

Central line-associated blood stream infections: characteristics and risk factors for mortality over a 5.5-year period

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Background/aim: Central line-associated bloodstream infections (CLABSIs) are associated with substantial morbidity and mortality and the infection rates vary in a wide range (high: 62.5%; low: 20%) in developing countries. We aimed to investigate the characteristics and the risk factors for mortality in patients with CLABSIs in intensive care units (ICUs) and provide the relevant data.

Materials and methods: The electronic medical records database and file records obtained through active surveillance by an infection control committee of a hospital were screened to identify patients with CLABSIs hospitalized from January 2008 through July 2013.

Results: A total of 166 CLABSI episodes in 158 patients out of 17,553 on 38,562 catheter and 94,512 hospitalization days were evaluated. The infection developed in catheterized patients at a median of 14 days (range 2–88), and the highest infection rate with 13.4% (n = 20) was the femoral region among the places where the catheter was inserted. Of the patients catheterized, 54.4% survived whereas 45.6% died. In patients having *Candida* infection, the mortality was significantly higher. High APACHE II scores and *Candida* infections were found to be significant risk factors associated with mortality.

Conclusion: APACHE II scores and bloodstream infection with *Candida* species were the most powerful predictors of mortality. In ICU practice, health-care givers must consider the emerging role of *Candida* for both invasiveness and mortality.

Key words: Intensive care unit, central line-associated bloodstream infections, nosocomial infection, mortality

1. Introduction

Central venous catheters (CVCs) are an essential part of care for critically ill patients, especially for those in intensive care units (ICUs). Patients in ICUs are more vulnerable to nosocomial infections compared to those in other wards of the hospital. As a routine intensive care practice, vascular access carries some potential risks, especially for bloodstream infections (1). Nearly 60% of nosocomial bacteremia has been reported to originate from vascular procedures (2). Besides their help for therapy, the use of CVCs can be associated with life-threatening infections (3). Central line-associated blood stream infections (CLABSIs) are associated with substantial morbidity and mortality (4). A recent survey from the United States reported more than 250,000 vascular catheter associated bacteremias and fungemias detected annually with a mortality rate of 12%–25% in critically ill patients (5,6). The reported mortality rates in developing countries have wide ranges as high as 62.5% and as low as 20% (1,7).

The main aim of the present study was to investigate the characteristics and the risk factors for mortality in patients with CLABSIs in ICUs and provide the relevant data.

2. Materials and methods

This study was conducted in Samsun Education and Training Hospital, a 620-bed hospital with 84 ICU beds. It is a tertiary reference hospital with a total of 62 beds for tertiary level care and the rest for primary level care. Of the 62 beds, 22 beds are allocated to the medical ICU, 22 beds are for the surgical ICU, 5 beds are for the cardiovascular surgery ICU, and 13 beds are for the burn care center. Tertiary level ICUs are units capable of providing complex, multisystem life support for an indefinite period and providing mechanical ventilation, extracorporeal renal support services, and invasive cardiovascular monitoring for an indefinite period. Primary level ICUs provide basic multisystem life support usually for shorter periods. However, our primary level ICU is not equipped to provide mechanical ventilation.

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The electronic medical records database and file records obtained through active surveillance of the infection control committee were evaluated to identify patients with CLABSIs hospitalized from January 2008 through July 2013. CLABSIs were defined in patients who had clinical signs of infection, as culture growth of the same bacteria from the blood taken from peripheral veins and catheter tip or blood taken from the catheter in patients who did not have a source of infection other than catheter origin. CLABSIs were recorded according to Center for Disease Control definitions (8). Patients who had another focus of infection were excluded the study. The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system was used to evaluate the disease severity during the hospitalization in the ICU (9). Patient age, sex, hospitalization period, underlying diseases, operations, total parenteral nutrition, blood products used, the hospitalization and the central venous catheter days infection arose, localization of catheter, mortality status, albumin level, microorganisms, and culture sensitivities were recorded.

The bacteriological isolation and antibiotic susceptibility tests were evaluated using the Phoenix 100 BD automated system (Becton Dickinson Diagnostic Systems) according to Clinical and Laboratory Standards Institute criteria (CLSI) (10). Blood cultures taken from catheter and peripheral veins were evaluated using a BACTEC 9050 (Becton Dickinson, ABD) automated device. Typing of *Candida* species was performed by germ-tube test.

Multidrug resistance (MDR) was defined as isolates resistant to at least three drugs in the following classes: β -lactams, carbapenems, aminoglycosides, and fluoroquinolones. Extensive drug resistance (XDR) was defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories). Pandrug resistance (PDR) was defined as nonsusceptibility to all agents in all antimicrobial categories (i.e. no agents tested as susceptible for that organism) (11).

2.1. Data analysis

Rates of invasive device use were calculated as total days invasive device used divided by the total days of hospitalization. The rates of device-related infections were calculated by dividing the number of device-related infections by the total number of days that the device was used in the study population as described by the National Healthcare Safety Network (NHSN) (12).

2.2. Statistical analysis

The data were analyzed using SPSS 17.0 and given as numerical (%) and median (min–max). Logistic regression analysis was used to predict risk and the chi-square test was used in comparison of categorical variables. The Mann-

Whitney U test was used to compare both groups with data that do not represent normal distribution. A P-value of less than 0.05 was considered statistically significant.

3. Results

This study included a total of 166 episodes of CLABSIs from 158 patients on 38,562 catheter and 94,512 hospitalization days in 17,553 patients that were hospitalized in ICUs between January 2008 and July 2013. Of the patients, 86 (54%) were male [mean age 67 ± 17 years (median: 72; 16–92), median hospitalization period 43 days (range, 5–287), and median hospitalization period prior to CLABSI was 25 days (range, 3–278)]. CLABSIs developed after the 10th catheter day in 65% ($n = 108$) of the patients. The median catheter day for infection was 14 days (range: 2–88), and the main region where the catheter was inserted was the femoral region in 13.4% ($n = 20$). Of the patients, 78% underwent endotracheal intubation and mechanical ventilation. Total parenteral nutrition and blood and blood products were given to 123 (78%) and 136 (86%) patients, respectively. According to the APACHE II score, disease severity during hospitalization was mean 25 ± 8 (median: 26; 6–45).

Of the patients, 86 (54.4%) survived whereas 72 (45.6%) died. Survivors and nonsurvivors were compared considering several parameters (Table). The female/male ratio was 32/54 and 40/32 for survivors and nonsurvivors, respectively, with a significant difference ($P < 0.05$). Albumin levels were significantly lower in nonsurvivors. The comparison of other parameters is shown in the Table. Forty-four patients had *Acinetobacter baumannii* infections and of them 15 (34%) died. Of the 35 patients with *Candida* infection, 24 died (68.5%) ($P < 0.01$). Approximately one-third of patients died before blood cultures were obtained. Antifungal therapy was initiated in 3.1 ± 1.9 days (median: 3; 1–10). The mortality rates were not significantly different between the patients. The catheter removal rate was significantly lower in patients who died ($P < 0.001$). No significant differences were found considering mortality in patients infected with *Acinetobacter*. However, the mortality was significantly higher in patients having *Candida* infection ($P < 0.01$). Logistic regression analysis showed that APACHE level II and *Candida* infection were the risk factors for mortality (Table).

3.1. Incidence of infection

The CLABSI rate in ICUs was 2–8 per 1000 catheter days between 2008 and 2013. The mean was 5.6 (5–7.2) in the medical ICU, 5 (2.5–8.08) in the surgical ICU, 2.45 (0–5.56) in the primary level ICU, 0.23 (0–1.3) in the cardiovascular ICU, and 2.83 (0–7.04) in the burn care unit per 1000 catheter days. CLABSI rate by years is shown in Figure 1. The catheter utilization rate was 13% (8%–21%) in the burn care unit, 18% (6%–25%) in the primary level ICU,

Table. Patients' characteristics and risk factors of survivors and nonsurvivors.

Variables	Total	Survivors	Nonsurvivors	P	Logistic regression		
	n (%)	n (%)	n (%)		Odds ratio	95% CI	P
Age (years) (mean ± SD)	67 ± 17	65 ± 17	68 ± 18	>0.05			
Female	72 (46%)	32 (37%)	40 (57%)	<0.05	0.51	0.26–1.01	0.05
Comorbidity	106 (64%)	54 (59%)	52 (70%)	>0.05			
Diabetes mellitus	53 (34%)	29 (34%)	24 (33%)	>0.05			
Neurological disease	29 (18%)	17 (20%)	12 (17%)				
Malignancy	16 (10%)	6 (7%)	10 (14%)				
Trauma	26 (16.5%)	16 (19%)	10 (14%)	>0.05			
Surgery	42 (26%)	24 (28%)	17 (24%)	>0.05			
Albumin (g/dL) (mean ± SD)	2.4 ± 0.4	2.5 ± 0.5	2.3 ± 0.4	<0.01	0.53	0.24–1.15	0.11
APACHE II (mean ± SD)	26 ± 7.6	24 ± 7.7	28 ± 7	<0.001	1.1	1.02–1.13	0.004
Endotracheal intubation	129 (78%)	66 (72%)	63 (85%)	<0.05	1.72	0.69–4.25	0.23
Etiology							
Gram negative	91 (55%)	58 (63%)	33 (45%)	<0.01			
Gram positive	40 (24%)	23 (25%)	17 (23%)				
Candida spp.	35 (21%)	11 (12%)	24 (32%)		3.4	1.51–7.53	0.003
MDR, gram negative	73 (81%)	44 (77%)	29 (88%)	<0.05			
<i>Acinetobacter</i> infected	44 (26.5%)	29 (32%)	15 (20%)	>0.05			
After the 10th catheter day	108 (65.1%)	60 (65.2%)	48 (64.9)	>0.05			
	Median (Min–Max)	Median (Min–Max)	Median (Min–Max)	P			
Length of stay prior infection	24 (3–278)	26 (3–175)	21 (5–278)	>0.05			
Length of stay	43 (5–287)	56 (5–287)	29 (7–287)	<0.001			
Catheter day	14 (2–88)	14 (3–88)	14 (2–64)	>0.05			

ICU: Intensive care unit, MDR: Multidrug resistant.

58% (24%–92%) in the medical ICU, 64% (37%–76%) in the surgical ICU, and 73% (59%–92%) in the cardiovascular ICU.

3.2. Microorganisms and antibiotic resistance

Of all the isolates, 52% were gram negative, 27% gram positive, and 21% were *Candida* spp. Thirty percent of all *Candida* isolates were *Candida albicans*. Analysis by years revealed the most frequent microorganisms as follows: *A. baumannii* (n = 2, 28.5%) and *Staphylococcus* spp. (n = 2, 28.5%) in 2008, *A. baumannii* (n = 4, 28.6%) and *Candida* spp. (n = 4, 28.6%) in 2009, *A. baumannii* (n = 12, 50%) in 2010, *Candida* spp. (n = 15, 30%) in 2011, *A. baumannii* (n = 13, 23.2%) in 2012, and *Klebsiella pneumoniae* (n = 7, 32%) in 2013 (Figure 2). Of all causative microorganisms, 3.5% were polymicrobial.

A total of 172 bacterial isolates were obtained. The most predominant bacterial isolate was *A. baumannii* (n

= 45, 26%), followed by *Candida* spp. (n = 37, 21.4%), *Staphylococcus* spp. (n = 25, 14.5%), *Enterococcus* spp. (n = 21, 12.1%), *K. pneumoniae* (n = 23, 13.2%), and *Pseudomonas aeruginosa* (n = 5, 2.8%). Of the gram-negative microorganisms 81% were MDR, 55% XDR, and 1.1% PDR. *K. pneumoniae* demonstrated 54.5% extended spectrum β lactamase (ESBL) and 4.2% carbapenem resistance. All *A. baumannii* isolates were multidrug resistant to *Acinetobacter* isolates. Thirty-nine had XDR (86.6%), whereas one isolate had PDR (2.2%). Carbapenem resistance was 91% in *A. baumannii*. Methicillin resistant *S. aureus* (MRSA) was as 66.7%, whereas the rate of methicillin resistant coagulase negative staphylococcus (MR-CNS) was 100%. Vancomycin resistant *Enterococcus* spp. was as 9.5%. Coagulase negative staphylococcus included *S. epidermidis* and *S. haemolyticus*.

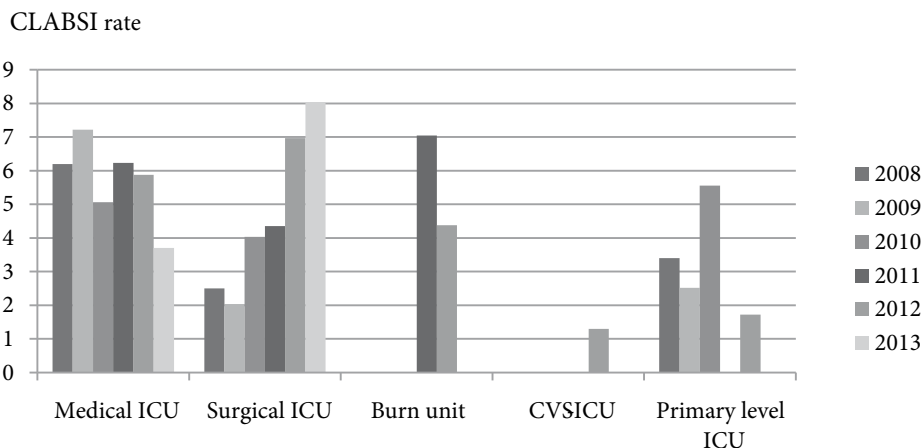


Figure 1. CLABSI rate by years. CLABSI: Central line-associated bloodstream infection, ICU: intensive care unit, CVS-ICU: Cardiovascular surgery ICU.

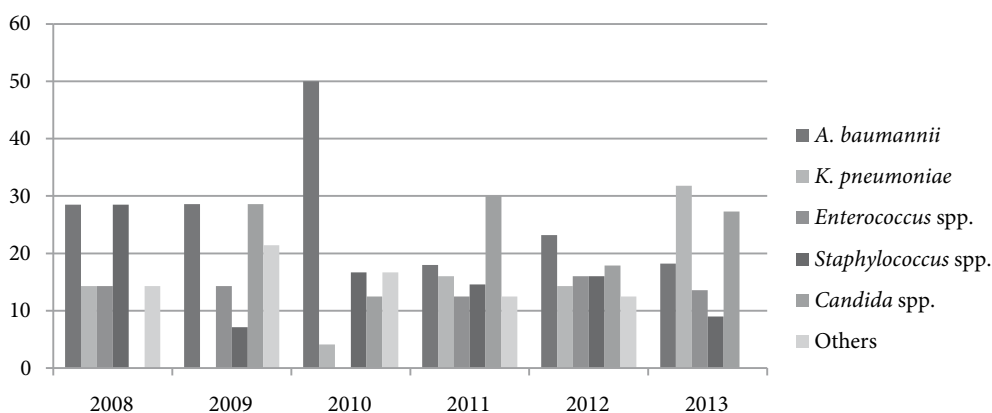


Figure 2. Distribution of microorganisms over 6 years.

4. Discussion

Although estimates for the incidence of CLABSI have varied, data from the United States indicated 80,000 catheter-related bloodstream infections due to use of central venous catheters with 15 million CVC days in ICUs each year (13). The NHSN system report gives some data about the rate of CLABSI in medical/surgical ICUs in 2012, which is pooled mean rates 1.2 (range 0–3) per 1000 catheter days (14). Rosenthal et al. reported the results of 55 ICUs in 8 developing countries in which CLABSIs comprised 30% of all device-associated infections or 12.5 cases (range 7.8–18.5 cases) per 1000 catheter days (15). Peng et al. from China reported that the mean rate of CLABSIs was 11.0 per 1000 central catheter days with a catheter utilization rate of 72.8% (16). We found the CLABSI rate in the medical ICU to be 5.6 (5–7.2) and 5 (2.5–8.08) in the surgical ICU per 1000 central catheter days. This was considered somewhat higher compared to the rates of developed countries, but it was considered reasonable in developing countries. A brief explanation

for these higher rates may be our deficiencies in maximum barrier precautions, inadequacy of nurses per patient in ICUs, increased rates of catheter use, and the longer periods of hospitalization.

We found that, of all isolates, 52% were gram negative and the most predominant bacterial isolate was *A. baumannii* followed by *Candida* spp. This was a different causative microbiological profile from the others observed in the past in which gram-positive microorganisms displayed dominance. Likewise, some institutions have observed an increase in catheter-associated infection caused by gram-negative bacilli (17). The past decade has witnessed an increasing occurrence of CLABSI caused by multiple resistant gram-negative rods, most notably *A. baumannii* (18). On the other hand, a recent multicenter Brazilian study showed that more than 50% of the all nosocomial blood stream infections were due to gram-negative bacilli. This study also disclosed a pattern of blood stream infections (BSIs) in Brazilian hospitals considerably different from the American experience with

a very high proportion of aerobic gram-negative bacteria (19). Similarly, Apostolopoulou et al. reported the 4 most frequently isolated pathogens, *A. baumannii* (47%), *K. pneumoniae* (19.8%), *P. aeruginosa* (12.6%), and *Candida* spp. (7.5%), from Greece (20). Candevir et al. from Turkey reported a CLABSI rate of 9.14 per 1000 central catheter days and the most common infecting organism was *A. baumannii* (21). CLABSIs caused by *A. baumannii* often occur in critically ill, immunosuppressed, highly antimicrobial agent-experienced patients (4).

Resistance to antimicrobials as a worldwide concern has a constant trend to increase. Microbiological resistance profiles revealed MRSA as 66.7%, *K. pneumoniae* as 54.5% ESBL, and *A. baumannii* isolates represented MDR 100%. XDR of 86.6%, along with carbapenem resistance that was 91% in *A. baumannii*, displayed very high resistance rates in our study compared to NHSN results (22). NHSN published 2009–2010 data about CLABSI resistance that was tremendously increasing (MRSA as 54.6%, ESBL in *K. pneumoniae* as 28.8%, resistance to carbapenems in *A. baumannii* as 62.6% and MDR as 67.6%). This report suggested that the problem of highly resistant gram-negative bacteria causing healthcare-associated infections is not limited to just a small subset of hospitals. In addition, it reinforced the need for prevention efforts designed to prevent the further emergence and spread of these pathogens (22). Deliberato et al. reported very high rates of resistance to carbapenems by nonfermentative gram-negative bacteria, higher mortality rates, and a shift to nonalbicans species of *Candida* (19). Our alarming results along with NHSN data represent the urgent need to take preventive measures for further transmission (22). Therefore, it is essential to use the antibiotics in appropriate indications and improve the immune state of patients for contribution to the prevention of multidrug-resistant pathogens and fungi-related BSIs.

Several factors influence mortality rates like causative microorganism, patient's general status, and severity of the disease. Olaechea indicated the variables affecting mortality in patients in ICUs. In addition to other variables, the authors reported in that study that fungi have higher mortality risk compared to bacteria (7). Until recently, *Candida* infections emerged mainly in patients with malignant diseases and in those who underwent organ transplantation. However, opportunistic fungal infections have dramatically increased in patients in ICUs (23) and invasive candidiasis is now an important and serious infective complication for patients managed in the ICU (24). Lundberg et al. found candidemia and APACHE II scores as an independent predictor of mortality in their study (25). The prognosis of critically ill patients with invasive candidiasis or candidemia is dreadful, with mortality rates frequently exceeding 40% (26). Besides

our higher rate of 68.5% of mortality in patients with candidiasis, Falagas et al. reported a systematic review of matched cohort studies in which the attributable mortality rates ranged from a nonsignificant 5% to a dramatic 71%, with six out of seven studies finding significantly higher mortality among case patients (27). Likewise, the results of the Extended Prevalence of Infection in the ICU Study (EPIC II), a multicenter study, revealed that of the 14,414 patients 99 patients had *Candida* BSIs with a prevalence of 6.9 per 1000 patients. Patients with *Candida* BSIs, compared with patients with gram-positive and gram-negative BSIs, had the greatest crude intensive care unit mortality rates (42.6%, 25.3%, and 29.1%, respectively) (28). We noted that, of the patients, 86 (54.4%) survived whereas 72 (45.6%) died. Of 35 the patients with *Candida* infection, 24 died (68.5%) ($P < 0.01$), which indicated that patients having *Candida* infection have a significantly higher mortality rate. APACHE II level and *Candida* infections were found to be risk factors for mortality (mean 25 ± 8). APACHE II, which is inevitably a higher score in our study, deteriorated patient-factor survival.

In searching for clues for the higher mortality rates in *Candida* infections and changing epidemiology of invasive mycoses, some authors suggested that the prolonged stay in the ICU was a factor (23), while others implicated that the CVC removal (29) or the underlying disease acuity, prevention, and prophylaxis in high-risk patients was an issue (23). Singh reported a brief and adequate explanation as to how the frequency of opportunistic fungal infections has increased. The increasing number of susceptible hosts, the introduction of newer modalities for hematopoietic stem cell transplantation, the evolution of organ transplantation practices, the use of novel immunosuppressive agents, and the current antimicrobial prophylactic strategies were reported to likely contribute to the changing epidemiology of invasive mycoses (30).

Thus, prevention and prophylaxis in high-risk patients may reduce the occurrence of invasive candidiasis (IC). However, studies addressing this issue do not directly indicate the problem of treatment delays when fungal BSIs occur (31). At this point, authors seemed not to have a strategy whether a targeted prophylaxis would be more useful than one of preemptive or early empirical therapy of infections documented before they produce clinical signs and symptoms or positive cultures (32). Although the latter strategy may be more appealing, Pfaller et al. reported that it was hindered by the lack of truly robust surrogate markers or nonculture-based methods for early detection of IC. Such methods are actively being developed but as yet are not widely available (23).

In conclusion, replacement by gram-negative microorganisms and fungal infections seems to continue and this shift may have a major role in mortality rates.

We found that, the most powerful predictors of mortality were APACHE II scores and BSI with *Candida* species. As the changing microbial spectrum considered, *Candida*

infections must increasingly be kept in mind not only for invasiveness but also as a leading causative agent for mortality.

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