Bacterial Distribution and Risk Factors of Nosocomial Blood Stream Infection in Neurologic Patients in the Intensive Care Unit

Shuixiang Deng,* Shengjie Feng,* Wei Wang, Hechen Zhu, and Ye Gong

Abstract

Objective: To investigate the risk factors and analyze the distribution of pathogens to provide a basis for the prevention of nosocomial blood stream infections (BSI) and reduce the incidence and mortality of nosocomial BSI in neurologic patients.

Patients and Methods: A retrospective chart review of neurologic patients admitted to an adult intensive care unit from January 2012 to December 2017 was conducted. Every positive blood culture, clinical demographic, microbiologic and laboratory result, as well as 28-day outcome data, were compiled on a data collection sheet. The clinical significance of each isolate was determined; in addition, the antimicrobial susceptibilities of causative pathogens and the most likely source were recorded.

Results: During the five-year study period, there were 121 nosocomial BSI yielding 151 isolates in 404 neurologic patients. Eighty-one percent of nosocomial BSI were monomicrobial. Gram-positive organisms caused 67.9% of these BSI, gram-negative organisms caused 32.1%, and fungi caused 0.8%. The crude incidence rate was approximately 29.9%, and the mortality of nosocomial BSI was as high as 29.8%. Intravascular lines were the most common source of nosocomial BSI (79.3%). The most common organisms causing BSI were coagulase-negative staphylococci (CoNS; 44.6% of isolates), *Staphylococcus aureus* (17.4%), *Klebsiella* species (11.5%), and *Acinetobacter* spp. (11.5%). Multivariable regression analysis revealed that the use of antibiotic agents in the 90 days prior (odds ratio [OR], 5.81; 95% confidence interval [CI], 3.18–10.62; $p=0.001$), brain trauma (OR, 0.28; 95% CI, 0.15–0.51; $p=0.001$), and transfusion (OR, 3.02; 95% CI, 1.45–6.29; $p=0.001$) were significant predictors of nosocomial BSI.

Conclusions: The incidence and mortality of nosocomial BSI were high in our neurologic patients. Strictly aseptic operations, hand hygiene, and reasonable use of transfusions and antibiotic agents are effective measures to prevent nosocomial BSI.

Keywords: bacterial features; intensive care unit; neurologic patients; nosocomial blood stream infections; risk factors

BECAUSE OF THE VARIOUS CATHETERS that are an indispensable part of current medical practice, critically neurologic patients are at an increased risk of actual or potentially life-threatening infectious complications, which require prompt diagnosis and treatment with appropriate antimicrobial agents to reduce the associated morbidity and mortality [1]. Nosocomial blood stream infections (BSI) are an important issue in neurocritical care because of secondary brain damage, severe complications, and increased morbidity and mortality in patients with neurologic disorders [2–7].

In the last decade, published articles have reported that approximately 250,000 patients acquired nosocomial BSI annually in the United States in the 1970s and that the costs associated with nosocomial BSI were enormous in critically ill patients, reaching \$34,500 to \$40,000 per survivor [8–10]. Mortality attributable to nosocomial BSI have been estimated to be as high as 35% [11,12]. Several previous reports have identified the epidemiologic features, species distribution, and risk factors of BSI in patients admitted to intensive care units (ICUs) [6–7,13–15], however, data regarding the bacterial

Department of Intensive Care Unit, HuaShan Hospital, Fudan University, Shanghai, China.

*These authors contributed equally to this work and are joint first authors.

features, species distribution, and risk factors of nosocomial BSI in neurologic patients in intensive care unit are scarce.

Nosocomial BSI is one of the most devastating preventable complications in critical care units if an elective surveillance program is in place [16,17]. The purpose of the present study was to investigate the risk factors for nosocomial BSI in neurologic patients to provide a basis for their prevention and to analyze the distribution of pathogens and their drug resistance to guide initiatives that would reduce nosocomial BSI through measures to decrease both incidence and associated mortality in neurologic patients in the ICU.

Patients and Methods

In total, 404 neurologic patients who were admitted to the ICU of our tertiary university teaching hospital from January 2012 to December 2017 were enrolled in this retrospective study. Patients were included if they fulfilled the following criteria: age over 18 years; admission for more than 48 hours; and presence of neurologic diseases such as acute brain trauma, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, brain tumor after surgery, and hypoxic-ischemic encephalopathy. Patients with pre-existing febrile illness, or immunosuppressive therapy, as well as patients with infections at other sites and those who did not survive for 48 hours after admission were excluded from the study. Blood cultures were ordered upon clinical suspicion of infection and at the discretion of the clinical team.

Intensive care unit-acquired BSI were defined when (1) occurring more than 48 hours after admission to the hospital [18], (2) sepsis was present according to criteria of the 2016 International Sepsis Definitions Conference [19], and (3) one or more positive blood cultures of a known pathogen were present. For coagulase-negative staphylococci and other common skin flora, at least two positive blood cultures with the same micro-organisms from blood samples obtained at least two hours apart but not exceeding a 48-hour period were required.

An episode of BSI was defined as all positive blood cultures being drawn within three days [15]. A positive blood culture occurring more than three days after the previous positive culture was classified as a separate episode of BSI. However, if a patient had the same organism from the same source isolated repeatedly, this was considered a single episode even if the cultures were drawn more than three days apart. The source of infection was retrospectively determined from written documentation by the infectious disease team, whose decision was based on objective clinical evidence, microbiologic data, and clinical judgment.

Clinical data collection

Data collected from the medical records for each patient were recorded onto a standardized collection sheet, and included demographic information, predisposing conditions, and important clinical parameters at the time of bacteremia, such as the patient's white blood cell (WBC) count, procalcitonin (PCT), C-reactive protein (CRP), and maximum temperature (or lowest temperature if the patient was hypothermic, i.e., 36.0°C). Also noted was any evidence of hemodynamic instability (shock), which manifested as hypotension (systolic blood pressure less than 90 mm Hg or a greater than a 30% decrease from baseline), a requirement for vasopressor medi-

cations to maintain adequate end-organ perfusion, or oliguria (<80 mL urine output over four hours) and a requirement for continuous renal replacement therapy to maintain kidney function. Finally, the probable sources of each bacteremic episode and positive blood culture result were also recorded. Based on these data, positive blood cultures were classified as either contaminants or true bacteremias. Only bacteremias believed to represent clinically significant BSIs were included in this study.

Microbiology laboratory processing

Blood was inoculated into media for processing with the automated continuous-monitoring blood culture system BACTEC System 9050 (Becton Dickinson, Franklin Lakes, NJ) using two 26-resin vials for aerobic cultures and one 27-resin vial for anaerobic cultures (10 mL in each vial). Two aerobic-plus F bottles and one lytic 10 anaerobic F bottle were used for the cultures (10 mL in each). For both systems, blood was incubated until flagged as positive or for five days. When blood cultures became positive, the broth was gram-stained and sub-cultured, and organisms were identified using standard methods.

Measurement of plasma PCT and CRP

According to the manufacturer's instructions, the PCT level was measured by an electrochemiluminescence immunoassay (ECLIA) BRAHMS PCT ELECSYS® (Thermo Fisher Scientific, Fairlawn, NJ) using an automated Roche Elecsys® and Cobase® immunoassay analyzer (Roche Diagnostics USA, Indianapolis, IN) [20]; the sensitivity of this assay is 0.02 ng/mL. The CRP level was determined using a fully automated IMMAGE Immunochemistry System (Beckman Coulter, Atlanta, GA); the lower limit of detection is 3.45 mg/L.

Statistical analysis

Normally distributed variables are presented as the mean $\pm$ standard deviation (SD), and non-parametric continuous variables are expressed as the median and interquartile ranges (IQR). Student t-tests, χ^2 tests, or Mann-Whitney U tests were used for between-group comparisons according to the data distribution. Multivariable regression analysis was performed to identify factors for nosocomial BSI. All statistical analyses were performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL), and a two-tailed p value <0.05 was considered to be statistically significant; all confidence intervals (CIs) were 95%.

Results

Patient demographics

Data from 480 charts were reviewed. Seventy-four cases were excluded because of incomplete data. Therefore, 404 neurologic patients were included in the primary analysis. Approximately 80% of our patients were mechanically ventilated during their ICU stay and had a central venous catheter during the entire ICU length of stay. The mean age of the patients was 56 years and ranged from 18 to 80 years; there were 280 males. The patient demographics and clinical characteristics are listed in Table 1. The most frequent underlying

TABLE 1. DEMOGRAPHICS AND PREDICTORS OF NOSOCOMIAL BLOOD STREAM INFECTIONS IN NEUROLOGIC PATIENTS

Parameters	Overall (n=404)		BSI (n=121)		No BSI (n=283)		p
Gender, n %							0.41
Female	124	(30.7)	41	(33.9)	83	(29.3)	
Male	280	(69.3)	80	(66.1)	200	(70.7)	
Age, mean $\pm$ SD, y	56 $\pm$ 14		56 $\pm$ 15		56 $\pm$ 14		0.944
Shock, n %	86	(21.3)	53	(43.8)	33	(11.7)	<0.001
DVC or PICC, n %	222	(55.0)	96	(79.3)	126	(44.5)	<0.001
Use of antibiotic agents in the 90 d before, n %	205	(50.7)	98	(80.9)	107	(37.8)	<0.05
Admission diagnosis							<0.001
Brain trauma	244	(60.4)	92	(76.0)	152	(14.7)	
Non-brain trauma	160	(39.6)	29	(24.0)	131	(46.3)	
Complications, n %							<0.001
0–1	285	(70.5)	58	(48.0)	227	(80.2)	
≥ 2	119	(29.5)	63	(52.0)	56	(19.8)	
Days in hospital, mean $\pm$ SD	16.8 $\pm$ 15.0		24.2 $\pm$ 21.4		13.7 $\pm$ 9.7		<0.001
Admission GCS							<0.001
Mild to moderate (9–15)	215	(53.2)	41	(33.9)	174	(61.5)	
Severe (3–8)	189	(46.8)	80	(66.1)	109	(38.5)	
Admission APACHE II Score, mean $\pm$ SD	13 $\pm$ 6		16 $\pm$ 6		12 $\pm$ 6		<0.05
Poor sterile field adherence to catheter-line insertion	191	(47.2)	99	(81.8)	191	(67.5)	<0.001
Intubation, n %	264	(65.3)	85	(70.2)	179	(63.3)	0.133
Mortality, n %	79	(19.6)	36	(29.8)	43	(15.2)	0.001
Mechanical ventilation, n %	262	(64.9)	81	(67.0)	181	(63.9)	0.565
Operation, n %	196	(48.5)	65	(53.7)	131	(46.3)	0.303
CRRT, n %	27	(6.7)	11	(9.1)	16	(5.7)	0.276
Admission highest temperature, mean $\pm$ SD, $^{\circ}$ C	37.2 $\pm$ 1.1		37.5 $\pm$ 1.6		37.1 $\pm$ 0.8		0.005
Admission WBC, mean $\pm$ SD, 10^9 /L	12.0 $\pm$ 4.8		12.6 $\pm$ 5.1		11.7 $\pm$ 4.6		0.104
Admission CRP, mean $\pm$ SD, mg/L	30.7 $\pm$ 39.3		34.5 $\pm$ 35.8		29.1 $\pm$ 40.6		0.203
Admission PCT, ng/mL (INQ)	0.21 (0.1, 0.6)		0.47 (0.2, 1.3)		0.15 (0.1, 0.4)		<0.001
Transfusion, n %	136	(33.7)	80	(66.1)	56	(19.8)	<0.001

BSI=blood stream infection; SD=standard deviation; GCS=Glasgow Coma Score; DVC=deep venous catheter; PICC=peripherally inserted central catheter; CRRT=continuous renal replacement therapy; WBC=white blood cell; CRP=C-reactive protein; PCT=procalcitonin.

conditions (recorded as diagnoses at admission) were acute brain trauma in 60% of patients and non-acute brain trauma in 40% of patients (cerebral infarction, 15%; cerebral hemorrhage, 18%; subarachnoid hemorrhage, 2.5%; brain tumor after surgery, 1.5%; other neurologic diseases, 3%). Overall, 79 patients died during hospitalization, accounting for a crude mortality rate of 19.6%.

Microbiologic features

Intensive care unit-acquired BSI was recorded in 121 patients (29.9 BSI episodes per 1,000 patient-days). Multiple episodes of BSI occurred in 16.5% of patients. A single source of infection was identified in 75.2% of patients; 12% had more than one source and 2% had no identifiable source. Of the episodes with only one documented source, intravascular catheters were the most common source (79.3%), followed by pneumonia (16%).

Twenty-five percent of all episodes of BSI were polymicrobial. Of 121 monomicrobial episodes, 65.4% of episodes were caused by gram-positive organisms and 32.2% by gram-negative organisms. Fungi were isolated in 0.8% of episodes. The rank order of the major pathogens is shown in Figure 1. Coagulase-negative staphylococci (CoNS) accounted for nearly half of all nosocomial BSI (44.6%).

Klebsiella species and *Acinetobacter baumannii* were the most common gram-negative organisms. The proportion of *Staphylococcus aureus* isolates and CoNS with methicillin resistance was 100%. Vancomycin resistance was not seen in *Enterococcus*. *Acinetobacter baumannii* and *Klebsiella* species were multi-drug-resistant pathogens in the study. For 50.7% of patients, there had been use of antibiotic agents in the 90 days before, and the antibiotic agents administered most often before admission were the third-generation cephalosporins and piperacillin/sulbactam. Thirty-six of the patients with nosocomial BSIs died during hospitalization, accounting for a crude mortality rate of 29.8%.

Risk factors for nosocomial BSI

Univariable analysis of nosocomial BSI showed that 11 factors were significantly ($p < 0.05$) associated with nosocomial BSI; all are listed in Table 2. Among the potential factors predisposing patients to nosocomial BSI, the most frequent risks included shock during hospitalization, use of antibiotic agents within 90 days before admission, requirement for a blood transfusion during hospitalization to maintain organ function, having a deep venous catheter (DVC) or percutaneously inserted central line catheter (PICC) in place, acute brain trauma, and poor sterile field adherence to

FIG. 1. Prevalence of organisms in nosocomial blood stream infection in patients with neurologic disease. Different colors represent different bacterial species; the name of the bacteria and its proportion are in boxes. Color image is available online at www.liebertpub.com/sur

catheter-line insertion. The outcomes of the multivariable regression model are shown in Table 3. After adjusting for all the significant factors identified in the univariate analysis, the odds ratio of antibiotic use within the 90 days before admission for developing nosocomial BSI was 5.81 (95% confidence interval [CI], 3.18–10.62; $p=0.001$). The odds ratio of developing BSI for subjects who had a long hospital stay was 0.97 (95% CI, 0.95–0.99; $p=0.001$). The odds ratio of developing BSI for patients with brain trauma was 0.28

(95% CI, 0.15–0.51; $p=0.001$). A blood transfusion requirement during hospitalization to maintain organ function increased the risk of nosocomial BSI (OR, 3.02; 95% CI, 1.45–6.29; $p=0.001$).

Discussion

This is the first study to report the rate, microbiologic features, and risk factors of nosocomial BSI in neurologic patients in a comprehensive ICU. Our results show that patients with traumatic brain injury are more prone to develop nosocomial BSI than patients with other neurogenic diseases.

Approximately 30% of the neurologic patients developed a hospital-acquired BSI, and the mortality of those neurogenic patients with hospital-acquired BSI during acute hospitalization reached 30%. Importantly, we need to identify modifiable risk factors to reduce this high morbidity and mortality.

TABLE 2. UNIVARIATE ANALYSIS OF NOSOCOMIAL BLOOD STREAM INFECTIONS IN NEUROLOGIC PATIENTS

Predictor	OR	95% CI	p
Admission highest temperature	0.72	0.57– 0.91	0.004
Shock	5.91	3.54– 9.84	<0.001
Use of antibiotic agents in the 90 d before	6.97	4.17–11.65	<0.001
Days stay in hospital	0.94	0.93– 0.96	<0.001
Admission GCS	0.32	0.21– 0.51	<0.001
Admission APACHE II Score	0.91	0.88– 0.94	<0.001
Transfusion	7.91	4.91–12.74	0.001
DVC or PICC	4.79	2.91– 7.88	<0.001
Admission PCT	0.92	0.85– 0.99	0.034
Brain trauma	0.37	0.23– 0.59	<0.001
Poor sterile field adherence to catheter-line insertion	2.86	1.83– 4.45	<0.001

OR=odds ratio; CI=confidence interval; GCS=Glasgow Coma Score; DVC=deep venous catheter; PICC=peripherally inserted central catheter.

TABLE 3. MULTIVARIABLE COMPETING RISKS ANALYSIS OF NOSOCOMIAL BLOOD STREAM INFECTIONS IN NEUROLOGIC PATIENTS

Predictor	OR	95% CI	p
Use of antibiotic agents in the 90 d prior	5.81	3.18–10.62	0.001
Days stay in hospital	0.97	0.94– 0.99	0.001
Transfusion	3.02	1.45– 6.29	0.001
Brain trauma	0.28	0.15– 0.51	0.001

OR=odds ratio; CI=confidence interval.

For example, disinfection of the skin should be scrupulously practiced when deep venous catheterization is performed in the emergency department or ICU, likewise, transfusion in these patients, reasonably used, should also be considered an indication for rigorous disinfection. The high rate of incidence and mortality of nosocomial BSI in this neurologic cohort is not consistent with the findings reported by other colleague in a nosocomial BSI study [21,22]. For example, changes in the body's defense function, staying in bed for an extended period, and dysfunction of the gastrointestinal tract of neurologic patients requiring intravascular lines to maintain treatment all increase the risk of nosocomial BSI. Intravascular lines were the most frequent source of nosocomial BSI in our study and were associated with both increased ICU stay and mortality, a finding that is consistent with the report by Ziegler et al. [23].

Recently published guidelines from the U.S. Centers for Disease Control and Prevention (CDC) for preventing intravascular device-related infections provide a framework for preventing nosocomial BSI [24]. Following these guidelines, measures have been taken to reduce nosocomial BSI in neurologic patients in our ICU, which include strictly aseptic operations, hand hygiene, strengthened education programs for doctors inserting catheters, training for nurses regarding catheter maintenance, and early removal of central venous catheters and urinary catheters [25].

In our study, the predominant pathogens of gram-positive isolates were similar to those reported in other studies that have shown an increased proportion of gram-positive organisms during the past few decades. In Spain, BSI isolates in the ICUs were CoNS (24.4%) and *Staphylococcus aureus* (17.5%) [26]. The National Nosocomial Infections Surveillance system (NNIS) in the United States, which studies isolates from ICUs, found CoNS (34%), *Staphylococcus aureus* (13%), and enterococci (13%) to be common organisms [27]. However, the predominant pathogens reported in pediatric patients at a tertiary care cancer center were gram-negative bacilli (GNB; 70.9%) [28]. Differences have been detected between resource adequacies, and the changing microbiologic pattern reflects the introduction of intensive treatment protocols as well as the use of CVCs and prophylactic antibiotics. The high proportion of *Staphylococcus aureus* isolates and CoNS with methicillin resistance, coupled with the multi-drug resistance of *Acinetobacter baumannii* and *Klebsiella* species, are consistent with the findings of European Antimicrobial Resistance Surveillance System [29] and necessitate urgent interventions, including creating awareness and establishing robust infection control and antibiotic stewardship programs for reducing the burden of nosocomial BSI [5].

After univariable and multivariable analyses, the factors that remained predictive of nosocomial BSI included administration of antibiotic agents during the 90 days before admission, ICU length of stay, patients with traumatic brain injury, and blood transfusion during hospitalization. This finding most likely reflects antibiotic-mediated changes in the endogenous bacterial flora, resulting in the development of more aggressive species capable of causing infection. Most patients were administered third-generation cephalosporins and piperacillin/sulbactam during the 90-days before admission, intensivists need to reduce the using of this kind of antibiotic, and patients with antibiotics before admission

should increase their intake of intestinal probiotics. Patients with traumatic brain injury are at high risk for the development of nosocomial BSI, because of the possible presence of unclean skin, the need for surgery, and the need for blood transfusions after major bleeding. Doctors and nurses should strengthen the monitoring and maintenance of venous catheters and the monitoring of clinical infections in this type of patient. A case control study [30] and a transfusion practice study [31] revealed an association between packed red blood cell (pRBC) transfusion and subsequent ICU-acquired BSI, which reminds us that avoiding unnecessary transfusions may decrease the incidence of nosocomial BSI.

The following limitations to the current study must be acknowledged. First, the study was retrospective in design, which may have introduced bias. Second, the sample size was relatively small. There was a large loss in sample size because of documentary inaccuracies (mostly from a lack of records regarding in-dwelling time for DVCs, detailed antibiotic use, and bacterial culture susceptibility results). Furthermore, this investigation was a single-site study, with no long-term outcome data available. Data such as long-term functional neurologic outcomes would be more useful for elucidating the effects of infections on long-term disability in neurologic patients, however, the present retrospective design prevented this analysis.

Conclusions

We observed that the proportion of nosocomial BSI is high and that the mortality of those neurogenic patients with hospital-acquired BSI during acute hospitalization reached 30%. Patients with traumatic brain injury are more prone to develop nosocomial BSI than patients with other neurogenic diseases. Importantly, we need to identify modifiable risk factors to reduce this high morbidity and mortality. Strictly aseptic operations, hand hygiene, and reasonable use of transfusions and antibiotics are the effective measures to prevent nosocomial BSI. This study highlights the need for a greater focus on nosocomial BSI research to reduce the overall disease burden by improving the outcomes of neurogenic patients with nosocomial BSI.

Acknowledgments

We would like to thank the medical staff of the Department of Intensive Care Unit for their participation in the study. Funded by: 18140901100; 20184Y0064; 2016ZB0202-01.

Author Disclosure Statement

The authors declare that they have no competing interest.

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Address correspondence to:

Dr. Ye Gong

Department of Intensive Care Unit

HuaShan Hospital

Fudan University

12 Wu Lu Mu Gi Middle Road

Shanghai 200040

China

E-mail: drgongyeicu@163.com