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Inflammatory response and clinical course of adult patients with nosocomial bloodstream infections caused by *Candida* spp.

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ABSTRACT

Candida spp. are an important cause of nosocomial bloodstream infection (nBSI) and are associated with significant morbidity and mortality. An historical cohort study was performed to evaluate the clinical course of 60 randomly selected adult patients with nBSIs caused by *Candida* spp. Patients with BSI caused by *Candida albicans* (n = 38) and non-*albicans* spp. (n = 22) were compared with 80 patients with *Staphylococcus aureus* BSI by serial systemic inflammatory response syndrome (SIRS) and APACHE II scores. The patients had a mean age of 52 years, the length of hospital stay before BSI averaged 21 days, and 57% of patients required care in an intensive care unit before BSI. The mean APACHE II score was 17 on the day of BSI, and 63% of BSIs were caused by *C. albicans*. Antifungal therapy within the first 24 h of onset of BSI was appropriate in 52% of patients. Septic shock occurred in 27% of patients, and severe sepsis in an additional 8%. Overall mortality was 42%, and the 7-day mortality rate was 27%. The inflammatory response and clinical course were similar for patients with BSI caused by *C. albicans* and non-*albicans* spp. In univariate analysis, progression to septic shock was correlated with high overall mortality, as was an APACHE II score >25 at the onset of BSI. In multivariate analysis, the APACHE II score at the onset of BSI and a systemic inflammatory response independently predicted overall mortality, but the 7-day mortality rate was only predicted independently by the APACHE II score. Clinical course and mortality in patients with *Candida* BSI were predicted by systemic inflammatory response and APACHE II score, but not by the infecting species.

Keywords APACHE II score, bloodstream infection, *Candida albicans*, candidaemia, nosocomial infection, risk-factors

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INTRODUCTION

Candida spp. are important causes of nosocomial bloodstream infection (nBSI) [1], particularly among patients in the intensive care unit (ICU). These infections are associated with high rates of morbidity and mortality [2–4]. The incidence of nBSI caused by *Candida* spp. has risen five- to 10-fold in the past 20 years. Currently, *Candida* spp. are the fourth leading cause of nBSI in the USA [5–8], and account for 8–15% of all hospital-acquired BSI in recent series [5,8–10]. During the last two decades, both the incidence of nosocomial candidaemia and the proportion of bloodstream infections caused by *Candida* spp. other than *Candida albicans* have continued to increase [8,10–14].

Triazoles are used widely for the treatment of systemic *Candida* infections, and their efficacy has been documented for both prevention [15–18] and treatment [19,20]. Since the 1990s, the use of fluconazole has increased substantially [14], and concerns have been voiced that greater use could lead to the selection of more resistant *Candida* spp. Prophylactic use of fluconazole in critical care units has selected *Candida krusei* and *Candida glabrata*, and resulted in outbreaks of infection caused by these relatively resistant pathogens.

The present study was conducted to evaluate the relationships between the inflammatory

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response, clinical course and outcome of nBSI caused by *Candida* spp.

MATERIALS AND METHODS

Setting

The Virginia Commonwealth University Medical Center (VCUMC) is a 750-bed tertiary care facility in Richmond, VA, USA. The hospital houses nine ICUs, including paediatric ICUs and a burns unit. Approximately 30 000 patients are admitted annually.

Study design

The Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) database [7] was used to identify all patients at VCUMC with a diagnosis of BSI caused by *Candida* spp. between 1 December 1998 and 31 May 2002. Patients were considered to have BSI caused by *Candida* spp. if at least one blood culture was positive for these organisms. Only monomicrobial episodes of BSI were included, and BSI episodes that represented relapses were excluded. However, second episodes occurring during separate hospital admissions were included as separate cases. Clinical data and isolates were collected concurrently by infection control practitioners using a standard case report form. The data collected included age, gender, location of the patient (ward vs. ICU), clinical service, duration of hospitalisation before the onset of BSI, predisposing clinical conditions and bloodstream pathogen. Predisposing clinical conditions included neutropenia (defined as an absolute neutrophil count <500/μL), peritoneal or haemodialysis, and intravascular catheters (i.e., central lines, arterial catheters, peripheral intravenous (IV) catheters). Sources of secondary BSI were recorded when cultures obtained from distant sites yielded the same pathogen. Adverse outcomes that occurred during the hospital stay were recorded. The clinical condition of each patient was classified according to systemic inflammatory response syndrome (SIRS) criteria (daily) and APACHE II score. Classifications were compared between patients with BSI caused by *C. albicans* and non-*albicans* species, as well as between patients with *Candida* BSI and 80 patients with BSI caused by *Staphylococcus aureus* from a previous study utilising the same methodology in a comparable patient population [21].

Definitions

The patients' physiological conditions before the BSI and at the onset of BSI were assessed using the APACHE II score [22]. The clinical condition of each patient during the BSI was classified as SIRS, sepsis, severe sepsis or septic shock using the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) [23]. SIRS was defined as two or more of the following: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or a $PaCO_2$ <32 mmHg; white blood cell count $>12 \times 10^9$/L or $<4 \times 10^9$/L, or the presence of >10% immature neutrophils. Sepsis was defined as SIRS associated with the isolation of *Candida* from at least one blood culture. Sepsis with the presence of hypotension or systemic manifestations of hypoperfusion constituted severe sepsis. Septic shock was defined as sepsis associated with hypotension that was unresponsive to IV fluid challenge, or the need for dopamine >5 μg/kg/min or any other vasopressor agent.

The presence of organ system failure was assessed using the criteria of Fagon *et al.* [24] with minor modifications: respiratory failure was defined as a FiO_2 >0.4 needed for >3 days in ventilated patients; cardiovascular failure as any need for epinephrine or norepinephrine, or a need for dopamine (>5 μg/kg/min) to maintain systolic blood pressure >90 mmHg; renal failure as decreased urine output (<500 mL/24 h) or an acute increase in serum creatinine level >2.0 mg/dL, or the requirement for acute dialysis or ultrafiltration; failure of the haematopoetic system as a platelet count $<100 \times 10^9$/L; and liver failure as serum bilirubin >5 mg/dL. The source of BSI was defined according to criteria published previously [7]. Antifungal therapy was considered appropriate if the patient received an antifungal agent to which the organism identified was susceptible.

Incidence

Admission data were collected between 1 January 1998 and 31 December 2001. Incidence rates were calculated as number of BSIs/10 000 hospital admissions.

Microbiological methods

Blood cultures were processed at the VCUMC. Identification to the species level was performed using standard microbiological procedures. MICs were determined using Etests (AB Biodisk, Piscataway, NJ, USA); this method has been shown to have a high correlation with NCCLS methods [25]. Results were confirmed using the NCCLS microbroth dilution method [26]. *C. albicans* ATCC 14053, *C. krusei* ATCC 14243 and *Candida parapsilosis* ATCC 22019 were used as controls.

Statistical analysis

Results were expressed as a mean ± SD, or as a proportion of the total number of patients or isolates. For continuous variables, mean values were compared using two sample *t*-tests for independent samples. Differences in proportions were compared using a Chi-square test or Fisher's Exact Test, as appropriate. Mean values are reported ±SD. All tests of significance were two-tailed, with α set at 0.05. The Mann–Whitney *U*-test was performed to test the equality of continuous variables. Independent predictors of the outcome of BSI were identified by means of stepwise logistic regression analysis, with a limit for entering and removing variables at 0.05. All statistical analyses were done using SPSS software (SPSS Inc., Chicago, IL, USA).

RESULTS

Study population and patient characteristics

During the study period, 2080 nBSIs were identified at VCUMC. Of these, 415 (20%) clinically significant episodes of BSI were identified in paediatric patients (aged ≤ 16 years). Of the remaining

episodes, 197 monomicrobial episodes of BSI were caused by *Candida* spp. From these, a sample of 60 patients (only one episode per patient) was selected randomly for further analysis.

Patients included in the study had a mean age of 52 ± 17.5 years (range 22–82 years); 55% were female. Thirty-four (57%) hospital-acquired BSIs occurred in the ICU setting. At the time of diagnosis of BSI, the most common clinical services were general surgery (26 patients, 43%), internal medicine (22, 37%), and haematology/oncology (7, 12%).

Underlying conditions (recorded as the diagnosis on admission) were classified as trauma (including burns) in 23 (38%) patients, followed by gastrointestinal symptoms in nine (15%) patients. Among the potential factors predisposing to BSI, intravascular devices were the most frequent. Central venous catheters were in place in 53 (88%) patients, followed by peripheral IV catheters in 12 (20%) patients and arterial catheters in 20 (33%) patients. Urinary catheters were in place in 41 (68%) patients. In total, 23 (38%) patients were receiving total parenteral nutrition. Haemodialysis was needed before the onset of BSI in 12 (20%) patients, while ventilatory support was needed for 26 (43%) patients. Overall, 25 patients died during hospitalisation, i.e., a crude mortality rate of 42%. The characteristics of the study population did not differ significantly from the overall population of patients with *Candida* BSI admitted to VCUMC during the study period.

Incidence

The hospital-wide incidence of BSI between 1998 and 2001 was 191/10 000 hospital admissions, and the overall incidence of BSI caused by *Candida* spp. was 16/10 000. When stratified by pathogen, hospital-wide incidence rates of BSI caused by *Candida* spp. varied between 8.5 and 0.4/10 000 admissions for *C. albicans* and *C. krusei*, respectively (Table 1). Incidence rates increased significantly over time (8.8 in 1998 vs. 20.8 in 2001), including those for both *C. albicans* (5.6 in 1998 vs. 11.6 in 2001) and non-*albicans* spp. (3.1 in 1998 vs. 9.1 in 2001).

Microbiological features

Among 2080 episodes of monomicrobial BSI that occurred at VCUMC during the study period, 197 (9.5%) episodes were caused by *Candida* spp. Of the 60 *Candida* isolates included in this study, *C. albicans* was the most common, accounting for 38 (63%) of *Candida* BSIs, followed by *C. parapsilosis* (*n* = 9, 15%), and *C. glabrata* (*n* = 8, 13%). These proportions were similar for the overall population of patients with *Candida* BSI at VCUMC (Table 1).

Table 1. Incidence and species distribution of *Candida* spp. isolated from monomicrobial bloodstream infection (BSI) in adult patients and the associated crude mortality (1998–2002; study population and all patients with *Candida* BSI)

		Study subset (*n* = 60)		All patients with *Candida* BSI (*n* = 197)	
Organism (*n*, patients)	BSI incidence (per 10 000 admissions)	%	Mortality (%)	%	Mortality (%)
Candida albicans (*n* = 38)	8.5	63.3	39.5	53.8	39.6
Candida glabrata (*n* = 8)	3.2	15.0	75.0	20.3	52.5
Candida tropicalis (*n* = 4)	1.9	13.3	25.0	12.2	40.0
Candida parapsilosis (*n* = 9)	1.6	6.7	22.0	10.2	33.0
Candida krusei (*n* = 1)	0.4	1.7	100.0	2.5	60.0
All *Candida* spp.	15.8	100.0	42.0	100.0	42.6

Median MICs of fluconazole were 0.38 mg/L (range 0.09–256 mg/L) for *C. albicans*, 64 mg/L (range 1.5–256 mg/L) for *C. glabrata*, and 1.0 mg/L (range 0.38–3.00 mg/L) for *C. parapsilosis*. NCCLS guidelines suggest a breakpoint of 64 mg/L for resistance [26]. On this basis, the frequency of resistance to fluconazole was 11% in *C. albicans*, 50% in *C. glabrata*, and 0% in *C. parapsilosis*.

Clinical course

Overall mortality was 40% in patients with BSI caused by *C. albicans*, and 45% in patients with BSI caused by non-*albicans* spp. Among the non-*albicans* BSI patients, crude mortality was lowest (22%) for the nine *C. parapsilosis* cases, and highest (75%) for the eight *C. glabrata* cases. Nineteen (50%) *C. albicans* isolates were recovered from patients in the ICU, compared with 15 (70%) non-*albicans* isolates (p 0.17). The mean time from hospital admission to onset of BSI averaged 26 days for *C. albicans* (range 6–56 days) and 22 days for non-*albicans* spp. (range 3–80 days). No significant seasonal patterns were observed.

Fig. 1 shows the inflammatory response of patients with *Candida* BSI over time, showing the percentage of patients with SIRS, severe sepsis, septic shock and those who died during

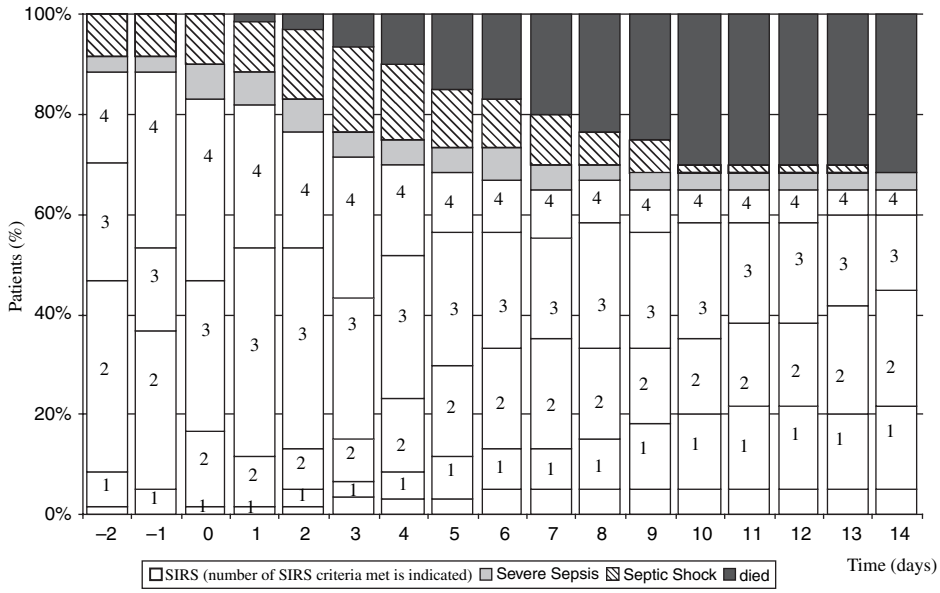

Fig. 1. Systemic inflammatory response syndrome (SIRS) over time in patients with *Candida* bloodstream infection. The figure shows the percentage of patients with SIRS, severe sepsis, septic shock and those who were deceased on a day-to-day basis. Among SIRS patients, the number of SIRS criteria met is shown in the respective bar.

the observation period. With regard to the entire observation period, severe sepsis developed in five (8%) patients with BSI caused by *Candida* spp., and septic shock occurred in an additional 16 (27%) patients. When patients with BSI caused by *C. albicans* were compared with those with BSI caused by non-*albicans* spp., there were no significant differences between the two groups with regard to initial or most severe inflammatory response during the course of BSI. In addition, the inflammatory response over time did not differ significantly, with maximum inflammatory response being recorded 3–7 days after the first positive blood culture. End-organ dysfunctions or hypoperfusion abnormalities were seen in 21 (35%) patients, the most common of which were acute renal failure (n = 11, 18%) or altered mental status (n = 10, 17%). Progression to septic shock was correlated with high overall mortality (RR 4.1; $p < 0.001$), as was an APACHE II score of >25 at the onset of BSI (RR 4.8; $p < 0.001$).

Among patients with BSI caused by *Candida* spp., 31 (52%) received appropriate treatment (based on the MIC data) within 24 h of the onset of BSI. While SIRS did not differ significantly over time, crude mortality was 52% among those who were treated appropriately within 24 h, compared with 31% among those who were not; however, those who were treated appropriately were also more severely ill (mean APACHE score 18 vs. 15). Patients with BSI caused by *C. albicans* did not differ significantly from patients with BSI caused by non-*albicans* spp. with regard to crude mortality rates (39% vs. 45% died, p 0.65). However, when stratified by markers of severity of illness at the onset of BSI, patients with high APACHE II scores were at higher risk for mortality ($p < 0.001$). Multivariate analysis showed that overall mortality was predicted independently by an APACHE II score of ≥25 at the onset of BSI (RR 1.2; p 0.001; Table 2), and development of severe sepsis or septic shock (RR 2.4; p 0.02). Other variables tested, including *C. albicans* vs.

Table 2. Multivariate analysis for 7-day mortality and hospital crude mortality in patients with *Candida* bloodstream infection

	7-day mortality			Hospital mortality		
	p	RR	95% CI	p	RR	95% CI
APACHE II score >25 on day of BSI	0.001	1.44	1.06–1.54	0.001	1.21	1.08–1.36
Severe sepsis or septic shock	0.160	NS		0.022	2.37	1.13–4.96
Mechanical ventilation	0.942	NS		0.539	NS	
Central venous catheter	0.212	NS		0.063	NS	
Arterial line	0.831	NS		0.705	NS	
Infection caused by *Candida glabrata*	0.585	NS		0.667	NS	
ICU stay	0.819	NS		0.218	NS	

ICU, intensive care unit; NS, not significant (variable not included in final model).

non-*albicans* spp., appropriate vs. inappropriate antifungal therapy within 24 h, and all significant univariate risk-factors, did not influence outcome. Mortality at 7 days after onset of BSI was predicted independently only by the APACHE II score at the onset of BSI (RR 1.5; p 0.001; Table 2).

Inflammatory response over time also correlated closely with the severity of the underlying pathophysiological conditions (as measured by APACHE II). Specifically, the clinical course was worse in patients who had an APACHE II score ≥ 25 at the onset of BSI (Fig. 2).

Compared with 80 patients with *S. aureus* BSI, the inflammatory response 48 h before and 14 days after the onset of BSI did not differ significantly (Fig. 3); however, there was a trend towards a more severe response in patients with *Candida* BSI (p 0.061). Considering only survivors, patients with *Candida* BSI had a prolonged inflammatory response that returned to baseline after an average period of 9 days after the onset of BSI, compared with 6 days in patients with *S. aureus* BSI. If survivors with higher and lower APACHE II scores (≥25 vs. <25 at onset of BSI) from both groups were compared, this difference was seen only for patients with an APACHE II score <25, whereas in patients with more severe underlying conditions, the return to baseline took 10 days for patients with *Candida* BSI, and 14 days for patients with *S. aureus* BSI.

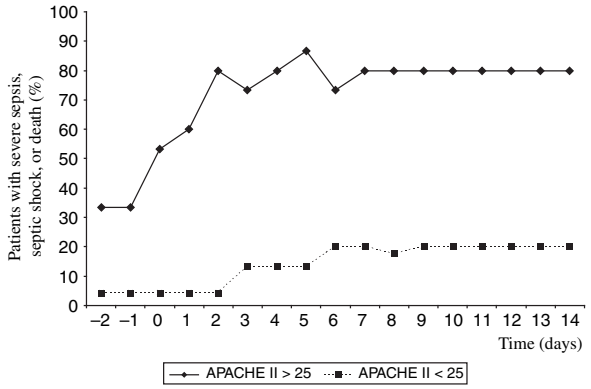

Fig. 2. Systemic inflammatory response syndrome (SIRS) over time, stratified by APACHE II score on day of bloodstream infection (APACHE II >25 vs. APACHE II <25). Day 0 is the day of first positive blood culture.

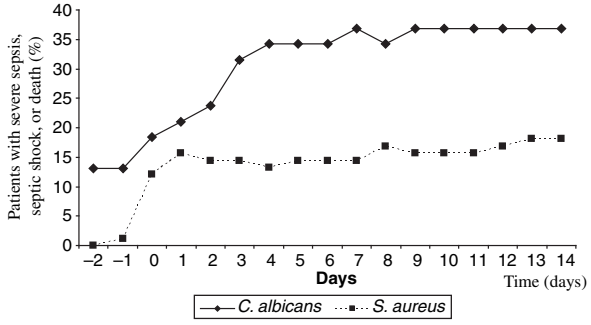

Fig. 3. Systemic inflammatory response syndrome (SIRS) over time, stratified by organism (*Candida albicans* vs. *Staphylococcus aureus*).

DISCUSSION

Invasive *Candida* infection accounts for up to 15% of all nosocomial infections in the ICU setting and is associated with a mortality rate of 40–60%, similar to that of septic shock [27,28]. Despite the increasing rates and high mortality of *Candida* BSI, this disease is frequently not recognised and is often treated inadequately. The present study aimed to define the systemic inflammatory response involved and showed that 27% of patients met the criteria for septic shock and 35% had end organ dysfunction, which are facts that many clinicians may not have appreciated fully. The 40% crude mortality rate was similar to that reported previously in the USA [8], and the 7-day mortality rate of 27% has been used by some workers to estimate the attributable mortality. Thus, this is a highly lethal infection. Nevertheless, half of the patients in the present study did not receive an appropriate drug within the first 24 h. This corroborates the data of Ibrahim *et al.* [29] and highlights the frequent absence of recognition and appropriate early treatment of candidaemia. In the present series, 24% of isolates were resistant to fluconazole. Only the APACHE II score and progression to severe sepsis or septic shock were statistically significant by multivariate analysis. However, because of the small number of patients in this series, neutropenia and corticosteroid therapy were not included in the analysis.

Fluconazole is used increasingly as the drug of choice for most patients with *C. albicans* fungaemia [30,31] as blood isolates with reduced susceptibility to fluconazole are very uncommon [32,33]. Among >3500 bloodstream isolates analysed in multicentre series, only 1% had reduced susceptibility to fluconazole [13,32–37]. In the present series the median MIC was 0.38 mg/L and 10% of *C. albicans* isolates (3/31) exhibited

decreased susceptibility to fluconazole. The absence of antifungal treatment has also been identified as a risk-factor for death in patients with *Candida* BSI in both univariate and multivariate analyses [38,39]. In the present series, there was no difference in clinical course or outcome between patients who received appropriate antifungal therapy within 24 h of onset of BSI and those who did not. The differences seen in the first days were most likely caused by the fact that patients who were more severely ill before the onset of BSI were also more likely to receive antifungal agents as part of their therapy. In addition, the present series may not have been large enough to detect small differences.

S. aureus is one of the leading causes of community-acquired and nosocomial BSI, causing considerable morbidity and mortality [40]. The clinical course of *S. aureus* BSI is usually severe, with crude mortality of 30–40% in several series [8]. In the present analysis, the progression to severe sepsis and septic shock showed no association with the pathogen (*Candida* spp. vs. *S. aureus*). Since the groups did not differ with regard to the initial presentation, the most severe presentation of inflammatory response within 14 days of detection, or the inflammatory response over time, it seems that BSI caused by *Candida* spp. is at least comparable to that caused by *S. aureus* with regard to clinical course, inflammatory response and mortality.

Among patients with *Candida* BSI, no difference in outcome was observed between patients with BSI caused by *C. albicans* or non-*albicans* spp. Again, the population investigated was relatively small, so that minor differences may not have reached statistical significance. However, insignificant variables were distributed almost equally, and no trend could be seen for any of the investigated variables that were not significant. Larger prospective studies will be necessary to confirm these results.

When inflammatory response over time was compared between patients with BSI caused by *Candida* spp. or *S. aureus*, the response in patients with *Candida* BSI seemed, generally, to be more severe. However, this difference was not consistent if patients were stratified by severity of underlying conditions, as measured by APACHE II score at the onset of BSI, and did not reach statistical significance. Analysis of a larger group of patients may be necessary to evaluate this question in detail. In addition, SIRS may not only measure the physiological response to BSI, but is also likely to be affected by underlying clinical conditions. In an analysis of a subset of the NORASEPT II trial, Hadley *et al*. [41] found that patients with *Candida* BSI had a higher rate of complications over time when compared with patients with bacterial BSI, but this analysis included only three patients with *Candida* BSI. Underlying clinical conditions seem to play a key role in the clinical course of BSI and, although difficult, it is necessary to control this parameter in order to reach valid conclusions concerning the impact of the causative pathogen on clinical course and outcome of BSI.

In summary, the clinical course in patients with BSI caused by *C. albicans* is similar to that in patients with BSI caused by non-*albicans Candida* spp., and to that in patients with BSI caused by *S. aureus*, and appears to be related more closely to the underlying condition of the patients than it is to the causative pathogen. Adverse outcome in the present study was predicted independently by a high APACHE II score at the onset of BSI, and by the development of severe sepsis or septic shock. This study confirms that BSI caused by *Candida* spp. has a high mortality rate and initiates a severe inflammatory response, leading to a clinical course comparable to that of *S. aureus* BSI, but with even higher mortality. In addition, *Candida* spp. seem to be under-appreciated as aetiological agents of severe BSI, leading to delayed recognition and inappropriate treatment.

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