Septic Shock Attributed to *Candida* Infection: Importance of Empiric Therapy and Source Control

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**Background.** Delayed treatment of candidemia has previously been shown to be an important determinant of patient outcome. However, septic shock attributed to *Candida* infection and its determinants of outcome have not been previously evaluated in a large patient population.

**Methods.** A retrospective cohort study of hospitalized patients with septic shock and blood cultures positive for *Candida* species was conducted at Barnes-Jewish Hospital, a 1250-bed urban teaching hospital (January 2002–December 2010).

**Results.** Two hundred twenty-four consecutive patients with septic shock and a positive blood culture for *Candida* species were identified. Death during hospitalization occurred among 155 (63.5%) patients. The hospital mortality rate for patients having adequate source control and antifungal therapy administered within 24 hours of the onset of shock was 52.8% (n = 142), compared to a mortality rate of 97.6% (n = 82) in patients who did not have these goals attained (P < .001). Multivariate logistic regression analysis demonstrated that delayed antifungal treatment (adjusted odds ratio [AOR], 33.75; 95% confidence interval [CI], 9.65–118.04; P = .005) and failure to achieve timely source control (AOR, 77.40; 95% CI, 21.52–278.38; P = .001) were independently associated with a greater risk of hospital mortality.

**Conclusions.** The risk of death is exceptionally high among patients with septic shock attributed to *Candida* infection. Efforts aimed at timely source control and antifungal treatment are likely to be associated with improved clinical outcomes.

**INTRODUCTION**

Severe sepsis and septic shock are the major causes of admission and death in intensive care units (ICUs) globally, with hospital mortality ranging between 30% and 50% [1–3]. Inappropriate initial antimicrobial therapy (IIAT), defined as an antimicrobial regimen that lacks in vitro activity against the isolated organism(s) responsible for the infection, can lead to treatment failures and adverse patient outcomes [4]. Individuals with bloodstream infection, pneumonia, and severe sepsis or septic shock appear to be at particularly high risk of excess mortality when IIAT is administered [5–13]. The most recent Surviving Sepsis Guidelines recommend empiric combination therapy targeting likely bacterial “and/or fungal” pathogens as a means to decrease the likelihood of administering IIAT [14]. Several recent investigations have demonstrated the importance of IIAT as an outcome predictor in patients with sterile site infections attributed to *Candida* species [15–18]. However, the prevalence of IIAT in patients with septic shock associated with *Candida* infection and its influence on patient outcomes has not been previously well described. Therefore, we performed a study with 2 goals: (1) to
examine the appropriateness of the antimicrobial therapy prescribed to patients with septic shock attributed to *Candida* infection, and (2) to understand the influence of appropriate antimicrobial therapy, and other potentially modifiable processes of care, on the outcome of patients with septic shock associated with *Candida* infection.

**MATERIALS AND METHODS**

Study Location and Patient Population

This study was conducted at a university-affiliated, urban teaching hospital: Barnes-Jewish Hospital (1250 beds). Over a 9-year period (January 2002–December 2010), all hospitalized patients with septic shock and a positive blood culture for *Candida* species were eligible for inclusion. Patients receiving comfort care and those with a do-not-resuscitate order were excluded. This study was approved by the Washington University School of Medicine Human Studies Committee.

Study Design and Data Collection

Utilizing a retrospective cohort study design, patients with culture-positive septic shock were identified by the presence of a blood culture positive for *Candida* species combined with primary or secondary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes indicative of acute organ dysfunction and the need for vasopressors. Patient specific baseline characteristics and process of care variables were collected from the automated hospital medical record, microbiology database, and pharmacy database of Barnes-Jewish Hospital.

The baseline characteristics collected included: age, gender, ethnicity, body mass index, comorbidities, and severity of illness. The Acute Physiology and Chronic Health Evaluation (APACHE) II [19] was calculated based on clinical data present during the 24 hours after the positive blood cultures were obtained. Infection-related characteristics examined were infection source, pathogen species, prior antibiotic exposure, source control, and the timing of antifungal therapy relative to the onset of septic shock. Other process-of-care variables assessed included total intravenous fluid administration in the first 24 hours following shock onset, transfusion of red blood cells, and the use of drotrecogin alfa (activated), corticosteroids, or granulocyte colony-stimulating factor. The primary outcome variable was all cause hospital mortality.

Definitions

To be included in the analysis, patients had to meet criteria for septic shock based on discharge ICD-9-CM codes for acute organ dysfunction, as previously described [1]. The organs of interest included the heart, lungs, kidneys, bone marrow (hematologic), brain, and liver. Patients were classified as having septic shock attributed to *Candida* infection if vasopressors (norepinephrine, dopamine, epinephrine, phenylephrine, or vasopressin) were initiated within 24 hours of the blood culture collection date and time that subsequently yielded a *Candida* species and no other infection potentially accounting for septic shock was present. Patients on vasopressors for greater than 24 hours prior to the collection of a blood culture that subsequently yielded a *Candida* species were excluded.

Antimicrobial treatment was classified as appropriate if the prescribed antibiotic regimen included an antifungal agent directed against the isolated *Candida* species and was administered within 24 hours of the onset of septic shock. Timing of antifungal therapy was determined from the interval between the onset of septic shock and administration of the first intravenous dose of antifungal therapy. Septic shock onset was defined as the start of a vasopressor agent. The timing of antifungal therapy was analyzed according to 2 intervals: therapy administered within 12 hours and within 24 hours of septic shock onset. Adequate source control was defined as removal of any preexisting central vein catheters or documented surgical or radiologic procedures to drain abscesses or other fluid collections thought to be the source of *Candida* infection within 24 hours of the onset of septic shock. Timing of central vein catheter removal was based on medical record review and confirmed with review of patient radiographs.

The Microbiology Laboratory did not routinely perform antimicrobial susceptibility testing on fungal isolates during the study period. Appropriate selection and dosing of the antifungal therapy was determined from the Infectious Disease Society of America guidelines and the package inserts of the antimicrobial agents [20].

Data Analysis

Continuous variables were reported as mean ± SD. The Student *t* test was used when comparing normally distributed data, and the Mann-Whitney *U* test was employed to analyze non-normally distributed data. Categorical data was expressed as frequency distributions and the χ² test was used to determine if differences existed between groups. We performed multiple logistic regression analysis to identify clinical risk factors that were associated with hospital mortality (SPSS, Inc, Chicago, IL). All risk factors that were significant at 0.20 in the univariate analysis were included in the corresponding multivariable analysis. All variables entered into the model were examined to assess for colinearity. All tests were 2-tailed, and a *P* value < .05 was determined to represent statistical significance.

RESULTS

Two hundred twenty-four patients with septic shock attributed to *Candida* infection as documented by a positive blood
White blood cell count

APACHE II score 24.8 ± 3.4 28.7 ± 3.6 <.001

Trauma/emergent surgery, n (%) 20 (29.0) 36 (23.6) .358

End-stage renal disease, n (%) 6 (8.7) 23 (14.8) .206

Cirrhosis, n (%) 6 (8.7) 29 (18.7) .057

Solid cell tumor with metastases (%) 6 (8.7) 29 (18.7) .057

Organ transplant, n (%) 2 (2.9) 7 (4.5) .725

Class IV congestive heart failure, n (%) 5 (7.2) 30 (19.4) .021

COPD, n (%) 3 (4.3) 15 (9.7) .402

Cardiovascular, n (%) 69 (100.0) 155 (100.0) 1.000

Renal 19 (27.5) 104 (67.7) <.001

Respiratory 30 (43.5) 136 (87.7) <.001

Hematologic 9 (13.0) 80 (51.6) <.001

Central nervous system 5 (7.2) 78 (50.3) <.001

Hepatic 7 (10.1) 74 (47.7) <.001

Coagulopathy 23 (33.3) 101 (65.2) <.001

Number of acquired organ dysfunctions 2.4 ± 1.4 5.2 ± 1.8 <.001

Table 1. Patient Characteristics and Acquired Organ Dysfunction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lived (n = 69)</th>
<th>Died (n = 155)</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td>Age, years</td>
<td>57.0 ± 15.7</td>
<td>63.4 ± 14.4</td>
<td>.003</td>
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<tr>
<td>Male, n (%)</td>
<td>38 (55.1)</td>
<td>90 (58.1)</td>
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<td>Ethnicity, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>White</td>
<td>55 (79.7)</td>
<td>118 (76.6)</td>
<td>.819</td>
</tr>
<tr>
<td>African American</td>
<td>13 (18.8)</td>
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<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.4)</td>
<td>2 (1.3)</td>
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</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.9 ± 7.0</td>
<td>27.4 ± 7.6</td>
<td>.647</td>
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<td>2 (2.9)</td>
<td>12 (7.7)</td>
<td>.236</td>
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<tr>
<td>Leukemia, n (%)</td>
<td>3 (4.3)</td>
<td>13 (8.4)</td>
<td>.402</td>
</tr>
<tr>
<td>Solid cell tumor with metastases (%)</td>
<td>6 (8.7)</td>
<td>29 (18.7)</td>
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<tr>
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<td>2 (2.9)</td>
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<td>23 (14.8)</td>
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<tr>
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<td>30 (19.4)</td>
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<td>End-stage renal disease, n (%)</td>
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<td>Trauma/emergent surgery, n (%)</td>
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<td>18 (11.6)</td>
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<td>APACHE II score (×10⁹/L)</td>
<td>24.8 ± 3.4</td>
<td>28.7 ± 3.6</td>
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<td>White blood cell count</td>
<td>17.2 ± 12.4</td>
<td>18.1 ± 19.6</td>
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<tr>
<td>Serum albumin (g/dL)</td>
<td>2.6 ± 0.6</td>
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<td>Acquired organ dysfunction, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular</td>
<td>69 (100.0)</td>
<td>155 (100.0)</td>
<td>1.000</td>
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<tr>
<td>Renal</td>
<td>19 (27.5)</td>
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</tr>
<tr>
<td>Number of acquired organ dysfunctions</td>
<td>2.4 ± 1.4</td>
<td>5.2 ± 1.8</td>
<td>&lt;.001</td>
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</table>

Values are expressed as mean ± standard deviation.
Abbreviations: APACHE, acute physiology and chronic health evaluation; COPD, chronic obstructive pulmonary disease.

culture were included in the study. Fourteen additional patients with candidemia and septic shock were not included in the analysis, as they had concomitant bacteremia that may have accounted for their infection. The mean age was 61.4 ± 15.0 years (range, 20–95 years) with 128 (57.1%) males and 96 (42.9%) females (Table 1). Sixty-five (29.0%) patients had an underlying malignancy and the mean APACHE II score was 27.5 ± 4.0 (range, 17–37). One hundred fifty-five patients (69.2%) died during their hospitalization. Nonsurvivors had significantly lower serum albumin, significantly greater age and APACHE II scores, were more likely to have class IV congestive heart failure, and a greater number of acquired organ dysfunctions compared to survivors (Table 1).

Forty-one patients (18.3%) received no antifungal therapy prior to their death due to delayed recognition of the presence of fungal infection. The mean time period between onset of septic shock and death in these 41 patients was 48.0 ± 25.4 hours (median 41.7 hours; 25th and 75th percentiles, 26.0 hours and 68.9 hours; range, 12.8 hours–109.1 hours). For these 41 patients, the mean time period between the collection of a blood culture that subsequently grew a *Candida* species and the reporting of that culture result was 55.8 ± 15.4 hours (median 55.0 hours; 25th and 75th percentiles, 43.0 hours and 68.5 hours; range, 29.0 hours–90.0 hours). Eight out of 41 (19.5%) had their *Candida*-positive blood culture results reported prior to death. One hundred eighty-eight patients (80.4%) received antifungal therapy that was determined to be appropriate for the species of *Candida* causing their infection and adequately dosed within 24 hours of shock. The remaining 3 patients (1.3%) received delayed antifungal therapy as defined by the receipt of treatment 24 hours after the onset of septic shock.

Hospital nonsurvivors were statistically less likely to have received antifungal therapy within 24 hours of the onset of shock and more likely to have received granulocyte colony-stimulating factor, red blood cell transfusions, inadequate source control, mechanical ventilation, and a greater total infusion of crystalloid solution compared to survivors (Table 2). The Kaplan-Meier curves in Figure 1 demonstrate that patients receiving appropriate antifungal therapy within 24 hours of the onset of shock (n = 180) had a significantly greater likelihood of survival compared to patients not receiving appropriate antifungal therapy within 24 hours of the onset of shock (n = 44). However, among the 183 patients who received antifungal therapy, there was no significant difference in the timing of that therapy relative to the onset of hypotension between survivors and nonsurvivors ([median with 25th and 75th percentiles] survivors: 756 minutes (522.5 minutes, 1120.25 minutes); nonsurvivors: 672.5 minutes (464.75 minutes, 899.5 minutes); P = .267) (Figure 2).

Sixty-two patients had inadequate source control related to the potential source of their *Candida* infection. In 45 (72.6%) of these patients, inadequate source control was due to failure to remove tunneled and nontunneled central venous catheters, subcutaneous ports, and dialysis catheters that were present when the patient had positive blood cultures for *Candida* species. Patients with underlying malignancy (lymphoma, leukemia, solid cell tumor with metastases) were more likely to have a tunneled catheter in place compared to patients without malignancy (15.6% vs 3.8%; P = .002). Fourteen patients (22.6%) had intra-abdominal sources of infection with inadequate source control, 1 patient (1.6%) had an intrathoracic source of infection with inadequate source control,
and 2 individuals (3.2%) had orthopedic infections with inadequate source control. Figure 3 shows that the presence of both delayed antifungal administration and inadequate source control had a similar risk of mortality compared to the presence of either one of these variables occurring alone.

Multivariate logistic regression analysis demonstrated that the presence of a solid cell tumor with metastases, class IV congestive heart failure, increasing APACHE II scores (1-point increments), inadequate source control, red blood cell transfusion, and delayed administration of antifungal therapy were independently associated with greater hospital mortality, while increasing serum albumin levels (1 g/dL increments) was independently associated with a lower risk of hospital mortality (Table 3). Hospital length of stay was significantly shorter for patients who received no antifungal therapy in the 24 hours following the onset of shock [8.5 days (4.25 days, 20.5 days) vs...
with septic shock attributed to *Candida* infection with positive blood cultures. This observation was confirmed in a multivariate analysis controlling for potential confounding variables. Our data also suggest that most patients with candidemia do not have concomitant bacteremia.

Most patients with septic shock do not have the microbial etiology of infection identified at the time that antibiotics are prescribed. Vincent et al examined 13,796 adult patients in a point prevalence study, of whom 7087 (51%) were classified as infected on the day of the study [21]. Seventy percent of infected patients had positive microbial isolates, while 30% were culture negative: 47% of the positive isolates were gram-positive, 62% gram-negative, and 19% fungal. Similar results have been demonstrated in studies of immune modulating therapies for sepsis where about a third of patients with sepsis are culture negative and fungemia accounts for less than 15% of the infections [22, 23]. Given the observed delay in establishing the microbiologic diagnosis of candidemia, several investigators have developed prediction algorithms aimed at allowing earlier identification of *Candida* bloodstream infection [24–26]. Unfortunately, these prediction tools have not undergone prospective validation in terms of improving patient treatment or clinical outcomes [26, 27].

Our study supports the recent observation of Guzman and coworkers that septic shock complicating candidemia is a near fatal condition [28]. In 2 previous studies conducted at our institution, inadequate source control and delays in the administration of antifungal therapy were found to be independent predictors of mortality for candidemia [15, 17]. The hospital mortality rates observed in those 2 earlier studies were 31.8% and 29.4%. However, the percentage of patients with septic shock was only 25.5% and 16.3%, respectively. It required 9 years of data from our institution to put together a similarly sized cohort of patients with septic shock due to *Candida* infection in order to conduct a statistically meaningful analysis.

Garey et al examined 192 patients with candidemia who did not receive prior antifungal therapy [16]. The hospital mortality rate was 25% for their cohort, and they identified a statistical relationship between increasing delay of antifungal administration from the time a positive blood culture was drawn and hospital mortality. However, less than half of their patients were in an intensive care unit. More recently, Das and colleagues examined 107 episodes of candidemia in a tertiary hospital in the United Kingdom with a crude mortality of 37% [29]. Only 14 (13%) of their patients had either severe sepsis or septic shock. The presence of septic shock was identified as an independent predictor of crude mortality. Our study differs from these earlier investigations in focusing only on patients with septic shock. Additionally, our study utilized an institutional database that allowed timing of antifungal

**DISCUSSION**

Our study demonstrated that delayed administration of appropriate antifungal therapy and inadequate source control were the most important determinants of outcome among patients

![Figure 3. Hospital mortality according to whether or not patients received antifungal therapy and adequate source control within 24 hours of the onset of septic shock. (P < .001 for the comparison of patients receiving both antifungal therapy and adequate source control within 24 hours of the onset of shock to the other 3 groups.)](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AOR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
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<td>Solid cell tumor with metastases</td>
<td>6.01</td>
<td>2.98–12.10</td>
<td>.010</td>
</tr>
<tr>
<td>Class IV congestive heart failure</td>
<td>4.96</td>
<td>2.53–9.68</td>
<td>.017</td>
</tr>
<tr>
<td>APACHE II Score (1-point increments)</td>
<td>1.37</td>
<td>1.26–1.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inadequate source control</td>
<td>77.40</td>
<td>21.52–278.38</td>
<td>.001</td>
</tr>
<tr>
<td>Red blood cell transfusion</td>
<td>6.49</td>
<td>4.06–10.38</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum albumin (1 g/dL increments)</td>
<td>0.42</td>
<td>0.30–0.59</td>
<td>.012</td>
</tr>
<tr>
<td>Delayed antifungal treatmentb</td>
<td>33.75</td>
<td>9.65–118.04</td>
<td>.005</td>
</tr>
</tbody>
</table>


Abbreviations: AOR, adjusted odds ratio; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval.

*Other covariates not in the table had a *P* value >.05, including age, corticosteroids, granulocyte colony-stimulating factor, and total crystalloid fluid administered within 24 hours of shock.

*Defined as patients who received no antifungal therapy within 24 hours of the onset of shock.
therapy relative to the onset of septic shock to be accurately assessed.

The basic management principles of septic shock focus on 3 key elements—appropriate antimicrobial therapy, hemodynamic resuscitation, and adequate source control [14, 30]. Fluid administration and the use of vasopressors appeared to be similar between survivors and nonsurvivors and were based on goal-directed endpoints at our institution during the study period [3]. Source control has previously been shown to be an important determinant of outcome for patients with serious infections attributed to Candida species [31, 32]. However, controversy exists regarding the need to remove all central venous catheters in candidemic patients [33]. Probably the least controversial issue is the importance of timely antimicrobial administration. Kumar et al showed that administration of adequate antimicrobial therapy within the first hour of documented hypotension was associated with a survival rate of 79.9%, and each 1-hour delay in antimicrobial therapy was linked to a 7.6% per hour decrease in survival [34]. Similarly, Ferrer et al evaluated 2796 patients with severe sepsis having a hospital mortality of 41.6% [13]. The only treatment independently associated with lower hospital mortality for the entire patient cohort was early broad-spectrum antibiotic treatment (treatment within 1 hour vs no treatment within first 6 hours of diagnosis). Our findings in septic shock attributed to Candida infection support the importance of early appropriate therapy as a determinant of patient outcome.

Given the overall importance of early appropriate therapy of septic shock attributed to Candida infection as an outcome determinant, clinical strategies facilitating the attainment of this goal are needed. Preliminary studies of biomarkers and rapid microbiologic diagnostic techniques hold promise for earlier identification of Candida species as the etiology of septic shock [35, 36]. Similarly, clinical and colonization-based prediction tools may assist in the identification of patients with candidemia [24–27, 37]. Unfortunately, these instruments lack adequate accuracy or can result in treatment delay that make them less than ideal clinical tools. Although unproven to improve outcomes, our results suggest that a strategy of empiric or preemptive therapy of septic shock with antifungal therapy is reasonable whenever patients are at risk for infection with Candida species [31]. However, such an approach has the risk of promoting unnecessary antifungal therapy. Therefore, if empiric or preemptive therapy for Candida infection is employed in septic shock, then efforts to de-escalate therapy should be instituted as soon as clinically and microbiologically indicated to avoid further promotion of resistance.

It is important to note that we identified variables other than delayed antifungal therapy and inadequate source control as potential predictors of mortality. Severity of illness, red blood cell transfusion, and comorbidities were associated with mortality in our multivariate analysis. Rex et al also found severity of illness to be associated with mortality in a study of candidemic patients treated with amphotericin or fluconazole [38]. However, they did not specifically examine for delays in therapy and excluded patients with high acuity of illness, having a mean APACHE II score of 16 in their patients. Our study focused on patients with septic shock where the risks of delayed therapies may be more likely to result in mortality.

There are several important limitations of our study that should be noted. First, the study was performed at a single center and the results may not be generalizable to other institutions. Second, we did not examine all aspects of care that may have influenced the clinical outcomes (eg, experience of the physicians, specific virulence factors). Third, we could not capture the reasons for the delays in antifungal therapy. Presumably, the clinicians treating these patients did not consider Candida species to be a likely cause of infection despite all these patients having received antibacterial therapy for septic shock. Similarly, we did not capture the reasons for delays in source control, nor could we exclude the possibility of concomitant bacterial infection in the 14 patients with intra-abdominal infection and lack of source control. Lastly, we did not perform measurements of minimum inhibitory concentrations (MICs) for the various antifungal agents employed to treat these infections nor did we directly assess antifungal susceptibility. It is possible that an imbalance in the MICs of pathogens in 1 group, or the presence of Candida species resistant to the antifungal agent employed (C. glabrata), could have explained, at least in part, our findings due to misclassification of patients.

In conclusion, we identified that delayed administration of appropriate antifungal therapy and inadequate source control were the most important determinants of outcome among patients with septic shock attributed to Candida infection with positive blood cultures. These findings suggest that it is vitally important to understand the factors contributing to outcome in septic shock in order to develop more optimal treatment strategies. The development of more rapid and accurate microbiologic diagnostic techniques appear to be needed given the rising rates of bloodstream infection and septic shock attributed to antibiotic resistant pathogens, including Candida species. Moreover, future studies are needed to determine the clinical usefulness of empiric antifungal therapy in patients with septic shock.

Notes

Acknowledgments. Dr. Kollef had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Kollef contributed to the study conception and design, statistical analysis, and critical revision of the manuscript. Dr. Micek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr. Micek contributed to the study conception and design, statistical analysis, and critical revision of the manuscript. Dr. Hampton contributed to acquisition of the data and critical revision for important intellectual content. Dr. Kumar contributed to the study conception and design as well as critical revision for important intellectual content. Mr. Doherty contributed to acquisition of the data and critical revision for important intellectual content.

Financial support. This work was supported by an unrestricted grant from Astellas. The sponsor had no role in any aspect of this investigation to include study conception and design, statistical analysis, and critical revision of the manuscript. Dr. Kolle's efforts were supported by the Barnes-Jewish Hospital Foundation. The research was supported by an unrestricted grant from Astellas.

Potential conflicts of interest. M. K. receives consulting fees from Merck, Cubist, and Hospira, and is on the speakers' bureau of Cubist and Hospira. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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