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Original Article

The epidemiology, antibiograms and predictors of mortality among critically-ill patients with central line-associated bloodstream infections

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Mortality

Abstract *Background/purpose:* For high risk of central line-associated bloodstream infections (CLABSIs) in patients of intensive care units (ICUs) and scarcely epidemiology and therapeutic recommendations in Asia, we aimed to evaluate the annual change in epidemiology, antibiogram, and risk factors for 14-day mortality.
Methods: A retrospective study of ICUs patients with CLABSIs at a medical center in Taiwan (2010–2016), where central line care bundle implemented since 2014, by reviewing clinical data, pathogens, and the antibiogram.
Results: Gram-negative bacteria (59.3%) were main microorganisms of CLABSIs, and 9.0% of all GNB were MDROs. *Acinetobacter* spp., *Enterobacter* spp., and *Stenotrophomonas maltophilia* were the most frequently isolated. In multivariate analysis, malignancy, inadequate empirical antimicrobial therapy, inadequate definite antimicrobial therapy, and infection by fungi or multidrug-resistant organisms (MDROs) were associated with 14-day mortality (all $p < 0.05$). The CLABSI incidence rate decreased from 5.54 to 2.18 per 1000 catheter-day (from 2014 to 2015) with improved compliance to care bundle. Carbapenem and aminoglycoside were

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suitable empirical drugs in the hospital setting when GNB is predominant for CLABSI. Significant decreasing susceptibility of ampicillin/sulbactam in *Enterobacter* spp. (36.7%—0.0%), and ampicillin/sulbactam (12.5%—0.0%), ceftazidime (100.0%—52.9%), and tigecycline (87.5% —35.3%) in *Serratia marcescens*.

Conclusion: We identified Gram-negative bacteria as leading pathogens of CLABSIs in a Taiwan medical center, and good compliance to care bundle is associated with reduced CLABSI incidence rate. Malignancy, infection by MDROs or fungi, inadequate empirical or definite antimicrobial therapy are significant factors for 14-day mortality.

Introduction

Central line-associated bloodstream infection (CLABSI) is the leading cause of healthcare-associated infection (HAI) worldwide and is responsible for significant mortality, extended duration of hospital stays, and excess health cost expenditures.[1—4] CLABSI is also the major problem for intensive care units (ICUs) due to the widespread use of central line in critically-ill patients. However, the data of evolution and changing epidemiology within a population of CLABSIs were rare in Asian countries,[5,6] made it difficult to recommend empirical therapy for pathogens coverage according to specific circumferences. The increasing rate of multidrug resistant Gram-negative pathogens in HAIs may also have impact on CLABSI outcome.[4,7,8] Despite the various global surveillance studies, e.g. Study for Monitoring Antimicrobial Resistance Trends (SMART) has monitored the *in vitro* susceptibility patterns of clinical Gram-negative bacilli to antimicrobial agents collected worldwide from intra-abdominal infections since 2002 and urinary tract infections since 2009,[9—11] there was limited information about the related epidemiology of CLABSIs.

In this study, we analyzed the episodes of CLABSIs over the 2010—2016 period in a Taiwan medical center, among patients admitted to adult ICUs with central lines placed in order to investigate the incidence rates, bacteriological profile, antimicrobial susceptibility pattern, and risk factors associated with 14-day mortality in this setting.

Methods

Study design and data collection

We performed a retrospective cross-sectional study for CLABSI in ICU cases over a 7-year period (from January 2010 to December 2016) at Kaohsiung Medical University Hospital, a medical center in Taiwan. This study was approved by the Institutional Review Board of the Kaohsiung Medical University Hospital. The hospital provided 117 adult ICU beds (30 medical ICU beds, 20 cardiac care unit beds, 13 neurologic ICU beds, 25 surgical ICU beds, 10 cardiac surgical ICU beds, 14 neurosurgical ICU beds, and 5 burn center beds), and all with a nurse-to-patient ratio of 1:2.

A CLABSI interventional bundle was implemented since October 2011 according to the recommendation of CDC guidelines[12] in two ICUs since October 2011 and in all ICUs since January 2014. A multidisciplinary central-line bundle is defined as a combination of education, interventions such as selection of appropriate insertion site, application of hand hygiene, cleaning of the skin with alcohol followed by 2% chlorhexidine, full barrier precaution during the insertion of a central line, and the maintenance included hand hygiene, proper dressing changes, aseptic technique for accessing and changing needleless connectors, and a daily review of catheter necessity.[13] The items of a checklist during surveillance for ensuring the precision and accuracy of measurement includes hand hygiene, appropriate skin disinfection, maximal sterile barrier, catheter insertion site evaluation, proper dressing coverage, closed system of the catheter, and aseptic technique before using connectors.

All participants aged ≥18 years admitted to ICUs and had one or more central line catheterization were enrolled. By reviewing the medical records of those patients with CLABSIs, both of an infectious-disease specialist and another infection control practitioner excluded all secondary bloodstream infections, and recorded baseline demographics, main diagnosis on ICU admission, underlying diseases, catheter insertion site, causative microorganisms, the length of ICU stay, 14-day hospital mortality and in-hospital mortality. A new episode was defined by a different pathogen isolated from subsequent blood cultures, given that a patient could develop more than one CLABSI episode. Empirical antimicrobial therapy was defined as prescription of at least a new antibiotic within 48 h when a CLABSI episode was concerned and had corresponding blood sampling. Furthermore, the annual *in vitro* susceptibility of microorganisms isolated from episodes of healthcare-associated infection (HAI) were collected. Appropriate antimicrobial therapy was considered when the pathogen was susceptible to any one of the agents administered during the CLABSI episode by *in vitro* testing or previously published data.[14,15]

Definition of terms

CLABSI was defined based on the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) definition in 2008.[12] A patient with a central venous catheter who has a recognized pathogen isolated from one or more blood cultures after 48 h of catheterization; or with the same skin commensals cultured

Table 1 Microorganisms identified as etiologic agents of CLABSIs.

Microorganism	Overall (n = 428)	Jan. 2010—Dec. 2013 (n = 170)	Jan. 2014—Dec. 2016 (n = 258)	*p*
Gram-positive bacteria	106 (24.8)	37 (21.8)	69 (26.7)	0.312
Staphylococcus aureus	15 (3.5)	6 (3.5)	9 (3.5)	
Coagulase-negative *staphylococci*	30 (7.0)	12 (7.1)	18 (7.0)	
Corynebacterium jeikeium	1 (0.2)	1 (0.6)	0 (0.0)	
Enterococcus spp.	60 (14.0)	18 (10.6)	42 (16.3)	0.201
Gram-negative bacteria	254 (59.3)	109 (64.1)	147 (57.0)	0.775
Enterobacteriaceae	113 (26.4)	46 (27.1)	67 (26.0)	1.000
Enterobacter spp.	37 (8.6)	18 (10.6)	19 (7.4)	
Escherichia spp.	14 (3.3)	7 (4.1)	7 (2.7)	
Klebsiella spp.	33 (7.7)	14 (8.2)	19 (7.4)	
Citrobacter spp.	5 (1.2)	3 (1.8)	2 (0.8)	
Serratia marcescens	24 (5.6)	4 (2.4)	20 (7.8)	
NFGNB	141 (32.9)	63 (37.1)	80 (31.0)	
Achromobacter spp.	1 (0.2)	0 (0.0)	1 (0.4)	
Acinetobacter spp.	41 (9.6)	20 (11.8)	21 (8.1)	
Aeromonas hydrophila	5 (1.2)	3 (1.8)	2 (0.8)	
Burkholderia cepacia	9 (2.1)	2 (1.2)	7 (2.7)	
Chryseobacterium spp.	9 (2.1)	2 (1.2)	7 (2.7)	
Elizabethkingia spp.	5 (1.2)	0 (0.0)	5 (1.9)	
Pseudomonas spp.	31 (7.2)	16 (9.4)	15 (5.8)	
Stenotrophomonas maltophilia	34 (7.9)	16 (9.4)	18 (7.0)	
Others[a]	6 (1.4)	2 (1.2)	4 (1.6)	
Anaerobe	3 (0.7)	1 (0.6)	2 (0.8)	1.000
Bacteroides spp.	2 (0.4)	1 (0.6)	1 (0.4)	
Prevotella spp.	1 (0.2)	0 (0.0)	1 (0.4)	
Fungus	100 (23.4)	43 (25.3)	57 (22.1)	0.565
Candida albicans	50 (11.7)	23 (13.5)	27 (10.5)	0.874
Candida dubliniensis	2 (0.4)	0 (0.0)	2 (0.8)	
Candida glabrata	16 (3.7)	7 (4.1)	9 (3.2)	
Candida parapsilosis	5 (1.2)	1 (0.6)	4 (1.6)	
Candida pelliculosa	2 (0.4)	0 (0.0)	2 (0.8)	
Candida tropicals	22 (5.1)	10 (5.9)	12 (4.7)	
Others[b]	3 (0.7)	2 (1.2)	1 (0.4)	
MDROs[c]	77 (18.2)	27 (15.9)	50 (19.4)	0.443
Gram-positive	39 (9.2)	13 (7.6)	26 (10.1)	0.398
VRE*	23 (5.4)	4 (2.4)	19 (7.4)	0.028
MRSA	12 (2.8)	6 (3.5)	6 (2.3)	0.553
Gram-negative	38 (9.0)	14 (8.2)	24 (9.3)	0.862
CREN	7 (1.6)	5 (2.9)	2 (0.8)	0.590
CRAB	25 (4.7)	12 (7.1)	13 (5.0)	0.506
CRPA	7 (1.6)	3 (1.8)	4 (1.6)	1.000
Mixed infection[d]*	34 (7.9)	21 (12.4)	13 (5.0)	0.010

[a] Other NFGNB included one *Providencia stuartii*, one *Shewanella algae*, two *Rhizobium radiobacter*, and two *Sphingomonas paucimobilis*.

[b] Other fungi included one *Scedosporium* species, and two unidentified *Candida* species.

[c] MDROs included methicillin-resistant *Staphylococcus aureus*, methicillin-resistant, coagulase-negative *Staphylococci*, vancomycin resistant *Enterococcus*, carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and multidrug-resistant *Acinetobacter baumannii*.

[d] The mixed infection episodes mostly included Gram-negative pathogens (19/34), followed by Gram-positive bacteria (13/34).

Data are presented as n (%).

CLABSI = central line-associated bloodstream infection; NFGNB = non-fermentative Gram-negative bacilli; MDROs = multidrug-resistant organisms; MRSA = methicillin-resistant *Staphylococcus aureus*; CRAB = carbapenem-resistant *Acinetobacter baumannii*; CRPA = carbapenem-resistant *Pseudomonas aeruginosa*.

*Statistical significance with $p < 0.05$.

from two or more blood cultures drawn on separate occasions; the pathogen is not related to an infection at another body site; and the patient has one or more of the following signs or symptoms: fever (≥38 °C), chills, or hypotension, CLABSI was confirmed.

Acute Physiology and Chronic Health Evaluation II (APACHE II) were applied within 24 h of admission of a patient to an ICU, and scoring ≥ 20 was classified to be severe that has a mortality rate beyond 40%. The underlying diseases were measured by Charlson comorbidity index,[16] and Pittsburgh bacteremia score greater than 4 indicated an advanced disease severity.

According to CDC/Healthcare Infection Control Practices Advisory Committee (HICPAC) guideline definition,[17] Multidrug-resistant organisms (MDROs) are microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents. Though various definitions of MDROs existed, MDROs were defined as methicillin-resistant *Staphylococcus aureus*, methicillin-resistant, coagulase-negative *Staphylococci*, vancomycin-resistant *Enterococcus*, carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and multidrug-resistant *A. baumannii* in the study. Multidrug-resistant *Acinetobacter* was defined as if any *Acinetobacter* spp. testing non-susceptible (i.e., resistant or intermediate) to at least one agent in three antimicrobial classes of the following six antimicrobial classes: aminoglycosides, fluoroquinolones, β-lactam/β-lactam β-lactamase inhibitor combination, sulbactam, anti-pseudomonal carbapenems, and antipseudomonal cephalosporins.

Table 2 The checklist and compliance of central line insertion and maintenance bundle.

Surveillance items/year	2014	2015	2016
Hand hygiene	92.3	91.4	92.6
Appropriate skin disinfection	95.3	96.4	93.5
Maximal sterile barrier	54.6	74.6	51.2
Catheter insertion site evaluation	92.3	99.1	99.2
Proper dressing coverage	100	100	100
Closed system of the catheter	100	100	100
Aseptic technique before using connectors	63.2	75.3	68.2

Data are presented as %.

Statistical analysis

The entered data were checked for accuracy and then for normality using the Kolmogorov–Smirnov test. Normally distributed quantitative variables are expressed as the mean and standard deviation (SD). Qualitative variables were expressed as a number and percentage, while the quantitative variables were expressed as the mean and standard deviation. The *t*-test or Mann–Whitney test was chosen for continuous variables, and chi-squared test or Fisher's exact test was used to compare categorical variables. Factors associated with acquiring CLABSIs and 14-day mortality rate were identified using multivariate logistic regression analysis. Backward stepwise logistic regression approach was applied to variables while entering into the model, and $p < 0.2$ was selected as a requirement for acceptance. The odds ratio (OR) and 95% confidence interval (CI) were calculated. Results with two-sided *p* values less than 0.05 were deemed statistically significant. All analyses were completed with Microsoft Excel 2016, and IBM SPSS (version 20.0).

Results

Over the whole study period from January 2010 to December 2016, a total of 405 patients with 428 episodes of CLABSIs were identified, and 118,025 catheter days were

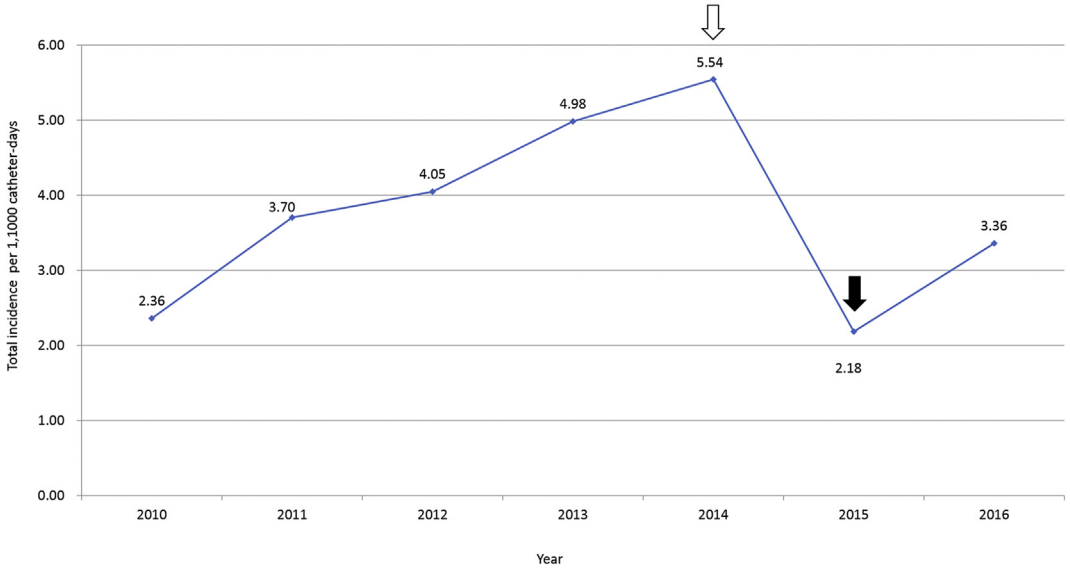

Figure 1. The secular trend of total CLABSI incidence in our adult ICUs (Arrow: the year of central line care bundle implementation; black arrow). CLABSI = central line-associated bloodstream infections, ICU = intensive care unit.

collected. The mean incidence rate of CLABSI of our adult ICUs was 3.47 per 1000 catheter days.

The microbiological distribution is listed in Table 1. Within the whole population, the leading pathogens associated with CLABSIs were gram-negative bacteria (59.3%), followed by gram-positive bacteria (24.8%), and fungi (23.4%). Non-fermentative Gram-negative bacilli (NFGNB) was the most common Gram-negative bacteria. *Enterococcus* spp. was the predominant Gram-positive bacteria. And *Candida albicans* was the most common fungi in the study. The most common GN isolates included *Acinetobacter* spp. (41/428, 9.6%), *Enterobacter* spp. (37/428, 8.6%), *Stenotrophomonas maltophilia* (34/428, 7.9%), *Klebsiella* spp. (33/428, 7.7%), *Pseudomonas* spp. (31/428, 7.2%), and *Serratia marcescens* (24/428, 5.6%).

No significant change in the percentage of Gram-positive pathogens (21.8% vs. 26.7%, $p = 0.312$) and *Enterococcus* spp. (10.6% vs. 16.3%, $p = 0.201$) before and after bundle implementation which started in 2014.

The accuracy of each item of the bundle-care checklist from 2014 to 2016 was listed in Table 2. We found improvement of compliance in 2015, no matter in appropriate skin disinfection (95.3%—96.4%), maximal sterile barrier (54.6%—74.6%), catheter insertion site evaluation (92.3%—99.1%), or aseptic technique before using connectors (63.2%—75.3%). During this period, the CLABSI rate of total adult ICUs at our hospital decreased obviously (5.54 per 1000 catheter-day in 2014 vs. 2.18 per 1000 catheter-day in 2015, Fig. 1), which disclosed the effectiveness of insertion and maintenance bundles.

There was an increase of Vancomycin-resistant strain (all were *Enterococcus faecium*), which was of statistically significance ($p = 0.028$). Though increased isolates of multidrug-resistant organisms (15.9% vs. 19.4%, $p = 0.443$), there was no significant time trend identified after detailed analysis of methicillin-resistant *S. aureus* (MRSA) (3.5% vs. 2.3%, $p = 0.553$), carbapenem-resistant *A. baumannii* (CRAB) (7.1% vs. 5.0%, $p = 0.506$), and carbapenem-resistant *P. aeruginosa* (CRPA) (1.8% vs. 1.6%, $p = 1.000$). Also, markedly reduced episodes of mixed infection (12.4% vs. 5.0%, $p = 0.010$) was noticed post bundle implementation. The secular pathogen-specific CLABSI rates focus on MDROs of the most importance, except those mentioned above, including carbapenem-resistant *Enterobacteriaceae* (CREn), and *Candida* spp. were shown in Fig. 2.

There was no difference between the 14-day mortality rate of CLABSIs of those with or without bundle intervention (71.8% vs. 65.5%, $p = 0.204$), despite a tendency to be improved. Factors associated with 14-day mortality in CLABSIs were shown in Tables 3 and 4. Via univariate analysis (Table 3), patients those had older age (≥65 years old), cardiovascular disease, renal disease, malignancy, ICU admission mainly for respiratory disease or sepsis, catheter placement in internal jugular vein, inadequate empirical antimicrobial therapy, infected by fungi, or resistant strains were more likely to expire within 14 days (all $p < 0.05$). By contrast, patients admitted for burn, received adequate definite antimicrobial therapy, longer duration since onset of CLABSI to catheter removal, and infected by Gram-negative bacteria were predisposed to survive within 14 days (all $p < 0.05$). By multivariate analysis (Table 4), the independent risk associated with 14-day mortality included the underlying disease of malignancy (OR 1.95, 95% CI 1.02—3.71), inadequate empirical antimicrobial therapy (OR 1.88, 95% CI 1.01—3.49), inadequate definite

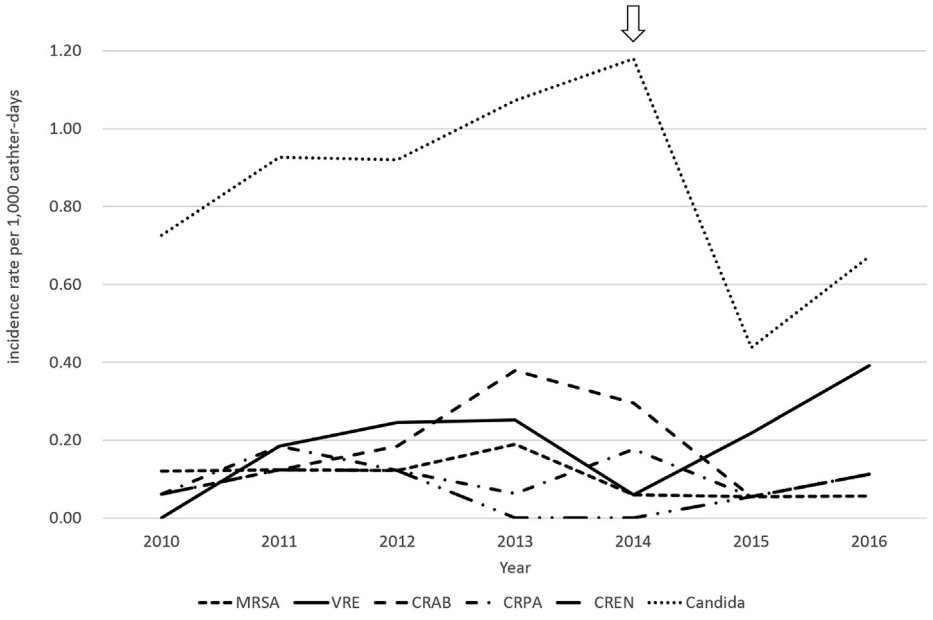

Figure 2. Annual incidence of CLABSI (per 1000 catheter-days) in different MDROs and *Candida* in our hospital (Arrow: the year of central line care bundle implementation). VRE = vancomycin-resistant *Enterococcus faecium*. MRSA = methicillin-resistant *Staphylococcus aureus*. CRAB = carbapenem-resistant *Acinetobacter baumannii*. CRPA = carbapenem-resistant *Pseudomonas aeruginosa*. CREn = carbapenem-resistant *Enterobacteriaceae*. CLABSI = central line-associated bloodstream infections, MDROs = multidrug-resistant organisms.

Table 3 Univariate analysis of the risk factors associated with 14-day mortality in patients with CLABSIs.

Variable	Survival (n = 291)	Mortality (n = 137)	*p*
Age (y)	62.8 ± 16.9	66.2 ± 15.8	
≥65	139 (47.8)	83 (60.6)	0.017
Male	193 (66.3)	89 (65.0)	0.827
Major diagnosis on ICU admission			
Cardiovascular disease	67 (23.0)	29 (21.2)	0.711
Neurological disease	57 (19.6)	11 (8.0)	0.002
Respiratory disease	109 (37.5)	78 (56.9)	<0.001
Gastrointestinal disease	54 (18.6)	35 (25.5)	0.099
Hepatobiliary disease	11 (3.8)	11 (8.0)	0.097
Genitourinary disease	3 (1.0)	1 (0.7)	1.000
Malignancy	7 (2.4)	6 (4.4)	0.364
Sepsis	128 (44.0)	89 (65.0)	<0.001
Trauma	34 (11.7)	9 (6.6)	0.121
Burn	16 (5.5)	1 (0.7)	0.016
APACHE II score	18.1 ± 8.7	22.3 ± 9.9	
0–9	40 (13.7)	22 (16.1)	0.557
10–19	123 (42.3)	50 (36.5)	0.291
≥20	128 (44.0)	65 (47.4)	0.533
Underlying disease			
Cardiovascular disease	62 (21.3)	44 (32.1)	0.022
Neurological disease	60 (20.6)	28 (20.4)	1.000
Respiratory disease	22 (7.6)	14 (10.2)	0.356
Gastrointestinal disease	29 (10.0)	18 (13.1)	0.325
Hepatobiliary disease	56 (19.2)	36 (26.3)	0.103
Renal disease	50 (17.2)	38 (27.7)	0.015
Autoimmune disease	18 (6.2)	8 (5.8)	1.000
Diabetes mellitus	106 (36.4)	52 (38.0)	0.830
Malignancy	54 (18.6)	44 (32.1)	0.003
Immunosuppression	1 (0.3)	2 (1.5)	0.241
Charlson comorbidity index	5.3 ± 3.2	6.5 ± 2.9	
≥8	79 (27.1)	41 (29.9)	0.565
Pitt bacteremia score	3.6 ± 1.8	4.8 ± 2.4	
>4	94 (32.3)	47 (34.3)	0.741
Place of line insertion			
ICU	137 (47.1)	70 (51.1)	0.469
Bundle	169 (58.1)	89 (65.0)	0.204
Anatomic site			
Internal jugular vein	149 (51.2)	91 (66.4)	0.003
Subclavian vein	75 (25.8)	25 (18.2)	0.088
Femoral vein	67 (23.0)	21 (15.3)	0.073
Treatment			
Inadequate empirical antimicrobial therapy	175 (60.1)	100 (73.0)	0.010
Inadequate definite antimicrobial therapy	9 (3.1)	61 (45.5)	<0.001
Catheter removal	166 (57.0)	82 (59.9)	0.601
Catheter removal from onset of CLBSI (d)	4.4 ± 7.7	3.1 ± 4.1	0.026
Microorganism			
Gram-positive bacteria	74 (25.4)	32 (23.4)	1.000
Gram-negative bacteria	187 (64.3)	67 (48.9)	0.009
Anaerobes	2 (0.7)	1 (0.7)	1.000
Fungi	51 (17.5)	49 (35.8)	<0.001
MDROs[a]	44 (15.1)	33 (24.1)	0.015
Gram-positive	20 (6.9)	19 (13.9)	0.011
Gram-negative	24 (8.2)	14 (10.2)	0.585
Mixed infection	20 (6.9)	14 (10.2)	0.252

[a] MDROs included methicillin-resistant *Staphylococcus aureus*, methicillin-resistant, coagulase-negative *Staphylococci*, vancomycin resistant *Enterococcus*, carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and multidrug-resistant *Acinetobacter baumannii*.

Data are presented as n (%), or mean ± SD.

CLABSI = central line-associated bloodstream infection; APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; MDROs = multidrug-resistant organisms.

Table 4 Multivariate analysis of the risk factors associated with 14-day mortality in patients with CLABSIs.

Variable	Regression coefficient	OR	95% CI	*p*
Age ≥65 years old	0.134	0.875	0.484−1.581	0.657
Major diagnosis on ICU admission				
Neurological disease	−0.351	0.704	0.286−1.734	0.445
Respiratory disease	0.252	1.286	0.671−2.466	0.449
Sepsis	0.231	1.260	0.643−2.470	0.500
Burn	−1.362	0.256	0.022−3.048	0.281
Underlying disease				
Cardiovascular disease	0.482	1.619	0.862−3.040	0.134
Renal disease	0.368	1.444	0.675−3.091	0.344
Malignancy	0.667	1.948	1.022−3.714	0.043
Internal jugular vein placement	0.206	1.229	0.678−2.229	0.497
Inadequate empirical antimicrobial therapy	0.631	1.879	1.011−3.493	0.046
Inadequate definite antimicrobial therapy	3.687	116.145	27.471−491.054	<0.001
Catheter removal from onset of CLABSI > 4d	0.336	1.399	0.673−1.554	0.972
Microorganism				
Gram-negative bacteria	0.462	1.588	0.701−3.597	0.268
Fungi	1.474	4.368	1.761−10.831	0.001
MDROs[a]				
Gram-positive	1.385	3.994	1.322−12.061	0.014

[a] MDROs included methicillin-resistant *Staphylococcus aureus*, methicillin-resistant, coagulase-negative *Staphylococci*, vancomycin resistant *Enterococcus*, carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and multidrug-resistant *Acinetobacter baumannii*.
CLABSI = central line-associated bloodstream infection; ICU = intensive care unit; OR = odds ratio; CI = confidence interval; MDROs = multidrug-resistant organisms.

antimicrobial therapy (OR 116.15, 95% CI 27.47−491.05), fungal infection (OR 4.37, 95% CI 1.76−10.83), and Gram-positive MDROs infection (OR 3.94, 95% CI 1.32−12.06).

In Table 5, we showed annual antimicrobial susceptibility pattern of the most common gram-negative bacteria causing HAIs at our hospital, including *Acinetobacter* spp., *Enterobacter* spp., *S. maltophilia*, *Klebsiella* spp., *Pseudomonas* spp., and *S. marcescens* (listed in the order of frequently isolated species of CLABSIs). Carbapenem became a better choice for Gram-negative bacterial infections due to fluctuated effectiveness of piperacillin/tazobactam and fluoroquinolones between different species, except its limited effect on *A. baumannii*. An alternative option would be using aminoglycoside (amikacin, gentamicin), for its good clinical responses on *Enterobacter* spp., *Pseudomonas* spp., and *S. marcescens*. For *Klebsiella* spp., there was a tendency of increased susceptibility of amikacin (71.9%−100%, $p < 0.001$), levofloxacin (67.2%−91.5%, $p < 0.001$) and piperacillin/tazobactam (59.4%−80.3%, $p < 0.05$). However, obviously declined *in vitro* susceptibility to ampicillin/sulbactam was observed on *Enterobacter* spp. (36.7%−0.0%, $p < 0.001$) and *S. marcescens* (12.5%−0.0%, $p < 0.001$). Furthermore, markedly decreased therapeutic effect of ceftazidime (100.0%−52.9%, $p < 0.001$) and tigecycline (87.5%−35.3%, $p < 0.001$) on *S. marcescens* were noted.

Discussion

To the extent of our knowledge, this is the first work from Asian countries that revealed the bacteriological profile of CLABSI in critically-ill patients and the trend of antimicrobial susceptibility pattern of CLABSI isolates. The mean rate of CLABSIs in our adult ICUs during 2010−2016 was 3.47 per 1000 catheter days, which was relatively lower compared to the mean average CLABSIs rate of ICUs in Taiwan medical centers in 2015 which was 4.3 per 1000 catheter days (data from Taiwan Nosocomial Infections Surveillance System, TNIS).[18]

In our study population, the causative pathogens of CLABSIs in ICUs were predominantly Gram-negative bacteria, especially non-fermentative Gram-negative bacilli. These findings were different from the results of Victorian surveillance program in Australia ICUs during 2009−2013,[19] which illustrated the most frequently identified pathogens to be *Enterococcus* spp. (26.3%), followed by *Candida* spp. (15.4%) and *S. aureus* (13.3%), and CLABSIs due to *Enterococcus* spp., *S. aureus*, and coagulase-negative *Staphylococcus* spp. displayed significant decreasing trend over time. Moreover, this distribution of our setting was also unparalleled to the results of CDC/NHSN reported, which figured out coagulase-negative *Staphylococcus*, *S. aureus*, *Enterococcus faecalis* were the leading pathogens in CLABSIs during 2011−2014.[20]

Based on our study, a total of 106 Gram-positive bacteria were isolated from CLABSI episodes, and 36.8% (39/106) of them were of MDROs. The increased yearly incidence rate ratio of VRE in *Enterococcus* spp. at our hospital (including non-ICU settings) showed a statistical significance of increasing ($p < 0.001$), this result was considered mostly compatible with the annual trend in Taiwan reported by TNIS in 2016.[21] Furthermore, *Enterococci* are present throughout the entire gastrointestinal tract (main reservoir) and survive in the environment for prolonged periods (>1 week). Except direct or indirect by fecal−oral

Table 5 *In vitro* susceptibility rate (%) of Gram-negative organisms isolated from HAI episodes.

Acinetobacter spp.	GM*	SXT*	PIP	SAM	AN	CIP	CRO	CAZ	FEP	LEV	MEM	TGC*	TZP	CS	IPM
2010	34.0	29.5	27.2	52.3	43.2	34.0	0.0	36.4	38.6	34.0	40.9	77.3	31.8	—	—
2011	40.0	42.5	25.0	55.0	45.0	37.5	12.5	37.5	40.0	37.5	40.0	87.5	37.5	—	—
2012	50.0	38.9	—	61.1	55.6	—	5.6	33.4	38.9	50.0	44.4	88.9	33.3	—	—
2013	50.0	47.5	—	55.0	47.5	—	5.0	37.5	40.0	45.0	40.0	90.0	40.0	100.0	—
2014	50.0	39.6	—	66.7	58.3	—	6.3	41.7	45.8	43.8	47.9	83.3	45.8	100.0	—
2015	50.0	44.7	—	63.2	55.3	—	—	47.4	50.0	47.4	52.6	97.4	50.0	100.0	—
2016	54.8	58.1	—	61.3	54.8	—	—	45.2	45.2	54.8	—	93.5	48.4	100.0	58.1

Enterobacter spp.	AM	GM	SXT	CMZ	PIP	SAM**	AN	CIP	CRO	CAZ	ETP	FEP	LEV	MEM	TGC	TZP	IPM
2010	2.0	87.8	81.6	2.0	57.1	36.7	100.0	85.7	61.2	57.1	93.9	91.8	85.7	98.0	91.8	59.2	—
2011	1.9	92.3	71.1	0.0	59.6	13.5	98.1	84.6	65.4	86.5	90.4	86.5	84.6	100.0	86.5	65.4	—
2012	0.0	82.0	65.6	0.0	—	11.4	100.0	—	47.5	50.8	85.2	93.4	73.8	100.0	75.4	63.9	—
2013	0.0	84.1	79.6	0.0	—	4.5	97.7	—	63.6	70.5	97.7	95.5	93.2	100.0	88.6	72.7	—
2014	0.0	93.1	86.2	3.4	—	0.0	100.0	—	58.6	75.9	96.6	100.0	93.1	96.6	100.0	72.4	—
2015	0.0	90.0	82.5	0.0	—	0.0	100.0	—	—	52.5	90.0	75.0	85.0	97.5	82.5	57.5	—
2016	0.0	90.0	75.0	0.0	—	0.0	97.5	—	—	47.5	92.5	80.0	77.5	—	82.5	47.5	95.0

Stenotrophomonas maltophilia	MI	SXT*	LEV**
2010	100.0	87.0	65.2
2011	100.0	81.8	90.9
2012	100.0	76.9	69.2
2013	100.0	74.8	91.7
2014	100.0	64.0	80.0
2015	100.0	64.3	85.7
2016	100.0	70.0	90.0

Klebsiella spp.	AM	CZ	GM	SXT	CMZ	SAM	AN**	CIP	CRO	CAZ	ETP	FEP	LEV**	MEM	TGC	TZP*	IPM
2010	0.0	54.7	60.9	54.7	73.4	43.8	71.9	67.2	70.3	65.6	90.6	70.3	67.2	93.8	75.0	59.4	—
2011	0.0	57.3	76.0	56.3	80.2	47.9	96.9	76.0	68.8	64.6	93.8	70.8	80.2	100.0	83.3	65.6	—
2012	0.0	61.9	75.3	56.7	86.6	59.8	92.8	—	68.0	68.0	92.8	73.2	76.0	99.0	79.4	69.1	—
2013	0.0	64.5	75.0	59.2	84.2	57.9	93.4	—	76.3	81.6	97.4	76.3	84.2	98.7	84.2	76.3	—
2014	0.0	56.3	65.5	57.5	78.2	51.7	98.9	—	73.6	66.7	93.1	85.1	71.3	96.6	79.3	71.3	—
2015	0.0	52.8	70.8	55.6	79.2	50.0	98.6	—	—	72.2	93.1	81.9	81.9	97.2	87.5	69.4	—
2016	0.0	59.2	77.5	64.8	80.3	56.3	100.0	—	—	69.0	97.2	83.1	91.5	—	87.3	80.3	98.6

Pseudomonas spp.	GM	PIP	AN	CIP	CAZ	FEP	LEV	MEM	TZP	CS	IPM
2010	82.2	76.7	94.5	78.1	79.5	80.8	74.0	83.6	76.7	—	—
2011	89.5	85.5	97.4	78.9	85.5	89.5	85.5	85.5	85.5	—	—
2012	91.2	—	98.2	—	84.2	87.7	71.9	82.5	68.4	—	—
2013	94.6	—	98.6	—	86.5	93.2	90.5	83.8	77.0	100.0	—
2014	97.3	—	98.6	—	84.9	87.6	79.5	86.3	80.8	98.6	—
2015	97.1	—	100.0	—	90.0	91.5	87.1	88.6	80.0	97.1	—
2016	93.3	—	98.3	—	86.7	81.7	88.3	—	76.7	100.0	76.7

Serratia marcescens	AM	GM	SXT	CMZ	PIP	SAM**	AN	CIP	CRO	CAZ**	ETP	FEP	LEV	MEM	TGC**	TZP	IPM
2010	0.0	87.5	87.5	62.5	62.5	12.5	100.0	62.5	75.0	100.0	87.5	87.5	62.5	100.0	87.5	75.0	—
2011	0.0	92.8	92.8	57.1	64.3	12.9	100.0	85.7	71.3	92.8	92.8	78.5	85.7	92.8	78.5	92.8	—
2012	0.0	92.3	100.0	69.2	—	15.4	92.3	—	76.9	84.6	84.6	84.6	84.6	100.0	84.6	84.6	—
2013	0.0	82.4	100.0	35.3	—	0.0	94.1	—	52.9	82.4	88.2	64.9	52.9	94.1	50.0	88.2	—
2014	0.0	80.9	80.9	47.6	—	0.0	100.0	—	57.1	85.7	100.0	66.7	80.9	100.0	61.9	95.2	—
2015	0.0	90.0	70.0	40.0	—	0.0	100.0	—	—	80.0	90.0	70.0	70.0	90.0	50.0	80.0	—
2016	0.0	94.1	94.1	29.4	—	0.0	100.0	—	—	52.9	100.0	58.3	47.0	—	35.3	94.1	100.0

Data are presented as percentage (%).

HAI = healthcare-associated infections; GM = Gentamicin; SXT = Co-trimoxazole; PIP = Piperacillin, SAM = Ampicillin/Sulbactam; AN = Amikacin; CIP = Ciprofloxacin; CRO = Ceftriaxone; CAZ = Ceftazidime; FEP = Cefepime; LEV = Levofloxacin; MEM = Meropenem; TGC = Tigecycline; TZP = Piperacillin/Tazobactam; CS = Colistin; IPM = Imipenem; AM = Ampicillin; CMZ = Cefmetazole; MI = Minocycline.

* Statistical significance with $p < 0.05$.

**Statistical significance with $p < 0.001$.

transmission, invasive devices are another important portal of entry.[22] Based upon previous studies, the incidence of newly acquired VRE was 21.9 per 1000 patient-days in an ICU setting, and each day in the ICU might increase the risk of acquiring VRE by 1.03 times.[23] The increase of VRE-CLABSIs of ICUs in Taiwan warrants monitor and further intervention besides the central line care bundle implementation.

After implementation of central line insertion and maintenance bundle since January 2014, the total CLABSI rate of adult ICUs at our hospital significantly declined in 2015 was observed. Among monitored items of the care bundle, the compliance of maximal sterile barrier precaution (54.6%—74.6%) during catheter insertion could be a key component. It indicated the compliance investigation is necessary to find out the specific deficit during the intervention period.

Some studies have addressed the CLABSI risk factors and their relation to mortality, but limited data distinctively for a patient with critical illness.[2,24—27] Further analysis for the factors related to 14-day mortality, patients with underlying disease of malignancies, been treated with inadequate antimicrobial therapy empirically (48 h within the occurrence of CLABSI), and infected by fungi or resistant, Gram-positive bacteria were independent risk factors. The only and major protective factor was appropriate antimicrobial therapy (OR 0.03, 95% CI 0.01—0.06).

For the importance of empirically inadequate antimicrobial therapy associated with higher 14-day mortality, the antimicrobial susceptibility pattern of leading pathogens, especially in an institution or area of high Gram-negative bacteria and MDROs burden becomes crucial.[28—31] Therefore, the results of our investigation may provide the recommendation for appropriate empirical antimicrobial therapy of CLABSIs in Taiwan ICUs. Based on our study, the most common GN isolates were *Acinetobacter* spp. (41/428, 9.6%), which has an average 50% or less susceptible rate to gentamicin, amikacin, ceftazidime, cefepime, levofloxacin, piperacillin/tazobactam, and meropenem. Despite administration of ampicillin/sulbactam, the susceptibility remained low with approximate 60%. Only tigecycline (mean: 88.2%) and colistin (100%) has excellent results. For the second one, *Enterobacter* spp. (37/428, 8.6%), piperacillin/tazobactam had a limited effect (mean: 62.7%), but good response up to 85—88% were reported by exposure to levofloxacin, tigecycline, cefepime, or gentamicin, and even higher when ertapenem, meropenem, or amikacin was considered. The followed *S. maltophilia* (34/428, 7.9%) remained been 100% susceptible to minocycline but had lowered sensitivity rate to Co-trimoxazole after 2014 (87%—70%, or less). Moreover, a fluctuated, but the gradually improved outcome was noted while levofloxacin was prescribed. *Klebsiella* spp. isolated from HAIs had relatively lower sensitivity rate (mean $<$ 80%) to the four generations of cephalosporin, piperacillin/tazobactam, anti-pseudomonal fluoroquinolones, and gentamicin. Only carbapenem (ertapenem, meropenem or imipenem) has better response of above 90%. Treatments for *Pseudomonas* spp., as a traditional concern, the susceptibility rate of common use antimicrobials were adequate, except an average below 80% sensitivity might occur when exposed to piperacillin/tazobactam. At last, if the growth of *S. marcescens* was concerned, cefmetazole, ceftriaxone, ceftazidime, cefepime, levofloxacin, ampicillin/sulbactam, or even tigecycline should be used with caution for their markedly declined susceptibility rates during past years. Nevertheless, for the impact of antibiotic diversity on acquisition of resistant microorganisms,[32,33] we strongly suggest that antibiotic prescription patterns balancing within different antimicrobials should be promoted to reduce the selection pressure that aids the development of resistance.

There are several limitations in our study. First, this is a retrospective study hence the bias in documentation was unavoidable. Second, the relatively larger burden of Gram-negative pathogens at our hospital was different from other institutions, given the fact that the results of epidemiological trends of our study needed to be interpreted with caution. However, due to limited information on patient characteristics, we could not make a detailed comparison between our population and other studies[19,20] to identify the possible causes of these differences. Third, our study was conducted at a single medical center of southern Taiwan, local difference should be taken into consideration when applying the results to clinical scenarios.

In summary, the increasing trend of CLABSIs caused by multidrug-resistant organisms has become an emerging issue and had a significant influence on mortality. The compliance and accuracy of central line care bundle play a key role in reducing CLABSI rate, especially maximal sterile barrier upon catheter insertion. Moreover, in institutions with CLABSIs caused predominantly Gram-negative bacteria, inadequate empirical antimicrobial therapy and inadequate definite antimicrobial therapy are major components relating to 14-day mortality.

Conflicts of interest

None declared.

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