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ORIGINAL ARTICLE

Central line-associated bloodstream infections among critically-ill patients in the era of bundle care

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Abstract *Background/Purpose:* Patients admitted to intensive care units (ICUs) are at high risk for central line-associated bloodstream infections (CLABSIs). Bundle care has been documented to reduce CLABSI rates in Western countries, however, few reports were from Asian countries and the differences in the epidemiology or outcomes of critically-ill patients with CLABSIs after implementation of bundle care remain unknown. We aimed to evaluate the incidence, microbiological characteristics, and factors associated with mortality in critically-ill patients after implementation of bundle care.
Methods: Prospective surveillance was performed on patients admitted to ICUs at the National Taiwan University Hospital, Taipei, Taiwan from January 2012 to June 2013. The demographic, microbiological, and clinical data of patients who developed CLABSI according to the National Healthcare Safety Network definition were reviewed. A total of 181 episodes of CLABSI were assessed in 156 patients over 46,020 central-catheter days.

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Results: The incidence of CLABSI was 3.93 per 1000 central-catheter days. The predominant causative microorganisms isolated from CLABSI episodes were Gram-negative bacteria (39.2%), followed by Gram-positive bacteria (33.2%) and *Candida* spp. (27.6%). Median time from insertion of a central catheter to occurrence of CLABSI was 8 days. In multivariate analysis, the independent factors associated with mortality were higher Pitt bacteremia score [odds ratio (OR) 1.41; 95% confidence interval (CI) 1.18—1.68] and longer interval between onset of CLABSIs and catheter removal (OR 1.10; 95% CI 1.02—1.20), respectively.
Conclusion: In institutions with a high proportion of CLABSI caused by Gram-negative bacteria, severity of bacteremia and delay in catheter removal were significant factors associated with mortality.

Introduction

Central lines are widely used in critically-ill patients. Since central lines are increasingly prevalent, it is important to note that central line-associated bloodstream infection (CLABSI) is a leading cause of preventable health care-associated infections (HAIs) and that catheter-related bloodstream infections (CRBSI) have resulted in longer hospital stays, higher hospital costs, and significant mortality.[1—3] Fortunately, surveillance of CLABSIs followed by implementation of improvement strategies can reduce CLABSI incidence and associated morbidity and mortality.[3,4]

After incorporating preventive measures into an interventional bundle, the authors of a 2006 study observed a decrease in CLABSI rate.[5] Following this observation, several studies conducted in Western industrialized countries proposed that achieving and maintaining a rate of zero CLABSI was possible with the implementation of preventive measures,[6—8] however, CLABSIs remain a major component of HAIs in developing countries, where the target of zero CLABSI was reached in only a few studies.[7,9] CLABSIs are observed more frequently in intensive care units (ICUs). The high rates of CLABSI in ICUs have been attributed to poor compliance with the interventional bundle, inappropriate development of additional preventive measures, and differences in microbiological epidemiology.[7] The causative microorganisms of CLABSIs reported from the developing countries were predominantly Gram-negative bacteria, with trends of increasing incidence in recent years.[10—13] With the aforementioned preventive measures, reduction in CLABSIs caused by *Staphylococcus aureus* was more significant than CLABSIs caused by Gram-negative bacteria and *Candida* spp.[14] Further analysis of microbiological data should enable further development of pathogen-specific preventive measures.

Although there have been many international CLABSI studies, few have focused on the clinical characteristics of CLABSIs in Asian countries.[7,15,16] In the 2011 report from the Taiwan Nosocomial Infections Surveillance System (TNIS), bloodstream infections topped the list of HAIs (39.8%) in ICUs in Taiwan. In this study, we aimed to evaluate the epidemiology, microbiological data, and risk factors associated with mortality from CLABSI among patients admitted to an ICU in a tertiary medical center.

Methods

Hospital setting and patient population

The National Taiwan University Hospital, Taipei, Taiwan is a large medical center that provides both primary and tertiary care. A CLABSI interventional bundle has been implemented according to the recommendations of Centers for Disease Control and Prevention (CDC) guidelines in all units of our hospital since 2011. The elements of the care bundle included hand hygiene, maximal barrier precautions, skin antisepsis with 2% chlorhexidine alcohol (Panion & BF Biotech, Inc., Taipei, Taiwan), optimal catheter site selection, catheter-site dressing regimens, and daily evaluation and removal of unnecessary catheters.[4] The daily mean of catheter-days was defined as the mean of daily number of total central-catheter days, and catheter utilization rate was calculated by dividing the number of catheter days by the number of patient days.[17,18] In 2011 before the implementation of bundle care, the rate of CLABSI was 7.40 per 1000 central-catheter days, with a daily mean of 89.0 catheter-days and a catheter utilization rate of 64.4% in ICUs.

In this study, a total of 150 adult ICU beds (44 medical ICU beds, 39 cardiac care unit beds, 12 neurologic ICU beds, and 55 surgical ICU beds) were included in the high-risk units under surveillance. The ratio of nurses to ICU patients was 1:2. Prospective active surveillance was performed by infection-control nurses in all adult patients admitted to ICUs between January 2012 and June 2013. Antimicrobial impregnated catheters were not routinely used unless patients developed recurrent bacteremia or were at high risk for catheter-related bloodstream infections, including those with higher Charlson comorbidity indices and nosocomial origins of infection.[19]

During the study period, all patients aged $\geq$ 18 years and having one or more central-line catheterization were enrolled in this study. We monitored CLABSI episodes from central-line insertion until catheter removal, discharge from the ICU, or death. Given that a patient could develop more than one CLABSI episode, a new episode was defined by the isolation of a different microorganism from subsequent blood cultures.[20]

Definition

CLABSI was defined according to the surveillance definition published by the National Healthcare Safety Network (NHSN) in 2008.[21] Briefly, at least one of the following criteria must be met in the absence of a site-specific infection and the presence of a central vascular catheter: (1) a recognized pathogen is cultured from one or more blood cultures or (2) the same common commensal is cultured from two or more blood cultures drawn on separate occasions in the presence of signs and symptoms of infection. In contrast with the definition for CLABSI used for surveillance purposes, we used CRBSI for clinical diagnosis and treatment. A definitive diagnosis of CRBSI was made when the conditions for CLABSI were met in conjunction with positive semi-quantitative tip cultures ($>$ 15 *colony-forming units per catheter tip segment*) or by a differential time-to-positivity of $>$ 2 hours in simultaneous blood cultures drawn from peripheral blood and via catheters.[22]

The definitions of the underlying diseases were applied according to the comorbid conditions of the Charlson comorbidity index.[23] In brief, the cardiovascular diseases included myocardial infarction, congestive heart failure, and peripheral vascular disease. The neurological diseases included cerebrovascular disease, dementia, and hemiplegia. The respiratory diseases included chronic pulmonary diseases (such as chronic obstructive pulmonary disease, chronic asthma, and pneumoconiosis). The hepatobiliary disease was defined as chronic hepatitis (such as chronic viral hepatitis with persistent or intermittent elevation in serum aminotransferase for $\geq$ 6 months) with or without portal hypertension. The renal diseases included end-stage renal disease and moderate-to-severe renal disease with reduced glomerular filtration rate or kidney damage ($<$ 60 mL/min/1.73 m^2 of body-surface area) for $>$ 3 months. The immunosuppressive status referred to patients with acquired immunodeficiency syndrome. Multidrug-resistance was defined by *in vitro* resistance to three different classes of antimicrobial agents. For example, multidrug-resistant *Acinetobacter baumannii* was defined as if *A. baumannii* was resistant to three or more of the following five antibiotic classes: aminoglycosides, ampicillin/sulbactam, antipseudomonal carbapenems, antipseudomonal cephalosporins, and fluoroquinolones. Bacteremia eradication was documented.

Data collection

We used a standardized case-record form to collect information from every CLABSI episode. Infection control practitioners performed active surveillance and recorded the general information, which included baseline demographics, length of ICU stay and hospitalization, type of ICU, type of catheter, and causative pathogen. An infectious-disease specialist excluded all secondary bloodstream infections by assessing the possibility of other site-specific infections. By reviewing the medical records of those patients with CLABSIs, we recorded their underlying diseases, diagnosis on ICU admission, clinical signs and laboratory data, characteristics of the catheter, antimicrobial therapy, catheter removal, and 14-day hospital mortality. Antimicrobial therapy was considered adequate when the antimicrobial regimen included any active antimicrobial agent to which the pathogen was susceptible by *in vitro* susceptibility testing results administered during this episode of infection. The study was approved by the Research Ethics Committee of the National Taiwan University Hospital (NTUH-201102049RC).

Statistical analysis

The incidence of CLABSIs and CRBSIs was expressed as episodes per 1000 central-catheter days, and a Poisson distribution was used to compare the incidence of CLABSI at baseline and during the study period. Categorical variables were compared with a Chi-square test or Fisher's exact test if the expected values were $<$ 10. Continuous variables were described as mean $\pm$ standard deviation (SD) and were compared using the Student *t* test, or were described as the median and range, and were compared with the Wilcoxon rank-sum test if their distributions were not normal. Factors associated with acquiring CLABSI or CRBSI and mortality were identified using multivariate logistic regression models, with variables entered into the model with a backward stepwise logistic regression approach with $p < 0.2$ as a requirement for acceptance. Ninety-five percent confidence intervals (CIs) of odds ratios (ORs) were computed. All tests were two-tailed and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

From January 2012 to June 2013, a total of 156 patients with 181 episodes of CLABSIs were identified among 46,020 central-catheter days of surveillance. The mean rate of CLABSI was 3.93 per 1000 central-catheter days, with a daily mean of 84.0 catheter-days and a catheter utilization rate of 61.1%. The rate of CLABSI decreased from 7.40 per 1000 central-catheter days at baseline (before implementation of CLABSI bundle) to 3.93 per 1000 central-catheter days after intervention ($p > 0.05$). Among the 181 episodes of CLABSIs, 31 episodes fulfilled the definition of CRBSI, with the mean rate of CRBSI at 0.67 per 1000 central-catheter days. The demographics and clinical characteristics of all patients with CLABSI, those with CLABSI not meeting criteria for CRBSIs, and those with CRBSI are summarized in Table 1.

Of the patients with CLABSIs, 113 (62.4%) were male with a mean age of 66.3 years. The major underlying disease was malignancy (42.5%), followed by cardiovascular disease (39.2%) and diabetes mellitus (35.4%). Patients were admitted to ICUs mostly for sepsis (55.8%), followed by respiratory disease (42.0%) and cardiovascular disease (17.1%). Less than half of the patients received total parenteral nutrition (TPN) and anti-fungal agents, and the average number of antibiotics used prior to CLABSI was three (it is not easy to be exposed to 0.1—0.9 antibiotics). On average, each patient underwent placement of 1.6 central lines, most of which had triple lumens (86.7%) and were placed in the internal jugular veins (59.7%) in an ICU

Table 1 Demographics and clinical characteristics of patients with CLABSIs and CRBSIs

Variable	CLABSI			*p*
	Overall (n = 181)	CLABSI (CRBSI excluded; n = 150)	CRBSI (n = 31)	
Age (y)	66.3 ± 15.8	65.4 ± 15.8	70.6 ± 15.6	0.036
Male	113 (62.4)	96 (64.0)	17 (54.8)	0.338
Underlying disease				
Cardiovascular disease	71 (39.2)	55 (36.7)	16 (51.6)	0.121
Neurological disease	48 (26.5)	42 (28.0)	6 (19.4)	0.321
Respiratory disease	28 (15.5)	25 (16.7)	3 (9.7)	0.327
Gastrointestinal disease	25 (13.8)	19 (12.7)	6 (19.4)	0.326
Hepatobiliary disease	38 (21.0)	31 (20.7)	7 (22.6)	0.812
Renal disease	59 (32.6)	47 (31.3)	12 (38.7)	0.425
Autoimmune disease	12 (6.6)	10 (6.7)	2 (6.5)	0.965
Diabetes mellitus	64 (35.4)	51 (34.0)	13 (41.9)	0.400
Malignancy	77 (42.5)	65 (43.3)	12 (38.7)	0.635
Immunosuppression	10 (5.5)	9 (6.0)	1 (3.2)	0.538
Charlson comorbidity index	4.6 ± 2.8	4.6 ± 2.8	4.5 ± 2.8	0.983
Major diagnosis on ICU admission				
Cardiovascular disease	31 (17.1)	24 (16.0)	7 (22.6)	0.376
Neurological disease	8 (4.4)	7 (4.7)	1 (3.2)	0.722
Respiratory disease	76 (42.0)	63 (42.0)	13 (41.9)	0.995
Gastrointestinal disease	16 (8.8)	15 (10.0)	1 (3.2)	0.226
Hepatobiliary disease	6 (3.3)	6 (4.0)	0 (0)	0.257
Genitourinary disease	10 (5.5)	8 (5.3)	2 (6.5)	0.804
Malignancy	9 (5.0)	7 (4.7)	2 (6.5)	0.677
Sepsis	101 (55.8)	85 (56.7)	16 (51.6)	0.606
Trauma	6 (3.3)	3 (2.0)	3 (9.7)	0.064
APACHE II score	21.7 ± 8.5	22.2 ± 8.4	19.4 ± 8.3	0.115
Receipt of TPN	29 (16.0)	21 (14.0)	8 (25.8)	0.103
Previous use of antibiotics	3.0 ± 1.9	3.1 ± 1.8	2.6 ± 2.2	0.061
Previous use of anti-fungal agent	68 (37.6)	58 (38.7)	10 (32.3)	0.502
Number of catheter	1.6 ± 0.6	1.6 ± 0.6	1.7 ± 0.6	0.496
Catheter lumen				
Single lumen	5 (2.8)	3 (2.0)	2 (6.5)	0.169
Dual lumen	19 (10.5)	15 (10.0)	4 (12.9)	0.631
Triple lumen	157 (86.7)	132 (88.0)	25 (80.7)	0.272
Anatomic site				
Internal jugular vein	108 (59.7)	95 (63.3)	13 (41.9)	0.027
Subclavian vein	29 (16.0)	21 (14.0)	8 (25.8)	0.103
Femoral vein	46 (25.4)	34 (22.7)	12 (38.7)	0.062
Place of line insertion				0.692
ICU	117 (64.6)	96 (64.0)	21 (67.7)	
Non-ICU	64 (35.4)	54 (36.0)	10 (32.3)	
Interval from ICU admission to onset of catheter infection (d)	12.0 (3—97)	11.0 (3—97)	18 (4—53)	0.019
Interval from catheter placement to onset of catheter infection (d)	8.0 (2—778)	8.0 (2—778)	13.0 (4—154)	<0.001
14-day mortality	70 (38.7)	62 (41.3)	8 (25.8)	0.106

Data are presented as n (%), mean ± SD, or median (range).
APACHE = acute physiology and chronic health evaluation; CLABSI = central line-associated bloodstream infection; CRBSI = catheter-related bloodstream infection; ICU = intensive care unit; TPN = total parenteral nutrition.

setting (64.6%). The median duration from ICU admission and placement of central lines to occurrence of CLABSIs was 12.0 days and 8.0 days, respectively. Patients with CRBSIs were older than patients with CLABSIs (70.6 years vs. 65.4 years, $p = 0.036$) and had a lower proportion of catheter placement in the jugular vein (41.9% vs. 63.3%, $p = 0.027$), longer ICU stay (18.0 days vs. 11.0 days, $p = 0.019$), and longer duration of catheterization (13.0 days vs. 8.0 days, $p < 0.001$; Table 1).

The etiological agents associated with CLABSIs and CRBSIs are listed in Table 2. The most common pathogens causing CLABSI following bundle care were Gram-negative bacteria (38.0%), followed by Gram-positive bacteria (34.7%), *Candida* spp. (24.0%), and anaerobes (4.7%).

Table 2 Causative microorganisms responsible for CLABSIs

Microorganism	CLABSI			
	Overall (n = 181)	CLABSI (CRBSI excluded; n = 150)	CRBSI (n = 31)	p
Gram-positive bacteria	60 (33.2)	52 (34.7)	8 (25.8)	0.340
Enterococcus spp.	39 (21.6)	35 (23.3)	4 (12.9)	
Coagulase-negative staphylococci	17 (9.4)	16 (10.7)	1 (3.2)	
Staphylococcus aureus	6 (3.3)	3 (2.0)	3 (9.7)	
Gram-negative bacteria	71 (39.2)	57 (38.0)	14 (45.2)	0.457
Enterobacteriaceae	26 (14.4)	18 (12.0)	8 (25.8)	
Citrobacter spp.	2 (1.1)	2 (1.3)	0 (0)	
Enterobacter spp.	6 (3.3)	4 (2.7)	2 (6.5)	
Escherichia coli	6 (3.3)	6 (4.0)	0 (0)	
Klebsiella spp.	4 (2.2)	2 (1.3)	2 (6.5)	
Proteus spp.	3 (1.7)	0 (0)	3 (9.7)	
Serratia marcescens	5 (2.8)	4 (2.7)	1 (3.2)	
NFGNB	49 (27.1)	36 (24.0)	10 (32.3)	
Acinetobacter spp.	12 (6.6)	10 (6.7)	2 (6.5)	
Achromobacter spp.	2 (1.1)	2 (1.3)	0 (0)	
Burkholderia cepacia	10 (5.5)	8 (5.3)	2 (6.5)	
Chryseobacterium spp.	10 (5.5)	8 (5.3)	2 (6.5)	
Pseudomonas spp.	7 (3.9)	3 (2.0)	4 (12.9)	
Stenotrophomonas maltophilia	4 (2.2)	3 (2.0)	1 (3.2)	
Others[a]	5 (2.8)	5 (3.3)	0 (0)	
Anaerobes	8 (4.4)	8 (5.3)	0 (0)	0.220
Bacteroides spp.	7 (3.9)	7 (4.7)	0 (0)	
Prevotella spp.	1 (0.6)	1 (0.7)	0 (0)	
Fungi	50 (27.6)	37 (24.7)	13 (41.9)	0.050
Candida albicans	21 (11.6)	18 (12.0)	3 (9.7)	
Candida glabrata	8 (4.4)	6 (4.0)	2 (6.5)	
Candida krusei	3 (1.7)	1 (0.7)	2 (6.5)	
Candida parapsilosis	3 (1.7)	3 (2.0)	0 (0)	
Candida tropicalis	12 (6.6)	7 (4.7)	5 (16.1)	
Others[b]	3 (1.7)	2 (1.3)	1 (3.2)	
Resistant strain[c]	47 (26.0)	39 (26.0)	8 (25.8)	0.982
Polymicrobial infections[d]	14 (7.7)	8 (5.3)	6 (19.4)	0.017

Data are presented as n (%).
CLABSI = central line-associated bloodstream infection; CRBSI = catheter-related bloodstream infection; NFGNB = non-fermentative gram-negative bacilli.
[a] Other NFGNB included two *Delftia* spp. (1.1%), one *Ralstonia* spp. (0.6%), and two *Sphingomonas paucimobilis* (1.1%).
[b] Other fungi included one *Candida guilliermondii* (0.6%), one unidentified *Candida* species (0.6%), and one *Saccharomyces cerevisiae* (0.6%).
[c] Resistant strains included carbapenem-resistant *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus*, methicillin-resistant coagulase-negative *staphylococci*, multidrug-resistant *Acinetobacter baumannii*, and vancomycin resistant *Enterococcus*.
[d] The 14 polymicrobial infections mostly included *Candida* spp. (n = 4), followed by *Chryseobacterium* spp. (n = 3), *Pseudomonas aeruginosa* (n = 3), *Stenotrophomonas maltophilia* (n = 3), and *Acinetobacter* spp. (n = 2).

Similar to the most common pathogens associated with CLABSI, the most common pathogens associated with CRBSIs were Gram-negative bacteria (45.2%), followed by *Candida* spp. (41.9%) and Gram-positive bacteria (25.8%). In both the CLABSI and CRBSI groups, the most common causative Gram-positive bacteria, Gram-negative bacteria, and fungi were *Enterococcus* spp., nonfermentative Gram-negative bacilli (NFGNB), and *Candida* spp. Among catheter infections, 26.0% of causative organisms were resistant strains. Compared with patients with CLABSIs, patients with CRBSIs had a higher percentage of *Candida* infections (41.9% vs. 24.7%, p = 0.050) and polymicrobial infections (19.4% vs. 5.3%, p = 0.017). Comparing the risk factors of acquiring Gram-positive versus Gram-negative bacteria, more patients with Gram-positive associated CLABSIs had chronic pulmonary disease (34.0% vs. 8.2%, p = 0.001) and received TPN (20.8% vs. 6.6%, p = 0.025). Gram-negative-bacteria-related CLABSIs significantly increased when the ICU stay lasted beyond 14 days (p = 0.019) (Figure 1).

The 14-day mortality of CLABSIs and CRBSIs was 38.7% and 25.8%, respectively. Factors associated with 14-day mortality in CLABSIs are shown in Table 3. By univariate analysis, patients with neurologic disease, catheter removal, and eradication of bacteremia (may need to define when repeat blood cultures to document eradication were taken, whether all had repeat blood cultures done,

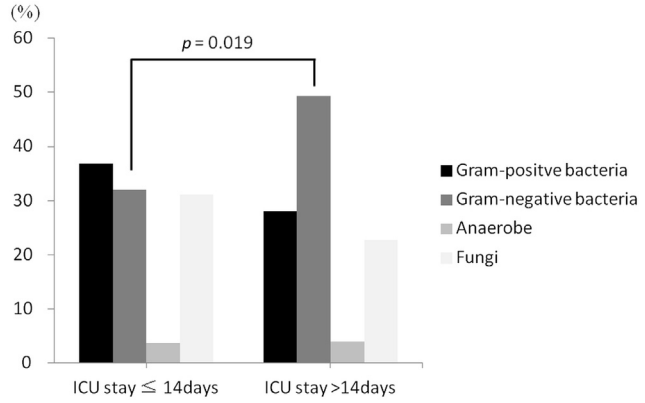

Figure 1. Microbiologic distribution associated with duration of ICU stay $\leq$ 14 days and $>$ 14 days. ICU = intensive care units.

etc. see Methods section) were more likely to survive beyond 14 days (all $p < 0.05$). By contrast, patients with catheter placement in the ICU setting and higher Pitt bacteremia scores with manifestations of shock and disseminated intravascular coagulopathy were more likely to die within 14 days (all $p < 0.05$). By multivariate analysis, increased Pitt bacteremia scores and intervals between onset of CLABSIs and catheter removal were independently associated with 14-day mortality risk (OR 1.41, 95% CI 1.18—1.68; OR 1.10, 95% CI 1.02—1.20, respectively), however, the underlying disease, diagnosis on admission, causative pathogen, setting of catheter insertion, anatomic site of catheter, and adequate or combined antimicrobial therapy were not associated with mortality. There was also no difference between the 14-day mortality rate of CLABSI caused by Gram-positive and that of CLABSI caused by Gram-negative bacteria (37.7% vs. 32.8%, $p = 0.581$). Of those patients with Gram-positive-bacteria-related CLABSIs, multivariate analysis showed that cardiovascular disease and higher Pitt bacteremia score (OR 3.83, 95% CI 1.06—13.87; OR 1.30; 95% CI 1.01—1.68, respectively) were the factors associated with 14-day mortality. Of those patients with Gram-negative-bacteria-related CLABSIs, only higher Pitt bacteremia score (OR 1.37, 95% CI 1.07—15.87) was the independent factor predicting 14-day mortality.

Discussion

To the best of our knowledge, there have been few surveillance studies of CLABSI from Asian countries after the NHSN first published the definition in 2008.[7,15,16] The present study aimed to evaluate the incidence, etiology, and factors associated with mortality of CLABSI in Asian adult ICUs. After implementation of CLABSI bundle care, the rate of CLABSIs in our ICUs decreased from 7.40 per 1000 central-catheter days to 3.93 per 1000 central-catheter days. In comparison with the CLABSI rate of ICUs in developing countries from 2004 to 2009 (6.8 per 1000 central-line days), our incidence was much lower.[24] At the time TNIS was launched in 2007, the average CLABSI rates ranged from 5.5 per 1000 central-catheter days and 3.5 per 1000 central-catheter days in the ICUs of medical centers and regional hospitals, respectively.[25] Our surveillance data were higher than the benchmarking data from NHSN hospitals in 2012, which was 1.3 per 1000 central-catheter days at the medical ICUs of major teaching hospitals. The incidence of CLABSIs in hospitals reporting to NHSN also varied with the type of hospital unit, which ranged from 0.8 per 1000 central-catheter days in surgical ICUs to 3.4 per 1000 central-catheter days in burn ICUs.[26] Hence, total elimination of CLABSIs may be a realistic goal for some units, but local differences must be addressed.

Our study adds information that could improve current prevention strategies and reduce CLABSI by addressing the changing etiology and clinical characteristics. The causative pathogens of CLABSIs in our ICU were predominantly Gram-negative bacteria, followed by Gram-positive bacteria and *Candida* spp. As there were no nosocomial outbreaks detected in our ICUs during the study period, the epidemiological trends in this study were considered consistent with recent studies and the serial surveillance report of TNIS,[25] however, these findings were different from the NHSN report and older studies, wherein Gram-positive bacteria were the predominant pathogens in central line-related bloodstream infections. The pathogen-specific incidence-density rates in 2010 according to NHSN surveillance data for *Enterococcus* spp., *Staphylococcus aureus*, Gram-negative rods, and *Candida* spp. were 0.28 CLABSIs per 1,000 central-catheter days, 0.14 CLABSIs per 1,000 central-catheter days, 0.26 CLABSIs per 1,000 central-catheter days, and 0.25 CLABSIs per 1,000 central-catheter days, respectively.[18,27,28] Accordingly, current guidelines of intravascular catheter-related infection by the Infectious Disease Society of America (IDSA) recommend routine empirical coverage for Gram-positive bacteria and only selective additional coverage for Gram-negative bacteria in neutropenic or severely ill patients, patients colonized with Gram-negative bacteria, or those who have a femoral catheter.[22]

After implementation of bundle care, change in the types of pathogens frequently isolated from central line-related bloodstream infections has been observed in several recent studies.[12,13] These studies recorded a significant reduction in CRBSI incidence caused by Gram-positive bacteria and an increasing trend of CRBSI caused by Gram-negative bacteria and fungi. Possible explanations for the increase of Gram-negative bacteria and fungi include the increasing complexity of the patient population and the implementation of infection control currently targeting Gram-positive organisms.[12,13]

There is considerable overlap between the definitions of CLABSI and CRBSI and we assume that diagnosis of CLABSI often overestimates the true number of infections that are attributable to central lines. Therefore, we compared the microbiological characteristics of CLABSI and CRBSI in this study. In both CLABSIs and CRBSIs, the predominant causative pathogens were Gram-negative bacteria. Patients with CRBSIs had fewer jugular catheter placements, longer ICU stay and interval from catheter insertion to onset of CLABSI, and more fungal and mixed pathogen infections. The mixed pathogens comprised mostly *Candida* spp. and NFGNB. A possible explanation for the fact that more fungi and mixed pathogens were identified in CRBSIs was that

Table 3 Factors associated with 14-day mortality in patients with CLABSIs

Variable	Univariate analysis			Multivariate analysis	
	Survival (n = 111)	Mortality (n = 70)	p	p	OR (95% CI)
Age (y)	66.5 ± 16.6	65.6 ± 14.7	0.570	—	—
Male	68 (61.3)	45 (64.3)	0.682	—	—
Underlying disease					
Cardiovascular disease	40 (36.0)	31 (44.3)	0.268	—	—
Neurological disease	35 (31.5)	13 (18.6)	0.054	0.063	—
Respiratory disease	19 (17.1)	9 (12.9)	0.440	—	—
Gastrointestinal disease	14 (12.6)	11 (15.7)	0.556	—	—
Hepatobiliary disease	23 (20.7)	15 (21.4)	0.909	—	—
Renal disease	35 (31.5)	24 (34.3)	0.700	—	—
Autoimmune disease	4 (3.6)	8 (11.4)	0.039	0.633	—
Diabetes mellitus	43 (38.7)	21 (30.0)	0.231	—	—
Malignancy	46 (41.4)	31 (44.3)	0.706	—	—
Immunosuppression	5 (4.5)	5 (7.1)	0.449	—	—
Charlson comorbidity index	4.4 ± 2.8	4.9 ± 2.9	0.277	—	—
Major diagnosis on ICU admission					
Cardiovascular disease	16 (14.4)	15 (21.4)	0.223	—	—
Neurological disease	8 (7.2)	0 (0)	0.022	0.999	—
Respiratory disease	44 (39.6)	32 (45.7)	0.420	—	—
Gastrointestinal disease	11 (9.9)	5 (7.1)	0.523	—	—
Hepatobiliary disease	3 (2.7)	3 (4.3)	0.562	—	—
Genitourinary	7 (6.3)	3 (4.3)	0.562	—	—
Malignancy	5 (4.5)	4 (5.7)	0.715	—	—
Infection	62 (55.9)	39 (55.7)	0.985	—	—
Trauma	5 (4.5)	1 (1.4)	0.260	—	—
APACHE II score	21.6 ± 8.4	21.9 ± 8.6	0.808	—	—
Clinical signs					
Shock	43 (38.7)	47 (67.1)	<0.001	0.859	—
AKI	50 (45.1)	41 (58.6)	0.076	0.536	—
DIC	24 (21.6)	30 (42.9)	0.002	0.142	—
Pitt bacteremia score	4.2 ± 2.6	6.5 ± 2.8	<0.001	<0.001	1.41 (1.18—1.68)
Pathogen					
Gram-positive bacteria	38 (34.2)	22 (31.4)	0.696	—	—
Gram-negative bacteria	47 (42.3)	24 (34.3)	0.280	—	—
Anaerobes	4 (3.6)	3 (4.3)	0.817	—	—
Fungi	27 (24.3)	23 (32.9)	0.211	—	—
Mixed organisms	9 (8.1)	5 (7.1)	0.813	—	—
Resistant strain	28 (25.2)	19 (27.1)	0.774	—	—
Number of catheters	1.5 ± 0.5	1.7 ± 0.7	0.066	0.283	—
Catheter lumen	2.8 ± 0.5	2.8 ± 0.4	0.816	—	—
Anatomic site					
Internal jugular vein	66 (59.5)	42 (60.0)	0.942	—	—
Subclavian vein	18 (16.2)	11 (15.7)	0.929	—	—
Femoral vein	28 (25.2)	18 (25.7)	0.941	—	—
Place of line insertion					
ICU	64 (57.7)	53 (75.7)	0.013	0.577	—
Treatment					
Adequate antibiotics	94 (84.7)	53 (75.7)	0.132	0.544	—
Combination of antibiotics	5 (4.5)	3 (4.3)	0.944	—	—
Catheter removal	97 (87.4)	50 (71.4)	0.007	0.999	—
Eradication of bacteremia	75 (67.6)	33 (47.1)	0.006	0.452	—
Interval from onset of CLABSI to adequate antibiotics (d)	2 (0—8)	1 (0—8)	0.870	—	—
Interval from onset of CLABSI to catheter removal (d)	1 (0—22)	2 (0—33)	0.051	0.021	1.10 (1.02—1.20)

Data are presented as n (%), mean ± SD, or median (range).
AKI = acute kidney injury; CI = confidence interval; CLABSI = central line-associated bloodstream infection; DIC = disseminated intravascular coagulopathy; ICU = intensive care unit; OR = odds ratio.

those pathogens prompted catheter removal according to IDSA guidelines and positive semiquantitative tip culture constituted the definition of CRBSI.[22] In previous studies, the specific patient population at risk for Gram-negative CRBSIs included patients with spinal cord injuries, femoral catheters, hematologic malignancy, gastrointestinal colonization, or prolonged stay in the ICU, whereas fungal CRBSI was associated with femoral catheters or administration of parenteral nutrition.[12,13,29,30] Given the fact that most patients in our study population had a malignancy as their underlying disease (42.5%) and had been exposed to many antibiotics (3), it is not surprising that Gram-negative bacteria caused 39.2% of CLABSIs in our ICUs. This epidemiological shift prompts the development of prevention strategies directed against Gram-negative bacteria, including empiric coverage.[29] In CLABSI associated with Gram-negative bacteria in our study, NFGNB were the most common pathogens. These pathogens are ubiquitously distributed in diverse environmental sources and are associated with central line placement, previous antibiotics, and steroid use.[31,32] The remaining causative Gram-negative bacteria, *Enterobacteriaceae* spp., were over-represented in patients with neutropenia following chemotherapy.

The strategies for decreasing CLABSIs associated with Gram-negative bacteria should focus on both protecting patients from the exogenous organisms and controlling endogenous sources.[33] Most present infection-control methods for preventing CLABSI, including contact isolation, skin disinfection, and hand hygiene, are focused on exogenous organisms, especially for Gram-positive skin flora. Studies showed that decolonization of endogenous organisms by selective oropharyngeal or digestive decontamination has benefits in preventing bloodstream infections associated with Gram-negative bacteria.[34,35] NHSN recently released revised CLABSI definitions that included a category of mucosal-barrier injury with laboratory-confirmed bloodstream infection to reduce the number of cases due to bacterial translocation in immunocompromised patients.[36,37] Implementation of these definitions and developments to reduce CLABSI caused by Gram-negative bacteria need further study.

Several studies have addressed CRBSI risk factors and prognosis in different clinical settings and populations, but the data specifically for critically-ill patients with CLABSIs are scarce.[38,39] In our analysis, there was no difference in mortality between patients with CLABSI and patients with CRBSI, and the severity of bacteremia and delay in catheter removal were the only two independent factors related to 14-day mortality in the CLABSI group. In previous CRBSI studies, two protective factors had been identified: catheter removal and appropriate antimicrobial therapy.[39] Our findings with regard to CLABSI are similar. Hence, CLABSI and CRBSI may be regarded as equivalent in studies to identify prognostic factors. In our study, the percentage of adequate empirical antibiotics was very high (84.7% in the CLABSI group and 75.7% in the CRBSI group). Thus, disease severity may be the major independent factor associated with mortality. Delayed catheter removal rather than the act of catheter removal was the other independent factor associated with mortality, highlighting the importance of timeliness.[39,40]

This study had several limitations and the results should be interpreted with caution. First, although our investigation was conducted prospectively over a period of 18 months using CLABSI data from a large medical center, our sample size was still limited to a single medical center. Second, the compliance rate of our interventional bundle and checklist was nearly 95%, so our findings may not be comparable to those in institutions whose compliance rates are substantially different from ours. Third, the definition of CLABSI had been changed since 2011, therefore, the comparison of incidence and microbiological distribution before and after implementation of bundle care should take note of these secular changes. Despite these limitations, we provide valuable information on the incidence and etiology of CLABSI and factors associated with mortality in CLABSIs in critically-ill Asian patients.

In conclusion, the increasing trend of CLABSI caused by Gram-negative bacteria and fungi after implementation of bundle care should not be ignored. In institutions with CLABSI caused predominantly by Gram-negative bacteria, additional infection-control measures to control endogenous flora spreading and empiric antibiotic for CLABSI are essential. The mortality of CLABSI was associated with the severity of bacteremia and delayed catheter removal.

Conflicts of interest

None declared.

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