, and a lipid preparation of amphotericin B in 6 (5%) patients. Eight (7%) patients received no antifungal treatment. One patient each received caspofungin and voriconazole as the initial therapy and were not included in the initial antifungal therapy analysis. The standard dose of fluconazole was 400 mg daily or the equivalent dose based on renal function. One patient was treated with 200 mg of fluconazole daily. Of 117 patients who were evaluable for initial antifungal therapy analysis, therapy was consistent with IDSA guidelines in 89 (76%) patients, and deviated from the guidelines in 28 (24%) patients (Table 3). Variation from guidelines included the use of fluconazole when either conventional or a lipid preparation of amphotericin B was indicated ($n = 18$), not receiving any antifungal therapy ($n = 8$), and use of lipid amphotericin B when fluconazole or conventional amphotericin B was indicated ($n = 2$). Variation from IDSA guidelines occurred in 23 (28%) of 83 patients on medical services and 5 (15%) of 34 patients on surgical services ($P = 0.16$). Mortality was higher among patients in the variation group (57%) than the agreement group (24%; $P = 0.003$) and was independent of APACHE II score. Mortality data were unavailable in 15 (13%) patients. Among the 92 patients for whom data on resolution of infection were available, resolution of infection was higher for patients in the agreement group (83%) than for patients in the variation group (55%, $P = 0.01$). The

Table 3
Variation of initial antifungal therapy from the IDSA guidelines and outcomes

	Agreement with IDSA guidelines (%)	Variation from IDSA guidelines (%)	P^a
No. of patients	89 (76)	28 (24)	NA
Mean APACHE II score	14.7	20.5	0.009
Medical patients	60/83 (72)	23/83 (28)	0.16
Surgical patients	29/34 (85)	5/34 (15)	
No. of deaths	19/76 (24)	14/26 (57)	0.003 ^b
No. of clinical resolution of infection	58/70 (83)	12/22 (55)	0.01

Values are given as n (%), mean, or n/N (%).

^a Fisher exact test unless otherwise specified.

^b Logistic regression analysis.

Table 4
Mortality in patients with infectious disease consultations and CVCs

	Deaths	<i>P</i>
Infectious diseases consult		
Yes	6 (18)	0.0083 ^a
No	27 (39)	
CVCs removed at diagnosis		
Yes	16 (27)	0.05 ^b
No	27 (39)	

Values are given as *n* (%).

^a Logistic regression analysis.

^b Fisher exact test.

distribution of *Candida* species did not differ significantly between the agreement and variation groups.

3.3. Infectious disease consultation

Thirty-seven (32%) of 119 patients were referred for infectious diseases consultation. Mortality information was unavailable in 3 (8%) patients who received infectious diseases consultation and 12 (15%) patients who did not receive infectious diseases consultation. Patients who received infectious diseases consultation had similar mean APACHE II scores compared with those patients who did not receive infectious diseases consultation (16.5 and 16.0, respectively). Mortality was 18% (6/34) in patients who received infectious diseases consultations versus 39% (27/68) in patients who were not referred for infectious diseases consultation, independent of APACHE II score ($P = 0.0083$, Table 4).

3.4. Central venous catheters

CVCs were removed in 90 (83%) of 109 patients and retained in 15 (14%) patients; status could not be determined in 4 patients. Fifty-nine (56%) of 105 patients in whom management of CVCs was known had CVCs removed within 24 hours of diagnosis of candidemia, and mortality rate was 27%, compared with 39% in patients in whom CVCs were retained beyond 24 hours or not removed ($P = 0.05$, Table 4). However, multivariate analysis using APACHE II score as a covariate showed this difference was not significant.

4. Discussion

The extent to which practice guidelines for the management of invasive candidiasis are used in clinical practice is not well documented. Controversy exists in the benefit of guidelines in the management of infectious diseases, and effectiveness of the IDSA guidelines for candidemia in clinical practice has not been evaluated. Data supporting a choice of antifungal therapy often results from clinical trials and retrospective observational studies, but these data do not necessarily reflect the approach to patient care in the clinical setting. Moreover, it is unclear if application of practice guidelines to day-to-day patient care will yield the same

outcomes as in controlled clinical trials. By examining the practice trends in the treatment of candidemia at our institution, we hoped to provide evidence that published guidelines for the treatment of candidemia are effective in the routine clinical setting.

IDSA guidelines suggest that the choice of antifungal agent at the onset of candidemia should be made on the basis of the clinical status of the patient, prior or current use of antifungal medications, and local *Candida* species and susceptibility patterns. The initial choice of antifungal agent is important, as species and susceptibility data may not be known for several days and may result in potentially ineffective therapy. In addition, the initial antifungal agent used should promote clinical resolution of candidemia and prevent complications of infection. In our study adherence to the IDSA guidelines was associated in lower mortality than deviation from the guidelines. Despite the higher APACHE II scores in the variation group than the agreement group, higher mortality in the variation group remained statistically significant after multivariate analysis. Although clinical factors beyond those described in this study may have contributed to the difference in mortality, this finding supports adherence to the guidelines.

Fluconazole alone was the most common antifungal agent used as initial therapy for candidemia in our population. Use of fluconazole when amphotericin B was indicated (e.g., a clinically unstable patient) accounted for the majority of the patients (64%) whose initial antifungal therapy varied from the IDSA guidelines. The preference for fluconazole as initial therapy in unstable patients may be because of ease of use of fluconazole, concerns over toxicity of conventional amphotericin, and cost of lipid formulations of amphotericin B. Although fluconazole has been used to treat candidemia in unstable patients, and initial therapy with fluconazole compared with amphotericin B in unstable patients was not found to affect outcome in a retrospective review, clinical trial data supporting the use of fluconazole in unstable patients are lacking (Anaissie et al., 1998). Some experts prefer amphotericin B in unstable patients for its broader spectrum of activity and fungicidal activity in contrast to the fungistatic activity of fluconazole (Pappas et al., 2004; Buchner et al., 2002; Edwards et al., 1997). We preferred to follow the recommendation for use of amphotericin B as initial antifungal therapy in unstable patients as suggested in the IDSA guidelines. In the absence of more convincing data from controlled clinical trials, reserving fluconazole for clinically stable patients is reasonable.

The attributable mortality rate of patients with candidemia is estimated to be 38–61%, supporting the recommendation that treatment is offered to all patients with candidemia (Pappas et al., 2003; Gudlaugsson et al., 2003; Wey et al., 1988). Among those patients whose initial antifungal therapy agreed with the IDSA guidelines, all-cause mortality was lower (24%) than the estimated attributable mortality from these prior studies and may be due to unmeasured factors of this specific patient population.

A larger study with a control population may better define attributable mortality. Some patients may have spontaneous resolution of candidemia without antifungal treatment, especially if removable foci of infection (e.g., CVCs) are present. The low mortality in patients who did not receive therapy in our study (no deaths reported in 6 patients for whom outcome data were available) was probably because of the combination of decreased severity of illness and removal of CVCs.

Removal of existing CVCs is recommended by the IDSA guidelines for the management of candidemia, despite the paucity of data strongly supporting this recommendation (Rex et al., 2000; Nucci and Anaissie, 2002). In our study, early removal of existing CVCs showed a trend toward decreased mortality (27% versus 39%). Although this difference was not statistically significant, a larger study is needed to further evaluate the effect of early removal of CVCs on outcomes.

Infectious disease consultation has been found to reduce antibiotic expenditures, improve rates of cure of infection, decrease mortality in patients with general infectious disorders, improve the general care of patients with community acquired pneumonia, prevent hospitalization of patients with AIDS, and improve clinical outcomes in patients with *Staphylococcus aureus* bacteremia (Fox et al., 2001; Fraser et al., 1997; Gomez et al., 1996; Fowler et al., 1998; Hirsch et al., 2001; Turner et al., 1994). The benefit of the infectious disease specialist in the care of patients with candidemia in a routine clinical setting has not previously been described. Infectious disease consultation at our institution appears to be beneficial for patients with candidemia as reflected by the difference in mortality (18% versus 39%). The effect of selection bias favoring decreased mortality with infectious diseases consultation cannot be excluded; however, this study provides evidence supporting the utilization of infectious diseases consultation services in the management of patients with candidemia and a need for a more thorough evaluation.

In summary, we found that initial management of candidemia was in accordance to the IDSA practice guidelines in the majority of patients at our institution—existing CVCs were removed and appropriate antifungal therapy was initiated. Variation of initial antifungal therapy from the guidelines was associated with higher mortality and a lower rate of clinical resolution of candidemia, supporting the use of these guidelines in our routine clinical care. Infectious disease consultation was noted to have a significant positive impact on overall mortality and may become more important as the number of therapeutic options to treat candidemia increases. A limitation of this study was the use of guidelines published in 2000. New guidelines for the management of candidemia have been recently published and include guidelines for use of caspofungin the use of which has greatly increased at our institution since the time of this study (Pappas et al., 2004). Validation of the new guidelines for the management of candidemia should be

performed in the clinical setting. It is important to remember that guidelines are merely guidelines, and not applicable to every clinical setting. We must understand that many factors influence the treatment of candidemia and use of the practice guidelines to assist in the management of patients with candidemia may result in better patient outcomes.

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