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Adherence to clinical practice guidelines for the treatment of candidemia at a Veterans Affairs Medical Center

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ABSTRACT

Objectives: The primary objective of this study was to examine the appropriateness of candidemia management at a Veterans Affairs Medical Center as recommended by the 2009 Infectious Diseases Society of America (IDSA) guidelines for treatment of *Candida* infections.

Methods: A retrospective analysis of 94 adult patients with blood cultures positive for *Candida* spp. was performed. Patients were stratified by severity of disease into two groups: non-neutropenic, mild-moderate disease (Group 1, n = 54, 56%) and non-neutropenic, moderate-severe disease (Group 2, n = 40, 42%).

Results: Adherence to the IDSA recommendations for recommended antifungal drug, dose, and duration of therapy was low in both groups (16.7% in Group 1 and 17.5% in Group 2). Although adherence was not associated with higher clinical resolution of infection (P = 0.111), it was associated with a significantly lower mortality rate (P = 0.001) when compared to variance from the guidelines at 6 weeks.

Conclusion: Although adherence to published guidelines for treating patients with candidemia was suboptimal at our institution, patients that were managed based on the guidelines had a statistically lower mortality rate.

Keywords: Candidemia, *Candida* infections, Veterans Affairs

Introduction

Candida spp. are currently estimated to be the fourth most common cause of nosocomial bloodstream infection (BSI) in the United States.[1] *Candida albicans* is still the most prevalent individual *Candida* species, but isolation of non-*C.albicans* continues to increase over time.[2] Candidemia is an opportunistic BSI occurring most frequently in immunocompromised patients and those with advancing age and frailty.[3] Early clinical manifestations of candidemia are largely non-specific, which can complicate initial treatment strategies.[4] In addition, compared to bacterial spp., the average time to positivity of *Candida* spp. in blood cultures is 48-72 h with some *Candida* spp. taking several days longer to grow.[4,5] This can further complicate management of infection leading to increased mortality. Overall mortality associated with candidemia is currently between 31% and 44% and is increased in infections due to more resistant species such as *Candida glabrata* and *Candida krusei*.[1,3,5,6]

The Infectious Diseases Society of America (IDSA) first published recommendations for the treatment of candidiasis in 2000.[7] These recommendations were updated in 2004 and again in 2009, driven by the availability of new and less toxic antifungal agents.[8,9] In the 2009 update, drugs in the echinocandin class were favored in critically ill patients or those with a previous history of azole exposure as this cohort was more likely to be infected with an azole-resistant organism.

While two studies have assessed adherence to the 2004 IDSA guidelines for the treatment of candidemia, we are unaware of other published reports of adherence to the 2009 guidelines.[9] In addition, the effect of guideline adherence on clinical outcomes is unknown. This study examines the management of candidemia at our institution including the impact of infectious disease (ID) consultation and recommendations according to the 2009 guidelines.

Methods

Study design

A single-center, retrospective, review of candidemia was carried out at our Veterans Affairs (VA) Medical Center which is an academic teaching institution with 357 acute care beds, a 40-bed spinal cord injury center, rehabilitation, geriatric unit, and an on-site ID consulting service. Non-neutropenic patients who had >1 blood culture(s) that were positive for a *Candida* species between July 1, 2009, and June 30, 2013, were identified using Theradoc™, a clinical surveillance system that is integrated with

the VA computerized patient record system. Electronic medical records were retrospectively reviewed to collect the following information: Patient demographics, Charlson comorbidity index at the time of hospital admission,[10] diabetes mellitus (defined as controlled [hemoglobin A1c <7.5%] or suboptimal [hemoglobin A1c >7.5%] according to institutional policy), use of broad-spectrum antibiotics for ≥7 days in the preceding 21 days before positive blood culture, previous antifungal use, presence of *Clostridium difficile* infection confirmed by polymerase chain reaction during hospitalization, and presence of *Candida* spp. in any site other than blood at any time before positive blood culture for *Candida* spp. The following data were collected as of the day the first positive blood culture was obtained: Presence of a central venous catheter (CVC), medical unit where the positive blood culture was taken, use of total parenteral nutrition, and immunosuppressive drugs and hemodynamic clinical status. Data collected once blood cultures yielded *Candida* spp. or afterward included initial antifungal agent chosen, loading dose (if applicable), maintenance dose, renal function with azole dose adjusted for renal insufficiency (<50 mL/min and adjusted for body weight when appropriate), time to initiation of antifungal after confirmation of candidemia, management of CVCs, consultation with ID service, time to follow-up blood cultures, and consultation with ophthalmology service for dilated eye examination.

Patients were excluded from the study if: (1) They were not hospitalized at the time of the positive culture confirming candidemia was present; (2) they were neutropenic; or (3) if the result of the positive blood culture was reported after the patient had expired or was discharged. The study was approved by the Institutional Review Board and the Research and Development Committee at our VA Medical Center before patient enrollment.

Study objectives

The primary objective of this research was to assess adherence to the recommendations from the 2009 IDSA update for the treatment of candidemia. Only non-neutropenic patients were categorized based on the severity of their disease into two groups according to IDSA recommendations defined as follows: mild-moderate disease (hemodynamically stable with systolic blood pressure ≥90 mm/Hg, Group 1); and moderate-severe disease (hemodynamically unstable, with systolic blood pressure <90 mmHg or stated as hemodynamically unstable by attending physician, Group 2). Patients who had previously been treated with azoles were stratified to Group 2.

Outcomes

The adherence to IDSA guidelines for management and treatment outcome was assessed for each treatment group. The primary outcome was the extent to which pharmacological and non-pharmacological recommendations from the 2009 IDSA guidelines update were observed. Pharmacological recommendations included a selection of an appropriate initial antifungal, use of a loading dose (where indicated) and correct maintenance dose. Non-neutropenic patients with mild-moderate disease (Group 1) are recommended to receive fluconazole, anidulafungin, caspofungin, micafungin, amphotericin B deoxycholate, or lipid formulation of amphotericin B with appropriate loading and maintenance doses. Non-neutropenic patients with moderate-severe disease (Group 2) are recommended to receive the same therapy as patients with mild-moderate disease with the exception of fluconazole because of the greater risk of infection by an azole-resistant *Candida* spp. Full adherence to IDSA recommendations was defined as correct initial antifungal, dose, and duration of therapy. Variance from IDSA guidelines was defined as incorrect initial antifungal, dose, or duration of therapy. The dosage was deemed correct if patients received the correct loading and maintenance doses adjusted for renal function when appropriate.

Non-pharmacological recommendations included the correct duration of therapy and removal of a CVC when appropriate. The IDSA recommends that patients receive 14 days of antifungal therapy after the first negative blood culture to document clearance of candidemia.

Secondary outcomes were to assess the impact of adherence to guidelines on patient outcomes. Patient outcomes included assessment of resolution of signs and symptoms of infection and all-cause mortality. The additional secondary outcomes assessed all-cause mortality at 6 weeks with regard to ID consultation, CVC removal, and the following IDSA recommended performance measures: Antifungal therapy initiated within 24 h and follow-up blood cultures drawn within 48 h of initial positive culture.

Statistical analysis

Descriptive statistics were used to evaluate patient background characteristics. Two-tailed Chi-square (or Fisher's exact test, when appropriate) and Student's *t*-test were used to assess for statistical significance. Statistical significance was assessed at $\alpha = 0.05$.

Results

Patients

Of 106 patients with >1 positive blood culture for *Candida* between July 1, 2009, and June 30, 2013, 94 patients met eligibility requirements. The most common cause for exclusion was non-treatment ($n = 10$), either because they had died before the positive blood culture was reported, or because of a decision not to treat due to palliative care status. Two neutropenic patients were excluded from the analysis (Table 1).

Candida species

Of 94 *Candida* isolates during the study, 36 (38.3%) were *C. albicans*, and 29 (30.8%) were *C. glabrata*. The numbers

Table 1: Patient demographics, stratified by disease severity[a]

Characteristic	Group 1 (*n*=54)	Group 2 (*n*=40)	*P* value
Males, no. (%)	54 (100)	35 (88)	0.01
Mean±SD age, year	68±12	63±11	0.06
Caucasian (%)	26 (48)	27 (68)	0.06
Black or African-American (%)	24 (44)	9 (23)	0.03
Hispanic or Latino (%)	2 (4)	3 (8)	0.65
American Indian or Alaskan Native (%)	1 (4)	0 (0)	1.00
Native Hawaiian or Pacific Islander (%)	0	1 (3)	0.43
Not reported (%)	1 (2)	0 (0)	1.00
Mean±SD Charlson Comorbidity index	3.48±2.06	4.2±2.42	0.11
Mean±SD Creatinine Clearance (mL/min)	64±33[b]	55±36	0.35
Medical patients (%)	32 (59)	31 (78)	0.06
Medicine/spinal cord injury (%)	25 (46)	13 (33)	0.18
Medical intensive care unit/cardiac care unit (%)	4 (7)	17 (43)	<0.01
Emergency room (%)	3 (6)	1 (3)	0.63
Surgical patients (%)	22 (41)	9 (23)	0.06
Step-down unit (%)	15 (28)	2 (5)	<0.01
Surgical intensive care unit (%)	7 (13)	7 (18)	0.54
CVC present (%)	37 (69)	32 (80)	0.21
Broad-spectrum antibiotics (%)	34 (63)	25 (63)	0.96
Colonization before fungemia (%)	19 (35)	21 (53)	0.09
Unifocal source (%)	18 (33)	19 (48)	0.17
Multifocal source (%)	1 (2)	2 (5)	0.57
Total parental nutrition (%)	23 (43)	12 (30)	0.21
Diabetes (%)	21 (39)	17 (43)	0.72
Controlled (A1c<9%) (%)	14 (26)	14 (35)	0.34
Uncontrolled (A1c>9%) (%)	7 (13)	3 (8)	0.51
Clostridium difficile positive (%)	6 (11)	8 (20)	0.23
Immunosuppression (%)	1 (2)	10 (25)	<0.01

[a]*P* values indicate pairwise comparison between Group 1 and Group 2. [b]*n*=53 in Group 1 for mean creatinine clearance. CVC: Central venous catheter, SD: Standard deviation

of isolates of other species and the proportions of *albicans* and non-*C. albicans* were similar between Groups 1 and 2 (Table 2).

Primary outcomes

In the 94 patients who were treated for candidemia, initial treatment was with an azole in 48 cases (fluconazole in 47, voriconazole in one case) or with an echinocandin in 44 cases (micafungin in 26, anidulafungin in 14, and caspofungin in four cases). No patient received amphotericin B as initial therapy. Four patients did not receive antifungal therapy; the reason for non-treatment is unclear.

Adherence to IDSA recommendations for initial antifungal therapy was correct in 79 of 94 (84%) patients. Correct drug and dose were, however, chosen in only 34 of 94 (36.2%) patients. When the recommended duration of therapy was also considered, adherence to guidelines was only 16 of 94 (17%).

Table 2: *Candida* spp. implicated in cases of candidemia, stratified by disease severity[a]

Candida species	Group 1	Group 2	Total
C. albicans (%)	24 (25)	12 (12.5)	36 (37.5)
C. glabrata (%)	15 (15.6)	12 (12.5)	29 (30.2)
C. tropicalis (%)	8 (8.3)	10 (10.4)	18 (18.7)
C. parapsilosis (%)	2 (2)	5 (5.2)	7 (7.2)
C. krusei (%)	3 (3)	0 (0)	3 (3.1)
C. guilliermondii (%)	0 (0)	1 (1)	1 (1)
Not identified (%)	2 (2)	0 (0)	2 (2)

[a]Data presented as number (percentage) for each group or for the total number of cases. *C. albicans: Candida albicans, C. glabrata: Candida glabrata, C. tropicalis: Candida tropicalis, C. parapsilosis: Candida parapsilosis, C. krusei: Candida krusei, C. guilliermondii: Candida guilliermondii*

Similar trends were observed for patients with mild to moderate (Group 1) or moderate to severe (Group 2) disease. As shown in Table 3, in Group 1, adherence to IDSA recommendations for initial antifungal was correct in 52 of 54 (96.2%) patients.

Correct drug and dose were, however, chosen in only 15 of 54 patients (27.7%). After including duration, adherence to guidelines was only 9 of 54 (16.7%) patients. In Group 2, adherence for initial antifungal was correct in 25 of 40 (62.5%) patients. Correct drug and dose were chosen in only 18 of 40 (45%) patients. Correct drug, dose, and duration of therapy were correct in 7 of 40 (17.5%) patients. When assessed by species type, choice of drug, dosage, and duration were correct for 4 of 36 (11.1%) patients with *C. albicans* and 12 of 60 (20%) patients with non-*C. albicans*.

Secondary outcomes

Although statistically insignificant, adherence to IDSA guidelines was associated with a trend toward greater likelihood of clinical resolution of infection (13 of 16 [81.2%] vs. 47 of 78 [60.2%], $P = 0.11$). However, all-cause mortality at 6 weeks was significantly lower in patients who were treated according to IDSA guidelines (0/16 [0%] vs. 33 of 78 [42.3%], $P = 0.001$).

Table 3: Primary outcomes (pharmacological and non-pharmacological IDSA recommendations)

Group 1, *n*=54 patients	
Correct initial antifungal agent	52 patients (96%)
Correct agent+correct loading and maintenance dose	15 patients (27.8%)
Correct agent, loading, maintenance doses, and duration of therapy	9 patients (16.7%)
Group 2, *n*=40 patients	
Correct initial antifungal agent	25 patients (62.5%)
Correct agent+correct loading and maintenance dose	18 patients (45%)
Correct agent, loading, maintenance doses, and duration of therapy	7 patients (17.5%)

*Data presented as number (percentage) of patients within each group. IDSA: Infectious Diseases Society of America

Among those patients whose therapy adhered to guidelines, clinical resolution of infection occurred in 8 of 9 (88.8%) Group 1 patients and 5 of 7 (71.4%) Group 2 patients (Table 4). Clinical resolution of infection in patients whose therapy did not adhere to guidelines occurred at different rates in Group 1 versus Group 2 patients: (37 of 45 [82.2%] vs. 10 of 33 [30.3%], respectively). When assessed by the group, adherence was not significantly associated with higher clinical resolution of infection within 6 weeks for Group 1 ($P = 1.00$) or Group 2 ($P = 0.81$) when compared to variance from guidelines.

Mortality at 6 weeks, however, was significantly lower in patients whose treatment followed IDSA guidelines (0 of 16 patients died, 0%) than in those whose treatment did not (33 of 78 patients died, 42.3%, $P = 0.001$). The rate of death in Group 1 and Group 2 patients differed based on whether they were treated in accord, or at variance, with IDSA guidelines (0 of 16 [0%] vs. 13 of 45 Group 1 patients [28.9%], $P = 0.09$), and 0 of 7 (0%) versus 20 of 33 (60.6%) Group 2 patients ($P \leq 0.01$).

The 6-week mortality rate was insignificantly higher in patients who had an ID consultation in Group 1 (12 of 38 patients) compared to those without a consultation (1 of 16; $P = 0.79$) (Table 4). Regarding CVC removal, 32 of 37 (86.4%) Group 1 patients and 28 of 34 (82.3%) of Group 2 patients who initially had a CVC present, underwent removal after

Table 4: Secondary outcomes in patients with adherence and variance from IDSA guidelines

Clinical resolution of infection	**Adherence to IDSA guidelines**	**Variance from IDSA guidelines**	***P* value**
Group 1 (%)	8/9 (88.8)	37/45 (82)	1.00
Group 2 (%)	5/7 (71.4)	10/33 (30.3)	0.81
Mortality	**Adherence to IDSA guidelines**	**Variance from IDSA guidelines**	***P* value**
Group 1 (%)	0/9	13/45 (28.8)	0.09
Group 2 (%)	0/7	20/33 (60.6)	<0.01
Mortality	**ID consult**	**ID not consulted**	***P* value**
Group 1	12/38	1/16	0.079
Group 2	11/31	7/9	0.05
Mortality	**CVC removed**	**CVC not removed**	***P* value**
Group 1	3/32	2/5	0.13
Group 2	11/28	3/6	0.67
Mortality	**Antifungal therapy begun within 24 h of positive culture**	**Antifungal therapy not begun within 24 h of positive culture**	***P* value**
Group 1	12/48	1/6	1.00
Group 2	18/37	0/3	0.24
Mortality	**Follow-up blood cultures w/in 48 h**	**No follow-up blood cultures/>48 h**	***P* value**
Group 1	6/31	7/23	0.35
Group 2	13/21	5/19	0.02

IDSA: Infectious Diseases Society of America, ID: Infectious diseases, CVC: Central venous catheter

the demonstration of candidemia (Table 4). Catheter removal was not significantly associated with a reduced mortality rate ($P = 0.13$ for Group 1; $P = 0.67$ for Group 2) (Table 4). 37 of 94 (39.4%) patients underwent ophthalmological examination after confirmation of candidemia, 87 of 94 (92.6%) patients had initial antifungal therapy started within 24 h of confirmation of candidemia and 54 of 94 (57.4%) patients had a follow-up blood culture within 24-48 h of initial positive blood culture (Table 4).

Discussion

Our results indicate strikingly low overall adherence to IDSA guidelines in the treatment of BSI due to *Candida* species at our VA Medical Center. The major changes in the 2009 update were the inclusion of the echinocandin class of antifungals and the stratification of patients into non-neutropenic versus neutropenic with a focus on risk factors for resistant *Candida* spp. Two previous studies have shown similar failures to comply with recommendations with 2004 guidelines, but to our knowledge, no study to date has assessed adherence to the 2009 guidelines or the impact of adherence on clinical outcomes and mortality.[5,11] Patel *et al.* found that 76% of patients were treated in accordance with 2004 guidelines.[11] A prospective observational study conducted by the prospective antifungal therapy alliance that considered initial antifungal choice, dosage (with loading and maintenance, when appropriate) and duration of therapy found a similar 76% adherence to guidelines.[5] That study did not include dosage adjusted for renal function. Accordingly, we considered adherence to include the correct initial antifungal drug and correct loading and maintenance doses with appropriate adjustments for renal function and at least 14 days duration of therapy after first blood culture negative for *Candida* spp. This may partly explain the low rate of guideline adherence in our study.

During the 4 years of this study, 46% of patients received an azole as initial therapy, and 42% received an echinocandin. Furthermore, low adherence may have been due to patients not receiving loading doses, receiving lower than recommended loading doses or dosing that was inappropriate for renal function. In addition, follow-up blood cultures, an important component of therapy recommendations, were not done in 28 patients. The 2009 IDSA guidelines recommend echinocandins as an initial option for all patients with candidemia regardless of risk for resistant species. The validity of this recommendation was borne out by the finding that 30% of isolates at our institution were *C. glabrata*, which has either dose-dependent susceptibility or resistance to azole antifungals. Some additional benefits of echinocandins compared to fluconazole include the lack of need for dose adjustment for renal function, standard dosing (not based on weight as for fluconazole or voriconazole) and improved activity against azole-resistant *Candida* spp. Micafungin also has an added benefit of not requiring a loading dose. These benefits can all lead to improved adherence to dosing recommendations and possibly improved outcomes. Although we did not compare azoles and echinocandins directly, echinocandins have been shown to have an advantage over fluconazole for the treatment of candidemia and other invasive candidiasis.[12,13]

Comparison of clinical outcomes and mortality rate in Groups 1 and 2 showed no significant association between removal of CVCs and improvement of clinical outcomes or reduced mortality. Patients received CVCs for the administration of total parenteral nutrition, vasopressor therapy and/or hemodialysis which may have made it less feasible to remove catheters even in the setting of candidemia thus affecting the assessment of clinical outcomes and mortality. The IDSA recommends CVC removal especially for non-neutropenic patients with documented cases of candidemia if possible, but controversy exists regarding this recommendation.[14]

Consultation with an ID specialist has been shown to be beneficial in the management of infections resulting in improved outcomes and reduced mortality.[15,16] An experimental study of the potential role for pharmacists in improving adherence to guidelines showed that time to appropriate antimicrobial therapy for fungal infection was significantly reduced, but in-hospital mortality and hospital costs were unchanged.[17] The higher mortality rate seen in Group 1 may have been due to delayed consultation of ID specialists by the primary service, as these patients were not considered as ill as patients in Group 2. A larger study assessing ID consultation may be warranted to further assess clinical significance.

There were several limitations to this study. First, this was a retrospective, observational chart review study which might not be used to demonstrate cause and effect, only associations. In addition, drug and dose received and duration of therapy are limited to chart documentation. Furthermore, since a majority of VA patient population is elderly, Caucasian and Black/African American males, this study may not represent the general population. Finally, the sample size studied may have been small. Because the primary objectives assessed adherence to IDSA guidelines, we aimed to maximize the number of patients enrolled.

Conclusion

In summary, our study shows that the rate of adherence to published IDSA guidelines for treating patients with candidemia was low at our institution. Although adherence to initial antifungal recommendations was appropriate, adherence to recommendations for dose and duration of therapy was suboptimal and most suboptimal in the sickest group of patients (Group 2). Adherence to recommendations was similar for *C. albicans* and non-*albicans* candidemia. However, mortality rate was lower in patients whose treatment adhered to IDSA guidelines compared to those whose treatment did not. The results of this study have been used to help educate health-care providers and create protocols for better antimicrobial

management of candidemia at our institution. Finally, the IDSA has just promulgated a new set of guidelines for the management of *Candida* infections. The present study should serve as an impetus to study adherence to those guidelines and the impact on outcomes.

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