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Risk Factors for Early Onset of Catheter-Related Bloodstream Infection in an Intensive Care Unit in China: A Retrospective Study

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Catheter-related bloodstream infection (CRBSI) is a life-threatening condition encountered in patients with long-term central venous catheter (CVC) indwelling. The objective was to investigate the clinical characteristics, treatment, and prognosis of CRBSI in the intensive care unit (ICU) in a Chinese center, as well as the risk factors for early CRBSI.

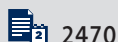
Material/Methods: A total of 73 CRBSI patients were retrospectively studied in relation to patients' clinical and epidemiological data, microbiological culture, and treatment. Patients were treated at the Taizhou Hospital of Integrated Traditional Chinese and Western Medicine in Zhejiang (Zhejiang Wenlin, China) between January 2010 and December 2012.

Results: In this Chinese center, the most common pathogens were Gram-positive cocci, followed by Gram-negative bacilli and fungi. A high prevalence of antibiotic-resistant pathogens was detected, and a higher percentage of non-*Candida albicans* spp. was observed. Multivariate analysis showed that an acute physiology and chronic health evaluation II (APACHE II) score >20 and >3 types of underlying diseases were independent factors associated with CRBSI occurring within 14 days of CVC indwelling. Untimely CVC removal and/or inappropriate use of antibiotics led to significantly longer time to defervescence and time to negative conversion of blood culture (all $P < 0.05$).

Conclusions: In this Chinese center, Gram-positive bacteria are predominantly detected in CRBSI. APACHE II score >20 and the presence of >3 types of diseases were associated with earlier CRBSI onset. Timely removal of CVC and appropriate use of antibiotics resulted in improved outcomes.

MeSH Keywords: **Blood • Catheter-Related Infections • Mortality • Risk Factors • Risk Management**

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Background

Central venous catheters (CVC) are often used in the intensive care unit (ICU) for monitoring and treatment of critically ill patients to provide long-term venous access. However, their use may result in nosocomial catheter-related bloodstream infection (CRBSI). Indeed, about 90% of all catheter-related infections are due to CVC [1]. The estimated number of CRBSI is approximately 250,000 annually in the United States [2–4], with an incidence of approximately 1.65 infections per 1000 central line days [5], and it was reported to be of 6.8 infections per 1000 central line days in Asia [6]. CRBSI are an important mortality and morbidity cause. Indeed, CRBSI is associated with a 2.27-fold increased risk of mortality in the ICU [7].

A number of risk factors for CRBSI onset are already known. Host factors such as chronic illness, bone marrow transplantation, immune deficiency, malnutrition, total parenteral nutrition, previous history of CRBSI, old age, and skin trauma increase the risk of CRBSI [8,9]. In addition, catheter factors also play a role in CRBSI onset, such as duration of catheterization, type of catheter, conditions of insertion, insertion site care, and skill of the person who inserted the catheter [10–13].

In cases of CRBSI, empiric antibiotic therapy must be started as soon as possible, and must be based on the clinical characteristics of the patients [14]. Catheter removal is necessary in cases of severe sepsis, hemodynamic instability, endocarditis, erythema, or bacteremia persisting after 72 hours of antibiotic therapy [14]. Once the responsible organism is identified, tailored antibiotic therapy may be started, and usually lead to better outcomes [14].

However, little is known about the risk factors for early CRBSI onset, and few data are available about the clinical manifestations and mortality of CRBSI in China. Therefore, the aim of the present study was to assess the risk factors and catheter characteristics of 73 cases of nosocomial CRBSI in the ICU between January 2010 and December 2012. We analyzed the clinical features and treatment outcomes, and provide evidence for early diagnosis and treatment of CRBSI, as well as risk factors for early CRBSI onset.

Material and Methods

Patients

This study was performed at the Taizhou Hospital of Integrated Traditional Chinese and Western Medicine in Zhejiang (Zhejiang Wenlin, China) in patients hospitalized in the ICU between January 2010 and December 2012. The Ethics Committee of the hospital approved the study, and waived the requirement for individual consent.

Patients were included if: 1) they developed bacteremia or fungemia while having a CVC or within 48 h of CVC removal; 2) fever ($>38^{\circ}\text{C}$), shivering or hypotension; and 3) no other apparent source of infection. In addition, at least one of the following criteria had to be met: 1) the same pathogenic agent was isolated from the catheter tip and from the peripheral venous blood (at least once), detected with a semi-quantitative method (each catheter fragment contained >15 bacteria/CFU) or quantitative method (each catheter fragment contained $>10^2$ bacteria/CFU); 2) intra-catheter and peripheral blood culture was positive, and the bacterial colony count in the intra-catheter blood was at least 3 times greater compared with the peripheral blood; or 3) the time to report the positive intra-catheter blood culture was at least 2 h earlier than that of the positive peripheral blood culture.

Patients were excluded if: 1) there was no clinical manifestation of bloodstream infection; or 2) other causes of bloodstream infection could not be excluded.

Data collection

The clinical data of patients with nosocomial CRBSI were collected and analyzed in accordance with the 2009 clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection from the Infectious Diseases Society of America (IDSA) [14]. Patients' age, sex, reason of ICU admission, underlying diseases, time and position of indwelling CVC, type of CVC, pathogenic identification, treatment, prognosis, and mortality attributable to CRBSI were reviewed.

Grouping

Timely removal of the catheter was defined as CVC removal within 12 h of fever onset. Appropriate antibiotic use was defined as the empirical use of antibiotics, which were confirmed to have covered the pathogenic bacteria in the drug sensitive test later. Patients with timely CVC removal and appropriate antibiotic use were assigned to Group A. Patients with timely CVC removal and inappropriate antibiotic use were assigned to Group B. Patients with untimely CVC removal and appropriate antibiotic use were assigned to Group C. Finally, patients with untimely CVC removal and inappropriate antibiotic use were assigned to Group D.

Statistical analysis

All continuous data are expressed as means \pm standard deviation (SD). Inter-group comparison of the measured data was performed using analysis of variance (ANOVA), and *t*-tests were used for post hoc analysis. Categorical data are presented as proportions, and were compared using chi-square tests,

using a segmentation approach to compare group pairs. The risk factors of early CRBSI were evaluated using univariate and multivariate logistic regression analyses. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). *P*-values <0.05 were considered statistically significant.

Results

Patients' characteristics

The 73 CRBSI patients included 42 males and 31 females, with a mean age of 63.2±21.3 years (range: 43-87 years). The mean time of CVC indwelling was 20.8±9.2 days (range: 7–39 days), and 64.3% of the participants had CVC indwelling for ≥14 days. There were 27, 20, 15, and 11 patients assigned to groups A, B, C, and D, respectively. Thirteen (17.8%) patients had a positive culture of the catheter tip. CVC was not removed or was replaced due to various reasons in 9 cases. CRBSI caused death in 19 patients (26.0%) (Table 1).

Reasons for ICU admission are listed in Table 1. There were 21 patients (28.8%) with ≤3 types of underlying diseases, 43 patients with 4 types of underlying diseases, and 9 patients (12.3%) with ≥5 types of underlying diseases.

Risk factors for early CRBSI

The known risk factors of CRBSI are displayed in Table 1. There were 23 cases (31.5%) with ≤3 high-risk factors of CRBSI and 50 cases (68.5%) with ≥4 high-risk factors. Univariate logistic regression analysis revealed that an Acute Physiology and Chronic Health Evaluation II (APACHE II) score >23, parenteral nutrition or transfusion of blood products, age >65 years, diabetes, >3 types of underlying diseases, renal insufficiency or multiple organ dysfunction syndrome (MODS), and immunosuppression or chemoradiotherapy were correlated with the occurrence of CRBSI within 14 days of CVC indwelling (Table 2). The factors that were statistically significant (*P*<0.05) in univariate analyses were included in the multivariate analysis. APACHE II score >20 and >3 types of underlying diseases were independent risk factors of CRBSI occurring within 14 days of CVC indwelling (Table 3).

Type of CVC and position of CVC indwelling

The types of CVC and the position of CVC indwelling are listed in Table 1. The duration of CVC indwelling until CRBSI occurrence is shown in Table 4. Femoral CVC showed the shortest time to CRBSI onset (14.2±5.1 days), followed by internal jugular CVC (20.9±8.0), and subclavian CVC (33.8±3.9) (all *P*<0.05). Time to CRBSI onset was longer with single-lumen CVC compared with dual-lumen CVC (33.7±3.9 vs. 16.9±6.3 days, *P*<0.05).

Table 1. Characteristics of 73 CRBSI subjects.

Characteristics	Value
Gender, male, n (%)	42 (57.5)
Age (year, mean ±SD)	63.2±21.3
No. of cases with underlying diseases, n (%)	
Sequelae of stroke	21 (28.8)
Malignant tumor	7 (9.6)
Acute leukemia	3 (4.1)
COPD	41 (56.2)
Chronic renal disease	37 (50.7)
Septic shock	51 (69.9)
Severe trauma	17 (23.3)
Severe pancreatitis	8 (11.0)
Diabetes	48 (65.8)
Cause of ICU admission, n (%)	
Severe pneumonia complicated by respiratory failure	43 (58.9)
Post-cerebral surgery respiratory failure	15 (20.5)
Post-general surgery severe pneumonia	12 (16.4)
Severe acute pancreatitis	3 (4.1)
Type of catheter, n (%)	
Single-lumen CVC	17 (23.3)
Double-lumen CVC	56 (76.7)
Catheter-indwelling site, n (%)	
Subclavian vein	12 (16.4)
Internal jugular vein	37 (50.7)
Femoral vein	24 (32.9)
Related risk factors, n (%)	
Use of broad-spectrum antibiotics	67 (91.7)
Stay in ICU for over 15 days	65 (89.0)
APACHE II score >23	57 (78.1)
Parenteral alimentation or transfusion of blood products	54 (73.9)
Age >65 years	53 (72.6)
Diabetes	52 (71.2)
>3 types of underlying diseases	52 (71.2)
Catheter-indwelling duration of >14 days	47 (64.3)
Renal dysfunction or MODS	17 (23.2)
Immunosuppression or chemotherapy and radiotherapy	13 (17.8)

CVC – central venous catheter; COPD – chronic obstructive pulmonary disease; ICU – intensive care unit; APACHE – Acute Physiology and Chronic Health Evaluation; MODS – multi-organ deficiency syndrome.

Table 2. Univariate analyses of early CRBSI (within 14 days after CVC indwelling).

Risk factor	Regression coefficient	OR	95%CI	P
Use of broad-spectrum antibiotics	22.204	4.398E9	0	0.999
Stay in ICU for over 15 days	22.322	4.947E9	0	0.999
APACHE II score >23	4.382	80	9.358–683.903	<0.001
Parenteral alimentation or transfusion of blood products	4.044	57.071	10.781–302.113	<0.001
Age >65 years	3.617	37.238	8.627–160.738	<0.001
Diabetes	3.308	27.321	7.088–105.311	<0.001
>3 types of underlying diseases	5.481	240	25.232–2282.843	<0.001
CVC indwelling >14 days	4.121	61.6	13.435–282.447	<0.001
Renal dysfunction or MODS	2.412	11.152	1.38–90.092	0.024
Immunosuppression or chemotherapy and radiotherapy	20.797	1.077E9	0	0.999

CVC – central venous catheter; ICU – intensive care unit; APACHE – Acute Physiology and Chronic Health Evaluation; MODS – multi-organ deficiency syndrome.

Table 3. Multivariate analysis of early CRBSI (within 14 days after CVC indwelling).

Risk factor	Regression coefficient	OR	95% CI	P
APACHE II score >23	2.011	7.471	1.516–36.804	0.013
>3 types of underlying diseases	2.564	12.990	3.249–51.935	<0.001

APACHE – Acute Physiology and Chronic Health Evaluation.

Table 4. Indwelling site and type of CVC.

	CVC site			Type of catheter	
	Subclavian vein (n=12)	Internal jugular vein (n=37)	Femoral vein (n=24)	Single-lumen (n=17)	Double-lumen (n=56)
Duration of indwelling catheter (d)	33.8±3.9***	20.9±8.0*	14.2±5.1	33.7±3.9***	16.9±6.3

* $P < 0.05$ vs. CVC in femoral vein; ** $P < 0.05$ vs. CVC in internal jugular vein; *** $P < 0.05$ vs. the double-lumen catheter. CVC – central venous catheter.

Pathogen identification

The most common pathogens were Gram-positive bacteria, followed by Gram-negative bacteria and fungi (all of which were *Candida* strains). Infection associated with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCoNS) were observed in 32 cases. Infection with extended-spectrum β -lactamase (ESBL)-producing bacteria was observed in 15 cases. Vancomycin-resistant enterococci (VRE) infection was seen in 5 cases. Carbapenem-resistant Gram-negative bacteria (CRGNB) were detected in 13 cases (Table 5).

Clinical manifestation

All 73 CRBSI patients manifested fever, with a body temperature ranging from 38.1 to 40.3°C, including 20 cases (27.3%) with a body temperature of 38.1–39°C, and 53 cases (77.7%) with a body temperature of >39°C. Routine blood test showed a mean white blood cell count of $19.6 \pm 9.3 \times 10^9/L$ (range: 12.1–30.2 $\times 10^9/L$), and a mean neutrophil count of $87.3 \pm 8.5\%$ (range: 82–91.2%). C-reactive protein (CRP) levels were ≥ 120 mg/L in all subjects, and 39 cases (53.4%) had CRP levels of >165 mg/L. Abnormal liver function (mild to moderate elevation of ALT and AST levels) was detected in 17 cases (23.2%).

Table 5. Bacteria identification in 73 cases with CRBSI.

Pathogenic bacteria	N (%)
Gram-positive bacteria	47 (64.3)
Coagulase-negative staphylococci	21 (28.8)
Methicillin-resistant coagulase-negative staphylococci (MRCoNS)	18 (85.7)
<i>Staphylococcus epidermidis</i>	14 (19.3)
<i>Staphylococcus haemolyticus</i>	4 (5.4)
<i>Staphylococcus saprophyticus</i>	3 (4.1)
<i>Staphylococcus aureus</i>	14 (19.3)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	14 (100.0)
Enterococci	12 (16.4)
Vancomycin-resistant enterococci (VRE)	5 (41.7)
<i>Enterococcus faecalis</i>	6 (8.2)
<i>Enterococcus faecium</i>	4 (5.4)
<i>Enterococcus gallinarum</i>	2 (2.8)
Gram-negative bacteria	19 (26.0)
<i>Acinetobacter baumannii</i>	6 (8.2)
<i>Pseudomonas aeruginosa</i>	4 (5.4)
<i>Stenotrophomonas maltophilia</i>	1 (1.4)
<i>Escherichia coli</i>	3 (4.1)
<i>Klebsiella pneumoniae</i>	3 (4.1)
<i>Burkholderia cepacia</i>	1 (1.4)
<i>Enterobacter cloacae</i>	1 (1.4)
Fungus	7 (9.7)
<i>Candida albicans</i>	3 (4.1)
<i>Candida parapsilosis</i>	2 (2.8)
<i>Candida glabrata</i>	1 (1.4)
<i>Candida tropicalis</i>	1 (1.4)

Abnormal renal function (except 6 cases with renal failure before enrollment in the study) was found in 27 cases (36.9%), with the highest serum creatinine level being 671 $\mu\text{mol/L}$. Circulation failure was observed in 23 cases (31.5%) and 27 cases (50.9%) were found to be complicated by MODS. Redness and swelling at the site of indwelling catheter was found in 14 cases (19.1%), including 7 cases (9.7%) with local purulent secretions.

Treatment and prognosis

The major treatment for patients with CRBSI was CVC removal and the use of effective antibiotics. We observed 47 cases with CVC being removed within 12 h after blood sampling, and all of them showed a rapid drop in body temperature following CVC removal. Seventeen cases had their CVC removed after a report of positive blood culture, while CVC was not removed in 9 cases. These 26 cases showed an unremarkable or slow drop in their body temperature. Empirical antibiotic therapy was administered to all subjects before confirmation of a positive blood culture, and was continued after positive blood culture was confirmed, or replaced by another antibiotic. The survivors showed a mean time to defervescence of 6.9 ± 2.1 days, and a mean time to negative conversion of blood culture of 6.4 ± 2.4 days (Table 6).

Discussion

The aim of the present study was to investigate the clinical characteristics, treatment, and prognosis of CRBSI in the intensive care unit (ICU) in a Chinese center, as well as the risk factors for early CRBSI. Among the 73 CRBSI patients enrolled in the present study, the major risk factors included advanced age, long-term catheter indwelling, parenteral nutrition, diabetes, and APACHE II score >23 , and >3 types of underlying diseases. Multivariate analysis showed that an acute physiology and chronic health evaluation II (APACHE II) score >20 and >3 types of underlying diseases were independent factors associated with CRBSI occurring within 14 days of CVC indwelling.

The univariate analyses results are in agreement with previously published data. Indeed, advanced age, long-term catheter indwelling, parenteral nutrition, diabetes, APACHE II score >23 , and >3 types of underlying diseases are well known risk factors of CRBSI. Patients with advanced age and multiple underlying diseases and diabetes usually show decreased immune function. In addition, parenteral nutrition provides an excellent environment for bacterial growth and reproduction. Parenteral nutrition was considered as an independent risk factor of CRBSI by previous studies [15,16].

It has been shown that CRBSI is more likely to occur with prolonged catheterization [17,18]. Our findings showed that significantly more subjects had catheter indwelling for ≥ 14 days compared with catheters indwelling for <14 days. The prolongation of catheterization by one day was reported to be associated with a 1.8-fold increased risk of CRBSI [19]. Early CRBSI may have serious implications for the patients since it can interfere with patient treatment. The results of the present study showed that poor patient condition, indicated by the APACHE II score, and high number of disease types were independently

Table 6. Effect of treatment on CRBSI prognosis.

Group	Survival (%)	Death (%)	Survivor	
			Time to defervescence (day)	Time to negative conversion of blood culture (day)
A (n=27)	26 (96.3)	1 (3.7)	5.1±1.3 [#]	4.3±1.2 [#]
B (n=20)	14 (70.0)	6 (30.0) ^{®,%}	8.3±0.6 ^{*,#}	8.3±0.9 ^{*,#}
C (n=15)	11 (73.3)	4 (26.7) ^{®,%}	8.2±1.3 ^{*,#}	8.1±1.8 ^{*,#}
D (n=11)	3 (27.2)	8 (72.8) [®]	11.2±0.3 [*]	10.8±1.7 [*]
Total (n=73)	54 (74.0)	19 (26.0)	–	–

® $P < 0.05$ vs. Group A; % $P < 0.001$ vs. Group A; % $P < 0.05$ vs. Group D; * $P < 0.01$ vs. Group A; # $P < 0.01$ vs. Group D. Group A: timely CVC removal and appropriate antibiotic use; group B: timely CVC removal and inappropriate antibiotic use; group C: untimely CVC removal and appropriate antibiotic use; group D: untimely CVC removal and inappropriate antibiotic use.

associated with an early CRBSI onset. Therefore, the prevention of CRBSI should be for a priority in critically ill patients with complicated diseases.

The mortality rate observed in the present study, 26.0%, was high. Indeed, the mortality rate from CRBSI is reported to be 8.8% in subjects aged >65 years, but only 3.8% in those aged <65 years [16]. This discrepancy may be due to severe and complicated diseases. Indeed, a large proportion of our patients had high APACHE II scores and a large number of concomitant diseases. Accordingly, a previous study showed that the mortality rate due to CRBSI in the ICU was 28.1% in critically ill patients [20].

The present study demonstrated that the position of CVC indwelling was closely associated with the time of CRBSI onset. The longest mean duration of catheterization was found in the subclavian vein at CRBSI onset, followed by the internal jugular vein. The shortest duration was observed in the femoral vein, as observed by previous studies [10,11,21]. Indeed, the perineal region is a major source of cutaneous microbial colonization. The skin at the subclavian vein is flat, which is easier to clean and disinfect, resulting in late CRBSI onset. Accordingly, the subclavian vein is recommended as the first choice of the site for catheterization in the IDSA guidelines, followed by the internal jugular vein and the femoral vein [14]. In addition, CRBSI occurred later when using the single-lumen catheter than with double-lumen catheter. Indeed, a significantly higher occurrence of CRBSI was observed with double-lumen catheters compared with single-lumen catheters [22].

In the present study, the most common pathogens causing CRBSI were Gram-positive bacteria, followed by Gram-negative

bacteria and fungi. CoNS were predominant in the Gram-positive bacteria, followed by MRSA, with 85.7% of the staphylococci resistant to methicillin, and 41.7% of the enterococci resistant to vancomycin. The most common Gram-negative bacteria were *Acinetobacter baumannii*, followed by *Pseudomonas aeruginosa*, in which ESBLs-producing bacteria were 80.0% and 68.4%, respectively, resistant to carbapenem antibiotics. The high prevalence of antibiotic-resistant bacteria may be associated with the wide use of broad-spectrum antibiotics in the ICU. *Candida albicans* constituted only 42.9% of *Candida* infections. In a systematic review of eligible studies related to CRBSI associated with parenteral nutrition published between 1970 and March 2012, the major pathogens were *Staphylococcus* spp., followed by Gram-negative bacillus and *Candida* spp. [15], which was consistent with the current study findings. However, the distribution of the causal agents in the present study was slightly different from that observed in the United States [4]. Therefore, the choice of empiric treatment should be made according to these possible geographical differences. Empirical selection of antibiotics should be based on patient clinical profile, such as recent history of antibiotic use, drug resistance or allergy, underlying diseases, clinical epidemiology, and health facility [23,24]. In addition, adequate anti-infective therapy for CRBSI should be administered to prevent complications such as inflammatory deep venous thrombosis and infectious endocarditis [25,26].

The present study had some limitations. The number of patients was small, and they all were from a single center. No control group was included, preventing us from studying the risk factors for CRBSI in China. However, the present study is the first to identify some risk factors for early CRBSI onset. More studies with larger sample sizes are necessary.

Conclusions

APACHE II score >20 and the presence of >3 types of diseases were associated with earlier CRBSI onset. In this Chinese center, Gram-positive bacteria are predominantly detected in CRBSI. Timely removal of CVC and appropriate use of antibiotics resulted in improved outcomes. Critically ill patients in the ICU should be particularly monitored for the appearance of CRBSI.

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Statement

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Conflict of interests

All authors declare that they have no conflict of interests.