Journal of Microbiology, Immunology and Infection (2018) 51, 644—651

Available online at www.sciencedirect.com

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Original Article

Multimodal interventions for bundle implementation to decrease central line-associated bloodstream infections in adult intensive care units in a teaching hospital in Taiwan, 2009—2013

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Received 28 April 2017; received in revised form 19 July 2017; accepted 2 August 2017
Available online 26 August 2017

KEYWORDS
Central line-associated bloodstream infection;
Catheter-related bloodstream infection;
Central line bundle;
Adult intensive care units;
Central venous catheter

Abstract *Background:* Central line (CL)-associated bloodstream infection (CLABSI) poses a major threat to patient safety and is associated with additional cost. This study investigated the sustained effect of multimodal interventions focusing on CL bundle improvement in the adult intensive care units (ICUs) of a teaching hospital in Taiwan.
Methods: A before—after prospective study was conducted in 17 adult ICUs of a medical center in northern Taiwan from January 2009 to December 2013. Many interventions that aimed to facilitate CL bundle implementation were initiated in January 2011. The incidence rates of CLABSI and catheter-related bloodstream infection (CRBSI) were compared between the baseline and intervention periods. Catheter utilization ratios and microbiological characteristics were also analyzed.
Results: The incidence rates of both CLABSI and CRBSI decreased significantly from the baseline to the intervention periods (from 9.27 to 7.66 per 1000 CL-days and from 1.51 to 0.89 per 1000 CL-days, respectively). The yearly incidence rate decreased by up to 31% (incidence rate ratio [IRR], 0.69; 95% confidence interval [CI], 0.59—0.81) for CLABSI and 59% (IRR, 0.41; 95%

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http://dx.doi.org/10.1016/j.jmii.2017.08.008

CI, 0.26–0.65) for CRBSI since the initiation of the interventions. The catheter utilization ratio also decreased from 0.71 to 0.63 ($p < 0.001$). Microbiological analysis showed that among all CLABSI isolates, the proportion of coagulase-negative staphylococci significantly decreased during the intervention period.

Conclusion: Implementing multimodal interventions focusing on CL bundle improvement was effective in reducing the incidence rates of CLABSI and CRBSI in Taiwan's adult ICUs.

Introduction

The use of central line (CL) catheters is an essential part of modern critical care. However, it also increases the risk of nosocomial bloodstream infection. CL-associated bloodstream infection (CLABSI) could result in a high mortality rate of 12–25% and would be associated with prolonged hospitalization and additional hospital expenses.[1–3] The prevalence of CLABSI was particularly high in intensive care units (ICUs), and considerable concern has been raised in recent years.[3,4]

To manage this health issue, the Institute for Healthcare Improvement recommended a CL care bundle consisted of five evidence-based strategies to facilitate the reduction of CLABSI.[5,6] These five strategies involve (1) hand hygiene improvement, (2) use of chlorhexidine-containing skin antiseptics with sterile dressing, (3) maximal sterile barrier precaution during catheter insertion, (4) optimization of catheter site selection, and (5) timely CL removal. The adoption of the CL care bundle resulted in a sustained reduction in CLABSI incidence both in general wards and ICUs.[7,8] In a recent meta-analysis involving 2216 adult ICUs, the median incidence of CLABSI decreased significantly from 5.7 to 2.0 per 1000 CL-days (incidence rate ratio [IRR], 0.45; 95% confidence interval [CI], 0.39–0.52) after the bundle implementation.[3] These findings support the effectiveness of bundle care, and the US Department of Health and Human Services has set the goal of "zero CLABSI," which has been achieved for a sustained period in several hospitals.[8–11]

The incidence of CLABSI in ICUs is several-fold higher in Asia than in the United States; therefore, management of this nosocomial infection remains a challenge in Asia.[3,12] In this study, we aimed to exam whether multimodal interventions, focusing on CL bundle improvement, can reduce the incidence of CLABSI and catheter-related bloodstream infection (CRBSI) in 17 adult ICUs at our institution.

Methods

Study setting and design

This study was conducted in a university-affiliated 2388-bed medical center located in northern Taiwan. A total of 17 adult ICUs (including medical ICUs, surgical ICUs, neurological ICUs, burn ICUs, and cardiac care units) consisting of 213 beds were included in this study. All patients who had been hospitalized to these ICUs between January 2009 and December 2013 were included. A before–after prospective study was conducted in two periods: a baseline period from January 2009 to December 2010 and an intervention period from January 2011 to December 2013.

Interventions

Through a series of cross talks between different departments or teams (including Center for Infection Control, Medical ICUs, Surgical ICUs, Department of Nursing, Department of General Affairs Office, etc.), multidisciplinary task force came out consensus of the following interventions, small-scale pilot studies were conducted, processes were modified accordingly, and new materials or facilities were introduced to daily practice. All of the interventions were implemented in our adult ICUs universally.

CL care bundle

Hand hygiene. The hospital-wide hand hygiene promotion program has been initiated in our hospital since 2004.[13] As a CL bundle element, hand hygiene before CL insertion was strictly required and enforced.

Maximal sterile barrier precaution. This involved the use of a sterile drape to cover a patient from head to toe for CL insertion. The original size of sterile drapes used in our hospital for CL insertion was too small (100 × 100 cm) to cover the patient thoroughly. As an intervention, two new forms of sterile drapes with a larger size were designed. The size of one form is 152 × 200 cm, with a hollow area of 10 × 10 cm for the convenience of catheter insertion (3M Steri-Drape fabric drapes, model 1034). The size of the other form is 228 × 300 cm, with a hollow area of 16 × 10 cm (3M Steri-Drape fabric drapes, model 9050).

Alcohol–chlorhexidine skin antiseptics. Originally, alcohol-based povidone–iodine was used for skin antisepsis before CL insertion. As an intervention, the use of alcohol-based povidone–iodine was switched universally to alcohol–chlorhexidine for skin antisepsis.

Optimal site for CL insertion. The indications of femoral site insertion were established, including a high risk of pneumothorax, unstable condition requiring emergent CL insertion, bleeding tendency, presence of other catheters or a wound over jugular and subclavian areas, or difficult approach of other potential insertion sites. The choice of the insertion site was left to the clinician's discretion; however, the indication should be stated in the medical record if the femoral site was chosen.

Timely CL removal. A paper-based CL daily review form was introduced in our ICUs since 2009. Clinicians were required to renew the information regarding the usage of an indwelling CL, including the indwelling time, insertion site, and indication to maintain the catheter, on a daily basis.

Technical innovations

Chlorhexidine transparent dressing. Current guidelines suggest replacing the catheter site dressing at least every 7 days to prevent CLABSI, and an earlier change is indicated if the dressing becomes damp or visibly soiled.[14] In Taiwan, high humidity commonly results in the dampening of the dressing, necessitating the replacement of the dressing every 2–3 days. We used a new form of chlorhexidine dressing (3M Tegaderm CHG chlorhexidine gluconate I.V. securement dressing, model 1657R), which has a better ability to absorb fluid and a transparent portion that facilitates the inspection of the skin around the insertion site in order to better determine the timing of dressing replacement.

One-piece drape. Two new forms of one-piece drape were introduced. Compared with the original form which comprised three smaller pieces of sterile cloth, the one-piece drape not only provides a larger area of coverage but also takes less time to spread out.

All-inclusive catheter cart. We designed a catheter cart containing all necessary supplies for CL insertion and bundle care.

Education and training

Education sessions regarding CLABSI-specific infection control measures and correct procedures for executing CL care bundle were regularly conducted by the Center of Infection Control during the intervention period. For new staff, a CL insertion teaching program including lectures and simulation training was compulsory and provided regularly.

Process indicators and outcome indicators

Outcome indicators included the incidence of both CLABSI and CRBSI per 1000 CL-days and the catheter utilization ratio. Process indicators included the compliance of the following three practices in CL bundle: (1) hand hygiene before catheter insertion; (2) maximal barrier precaution including a mask, hair cap, sterile gown, sterile gloves, and sterile drape from a patient's head to toe; and (3) appropriate use of chlorhexidine antiseptics. These three indicators were chosen because they are feasible to approach and measurable with high inter-individual agreement. Outcome indicators were collected routinely as a part of prospective hospital-wide surveillance of healthcare-associated infection.[15] Process indicators were collected only from 2013, after most interventions had been fully implemented.

Definitions and data collection

The outcome indicators were mainly collected based on a web-based, hospital-wide healthcare-associated bloodstream infection surveillance and classification system.[16] Since 2013, infection control nurses (ICNs) have performed regular field inspections for CL insertion at ICUs. If any violation to the CL bundle elements was observed, the observing ICN would interrupt the procedure immediately (in nonemergency situations) and provide instructions.

The monthly incidence rates of CLABSI and CRBSI were calculated by dividing the number of CLABSI or CRBSI by the number of CL-days in a given month. The catheter utilization ratio was calculated by dividing the number of CL-days by the number of patient-days. Patients with more than one CL catheter in place were only counted once. The demographic, clinical, and microbiological data were collected from the electronic database of the hospital.

The definition of CLABSI was in accordance with that proposed by the Centers for Disease Control.[17] A CRBSI case in this study was defined as a patient of whom CL catheter tip culture yielded the same pathogens ($\geq$15 colony-forming units) as those grew in the peripheral blood culture.

All data were collected on a routine basis, and the analysis was performed retrospectively. Therefore, informed consent was waived. The study protocol was approved by the Institutional Review Board of National Taiwan University Hospital (IRB No. 201303079RINC).

Statistical analysis

Comparisons between the baseline and intervention periods were performed using the chi-squared test or Fisher's exact test for categorical variables and the Student's t test for continuous variables. In addition, we compared the incidence rates of both CLABSI and CRBSI between the two periods and calculated the incidence rate ratio (IRR) and incidence rate reduction by normal-theory test. A p-value of <0.05 obtained using two-sided tests was considered significant. The analysis was performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The demographics and characteristics of patients are presented in Table 1. In total, 84,103 patients were analyzed, of whom 31,966 and 52,137 were analyzed during the baseline and intervention periods, respectively. Compared with those analyzed during the baseline period, fewer patients analyzed during the intervention period had chronic diseases, but more patients received a diagnosis of malignancy. Although the mean scores of the Charlson index were not significantly different between the two periods, the mean duration of hospital stay was significantly shorter during the intervention period.

During the baseline period, 66,694 CL-days were recorded, with the catheter utilization ratio being 0.71. During the intervention period, when the number of recorded CL-days was 95,789, the catheter utilization ratio decreased to 0.63 ($p < 0.001$). The incidence rate of CLABSI per 1000 CL-days decreased from 9.27 during the baseline period to 7.66 during the intervention period ($p < 0.001$). Furthermore, the incidence rates of CRBSI per 1000 CL-days were 1.51 and 0.89 during the baseline and intervention periods, respectively ($p < 0.001$; Table 1).

Table 1 Patient characteristics and outcome indicators during the baseline and intervention period.

	Period		p-Value
	Baseline	Intervention	
Parameter	200,901–201,012 (n = 31,966)	201,101–201,312 (n = 52,137)	
Male	19,187 (60.02%)	32,179 (61.72%)	<0.001
Admission department			<0.0001
Medical	16,138 (50.44%)	24,177 (46.37%)	
Surgical	15,172 (47.41%)	26,304 (50.44%)	
Emergency	336 (1.05%)	1107 (2.12%)	
Pediatric	350 (1.09%)	549 (1.05%)	
Age, *y* (mean ± SD)	61.56 ± 17.67	61.68 ± 17.33	0.329
Hospital stay in days	16.22 ± 24.01	15.74 ± 23.40	0.004
Charlson index	4.18 ± 4.44	4.14 ± 4.49	0.148
Co-morbidity			
Congestive heart failure	2624 (8.20%)	4005 (7.68%)	0.007
Cerebrovascular disease	3264 (10.20%)	4870 (9.34%)	<0.001
Chronic pulmonary disease	1431 (7.60%)	3421 (6.56%)	<0.001
Liver cirrhosis	1578 (4.93%)	1936 (3.71%)	<0.001
Diabetes mellitus	7279 (22.77%)	11,034 (21.16%)	<0.001
Autoimmune disease	239 (0.75%)	242 (0.46%)	<0.001
Moderate or severe renal disease	2733 (8.54%)	3241 (6.22%)	<0.001
Any tumor	14,296 (44.68%)	24,827 (47.62%)	<0.001
Metastatic tumors or refractory leukemia	5579 (17.44%)	9547 (18.31%)	0.001
Patient-days[a]	94,332	151,639	
Central line-days[b]	66,694	95,789	
Catheter utilization ratio	0.71	0.63	<0.001
Case number of CLABSI	618	734	
CLABSI incidence rate (per 1000 CL-days)	9.27	7.66	<0.001
Case number of CRBSI	101	85	
CRBSI incidence rate (per 1000 CL-days)	1.51	0.89	<0.001

[a] The total number of days that patients had been staying in ICU during the selected time period.
[b] The total number of days that patients had central line catheter(s) use during the selected time period.
Abbreviations: CL: central line; CLABSI: central line-associated bloodstream infection; CRBSI: catheter-related bloodstream infection.

Since the implementation of the interventions, the incidence rate of CLABSI per 1000 CL-days had decreased to 6.42 in the third year, indicating an incidence rate reduction of 31% (IRR, 0.69; 95% CI, 0.59–0.81; $p < 0.001$). Moreover, the incidence rate of CRBSI decreased to 0.62 in the same year, with an incidence rate reduction of 59% compared with that during the baseline period (IRR, 0.41; 95% CI, 0.26–0.65; $p < 0.001$; Table 2). The quarterly incidence rates of CLABSI and CRBSI during the study period are shown in Fig. 1.

We identified 110 different pathogens from 1352 CLABSI episodes during the study period. Most bloodstream infection episodes involved only one pathogen (83.9%), whereas more than one pathogen was identified in 16.1% of episodes. During the baseline period, the identified pathogens for CLABSI comprised Gram-negative bacteria (59.7%), Gram-positive bacteria (27.3%), and fungi (13.0%). During the intervention period, the distribution of pathogens was similar. The most common pathogens during both periods were *Enterococcus* species (including vancomycin-resistant enterococci), *Acinetobacter baumannii* (including multidrug-resistant *A. baumannii*), and *Candida* species (including *albicans* and non-*albicans* species) (Table 3). The percentage of coagulase-negative staphylococci (CoNS) identified as a CLABSI-causing pathogen was lower during the intervention period than during the baseline period (4.8% vs. 7.6%, $p = 0.030$), whereas non-*albicans Candida* species were isolated more often during the intervention period (9.3% vs. 6.2%, $p = 0.034$). Similarly, for CRBSI episodes, the most common pathogens were *Enterococcus* species, *A. baumannii*, and *Candida* species. The percentage of CoNS decreased from 7.9% (8/101) during the baseline period to 3.7% (3/82) during the intervention period; however, this decrease was not significant. By contrast, the percentage of non-*albicans Candida* species increased from 5.0% (5/101) during the baseline period to 13.4% during the intervention period (11/82; $p = 0.044$).

During the intervention period, 64 education sessions were held. More than 90% of the medical stuff in our hospital participated in at least one session. For the new staff, the additional training program was compulsory, and the completeness rate was 100%.

The number of CL insertion being audited by the ICNs in 2013 for compliance measure varied between 8 and 23 in each quarter. Among individual practices, maximal barrier precaution had the lowest compliance (45.5–73.9%). The compliance of hand hygiene and chlorhexidine antiseptic use were both above 80%.

Table 2 The annual incidence rate (IR) of CLABSI and CRBSI.

Parameter	Years	Patient-days	CL-days (catheter utilization)	CLABSI cases	CLABSI cases/1000 CL-days (IR)	IR ratio (95% CI)	IR reduction (%)	*p*-Value
CLABSI	Baseline (2009–2010)	94,332	66,694 (70.7%)	618	9.27	1 (baseline)	—	—
	Intervention							
	2011	50,197	32,500 (64.7%)	298	9.17	0.99 (0.86–1.14)	1	NS
	2012	50,751	31,047 (61.2%)	229	7.38	0.80 (0.68–0.93)	20	0.003
	2013	50,691	32,242 (63.6%)	207	6.42	0.69 (0.59–0.81)	31	<0.001
CRBSI	Baseline (2009–2010)	94,332	66,694 (70.7%)	101	1.51	1 (baseline)	—	—
	Intervention							
	2011	50,197	32,500 (64.7%)	34	1.05	0.69 (0.47–1.02)	31	NS
	2012	50,751	31,047 (61.2%)	31	1.00	0.66 (0.44–0.98)	34	0.038
	2013	50,691	32,242 (63.6%)	20	0.62	0.41 (0.26–0.65)	59	<0.001

Abbreviations: CL: central line; CLABSI: central line-associated bloodstream infection; CRBSI: catheter-related bloodstream infection.

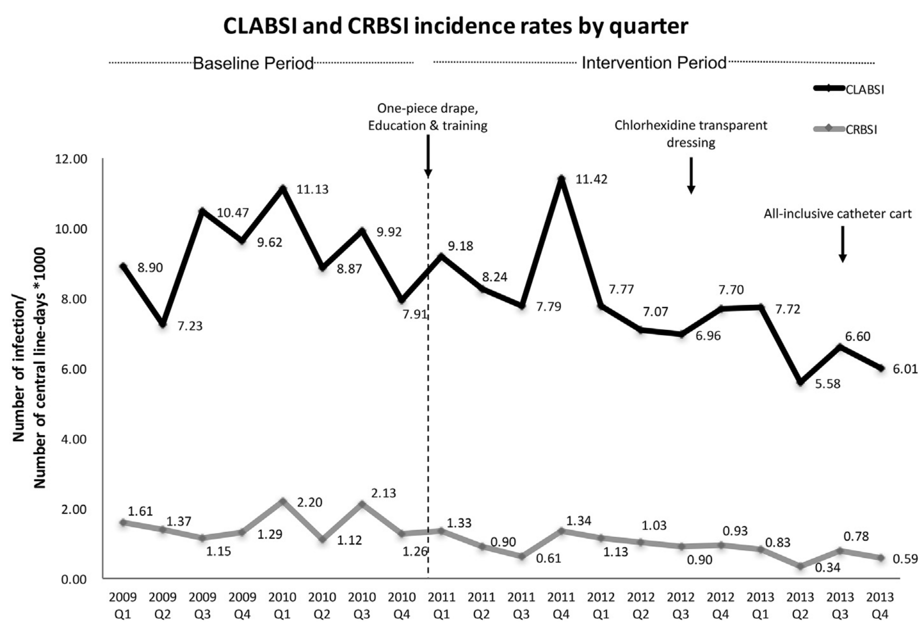

Fig. 1. The quarterly incidence rates of central line-associated bloodstream infection (CLABSI) and catheter-related bloodstream infection (CRBSI).

Discussion

Since CLABSI was regarded as a preventable event, efforts have been made worldwide to reduce the incidence of CLABSI in ICUs. The implementation of CL bundle has been proven to be effective and was promoted as an essential component in most CLABSI reduction campaigns. In the present study, the incidence of CLABSI per 1000 CL-days in our adult ICUs decreased from 9.27 during 2009–2010 to 7.66 during 2011–2013 (31% reduction) after the initiation of the bundle-based interventions. Similarly, the catheter utilization ratio decreased from 70.7% during the baseline period to 61.2% in 2012 during the intervention period; this decrease can be attributed to the timely catheter removal. Studies published during a similar period have reported that CLABSI incidence per 1000 CL-days decreased from 9.3 to 5.1 (45% reduction) in Brazil, 2.2–0.5 (77% reduction) in Australia, 6.4–3.9 (53% reduction) in India, 3.6–1.8 (50% reduction) in Spain, and 4.7–1.8 (61% reduction) in Korea after implementing bundle-based multidisciplinary measures.[5,9,18–20]

Consistent with the findings of several previous reports,[21,22] our hospital was unable to achieve a "zero" or "near-zero" CLABSI incidence after implementing bundle care and infection prevention programs. A recent national survey of adult ICUs in the United States reported that lower CLABSI incidence rates were significantly associated with high (>95%) overall bundle compliance.[23] The suboptimal compliance rate in the present study, particularly for maximal sterile barrier precaution, might partly explain

Table 3 Identified pathogens causing central line-associated bloodstream infections.

Pathogen	Baseline period ($n = 618$)	Intervention period ($n = 734$)	p-Value
Enterococcus species	87 (14.1%)	116 (15.8%)	NS
Acinetobacter baumannii	81 (13.1%)	87 (11.9%)	NS
Candida species (non-*albicans*)	38 (6.2%)	68 (9.3%)	0.034
Candida albicans	42 (6.8%)	58 (7.9%)	NS
Klebsiella species	41 (6.6%)	51 (7.0%)	NS
Pseudomonas aeruginosa	40 (6.5%)	47 (6.4%)	NS
Staphylococcus aureus	35 (5.7%)	38 (5.2%)	NS
Coagulase-negative staphylococci	47 (7.6%)	35 (4.8%)	0.030
Enterobacter species	36 (5.8%)	35 (4.8%)	NS
Escherichia coli	30 (4.8%)	34 (4.6%)	NS
Stenotrophomonas maltophilia	30 (4.8%)	26 (3.5%)	NS
Burkholderia cepacia complex	10 (1.6%)	21 (2.9%)	NS
Serratia species	9 (1.5%)	19 (2.6%)	NS
Others	92 (14.9%)	99 (13.5%)	NS

why our CLABSI incidence rate reduction is considerably lower than that reported in other studies.[5,9,20] A previous study in Taiwan reported the same problem.[24] In the clinical scenario, maximal sterile barrier precaution is relatively labor intensive and time consuming compared with other bundle elements; thus, its complete application is more difficult.

The baseline incidence of CLABSI in our ICUs was 9.27 per 1000 CL-days, which was considerably higher than that reported in the United States (0.96 per 1000 CL-days).[23] Because we included ICU patients from one of the largest medical and referral centers in Taiwan, the higher CLABSI incidence may be attributed to the more complicated condition of patients, which predisposed them to bloodstream infection. This is demonstrated by the older age and longer average hospital stay of patients in our study compared with those of patients in other single-hospital studies.[9,19]

Gram-negative bacteria were the main pathogens causing CLABSI in this study, which might reflect the fact that a high proportion of studied patients had underlying malignancies (Table 1).[25] Similarly, the significantly increased incidence of CLABSI caused by non-*albicans Candida* species might be attributed to the significantly higher proportion of patients with malignancy during the intervention period than during the baseline period or to the widespread use of fluconazole for both prophylaxis and empirical therapy in ICU patients.[26,27] By contrast, the percentage of CoNS identified as a CLABSI-causing pathogen was significantly lower during the intervention period. Leblebicioglu et al. reported a similar result, which might be attributed to the effect of CL bundle that mainly protects against CLABSI through skin-colonizing microorganisms.[28]

Several innovative tools were incorporated into our interventions to facilitate CL bundle implementation. For example, we designed an all-inclusive catheter cart and a prepackaged catheter insertion set to enhance accessibility to all necessary supplies.[29,30] The aim of each technical innovation was to motivate behavioral changes so that the staff can be more adherent to the bundle. However, unfamiliarity to new tools, such as the one-piece drapes introduced in our study, might partly explain the limited beneficial effects of technical innovations in our study. Once the medical staff members go through the "learning" or "adaptation" period, the beneficial effects of innovative tools might be more enhanced.

How to confirm the direct relationship between the bundle-based interventions and the reduction of CLABSI was a challenging issue. Admittedly, the decreasing CLABSI incidence during our intervention period might also be attributed to other concomitant infection control measures, such as environmental cleaning and cohort isolation. In previous studies, the improvement of bundle compliance was often used as a proof for the causality between the interventions and the decreased infection.[5,18,21] Unfortunately, the bundle compliance was measured since the last year in this study, and the small number of compliance records would further compromise the reliability of the information. Continuous surveillance of the bundle compliance would help to validate the effect of our multimodal interventions on CLABSI incidence.

The strengths of our study are as follows. This is one of the largest single-center studies focusing on CL bundle, enrolling 245,971 patient-days and 162,483 CL-days in five years. The participating adult ICUs were all within the same hospital; thus, the daily practice, education program, and surveillance system were highly comparable. In other words, the inter-ICU variance, which is a common issue encountered in other multicenter studies, could be minimized. In addition, we report the incidence rate of not only CLABSI but also CRBSI to further validate the effectiveness of our interventions. CLABSI surveillance is usually suggested for quality improvement, with a simpler definition than that of CRBSI, and is easier to be monitored in most clinical settings. However, CLABSI is less specific in determining the causal relationship between catheter colonization and bacteremia, and it may overestimate the true incidence of bloodstream infections originating from CLs.[31,32]

This study has several limitations. First, the inclusion of only one medical center might limit the generalizability of our study results to different hospital settings. Second, because we used a before—after comparison approach to evaluate our interventions, some unmeasured temporal changes, which would also affect the CLABSI incidence, could not be adjusted. Last, as mentioned before, the information about bundle compliance was incomplete, and we cannot definitely prove the causality between our interventions and the reductions in CLABSI. Nevertheless, the information about bundle compliance revealed that maximal sterile barrier precaution was the bundle element that was most difficult to comply, and it helped us to design further quality improvement program.

In conclusion, our study results demonstrate that the implementation of a set of multimodal interventions was effective in reducing the incidence rates of CLABSI and CRBSI in adult ICUs. However, whether a more personalized customization of technical innovations can enhance the compliance of bundle care and confer additional infection rate reduction should be investigated in future studies.

Conflict of interest

All authors declare no conflicts of interest.

Acknowledgments

The authors are grateful to the hospital staff for their commitment to improve patient safety and reduce healthcare-associated infections. The authors would also like to acknowledge the effort of members of the NTUH Center for Infection Control in designing, implementing and monitoring the CL bundle. This study was partially funded by the Centers for Diseases Control, Taiwan PC-933 and PC-972. Care Bundle for Prevention of Central Line-Associated Bloodstream Infection.

References

1. Centers for Disease Control and Prevention (CDC). Vital signs: central line-associated blood stream infections — United States, 2001, 2008, and 2009. *MMWR Morb Mortal Wkly Rep* 2011;**60**:243—8.
2. Tarricone R, Torbica A, Franzetti F, Rosenthal VD. Hospital costs of central line-associated bloodstream infections and cost-effectiveness of closed vs. open infusion containers. The case of intensive care units in Italy. *Cost Eff Resour Alloc* 2010;**8**:8.
3. Ista E, van der Hoven B, Kornelisse RF, van der Starre C, Vos MC, Boersma E, et al. Effectiveness of insertion and maintenance bundles to prevent central-line-associated bloodstream infections in critically ill patients of all ages: a systematic review and meta-analysis. *Lancet Infect Dis* 2016;**16**:724—34.
4. Dudeck MA, Edwards JR, Allen-Bridson K, Gross C, Malpiedi PJ, Peterson KD, et al. National Healthcare Safety Network report, data summary for 2013, Device-associated Module. *Am J Infect Control* 2015;**43**:206—21.
5. Jeong IS, Park SM, Lee JM, Song JY, Lee SJ. Effect of central line bundle on central line-associated bloodstream infections in intensive care units. *Am J Infect Control* 2013;**41**:710—6.
6. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;**355**:2725—32.
7. Alvarez-Moreno CA, Valderrama-Beltran SL, Rosenthal VD, Mojica-Carreno BE, Valderrama-Marquez IA, Matta-Cortes L, et al. Multicenter study in Colombia: impact of a multidimensional International Nosocomial Infection Control Consortium (INICC) approach on central line-associated bloodstream infection rates. *Am J Infect Control* 2016;**44**:e235—41.
8. Scheck McAlearney A, Hefner JL, Robbins J, Harrison MI, Garman A. Preventing central line-associated bloodstream infections: a qualitative study of management practices. *Infect Control Hosp Epidemiol* 2015;**36**:557—63.
9. Entesari-Tatafi D, Orford N, Athan E. Effectiveness of a care bundle to reduce central line-associated bloodstream infections. *Med J Aust* 2015;**203**:138.
10. Yaseen M, Al-Hameed F, Osman K, Al-Janadi M, Al-Shamrani M, Al-Saedi A, et al. A project to reduce the rate of central line associated bloodstream infection in ICU patients to a target of zero. *BMJ Qual Improv Rep* 2016;**5**. pii: u212545.w4986.
11. Wallace MC, Macy DL. Reduction of central line-associated bloodstream infection rates in patients in the adult intensive care unit. *J Infus Nurs* 2016;**39**:47—55.
12. Ling ML, Apisarnthanarak A, Madriaga G. The burden of healthcare-associated infections in Southeast Asia: a systematic literature review and meta-analysis. *Clin Infect Dis* 2015;**60**:1690—9.
13. Chen YC, Sheng WH, Wang JT, Chang SC, Lin HC, Tien KL, et al. Effectiveness and limitations of hand hygiene promotion on decreasing healthcare-associated infections. *PLoS One* 2011;**6**:e27163.
14. Ling ML, Apisarnthanarak A, Jaggi N, Harrington G, Morikane K, Thu le TA, et al. APSIC guide for prevention of central line associated bloodstream infections (CLABSI). *Antimicrob Resist Infect Control* 2016;**5**:16.
15. Chuang YC, Chen YC, Chang SC, Sun CC, Chang YY, Chen ML, et al. Secular trends of healthcare-associated infections at a teaching hospital in Taiwan, 1981—2007. *J Hosp Infect* 2010;**76**:143—9.
16. Tseng YJ, Wu JH, Lin HC, Chen MY, Ping XO, Sun CC, et al. A web-based, hospital-wide health care-associated bloodstream infection surveillance and classification system: development and evaluation. *JMIR Med Inform* 2015;**3**:e31.
17. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;**36**:309—32.
18. Menegueti MG, Ardison KM, Bellissimo-Rodrigues F, Gaspar GG, Martins-Filho OA, Puga ML, et al. The impact of implementation of bundle to reduce catheter-related bloodstream infection rates. *J Clin Med Res* 2015;**7**:857—61.
19. Jaggi N, Rodrigues C, Rosenthal VD, Todi SK, Shah S, Saini N, et al. Impact of an International Nosocomial Infection Control Consortium multidimensional approach on central line-associated bloodstream infection rates in adult intensive care units in eight cities in India. *Int J Infect Dis* 2013;**17**:e1218—24.
20. Palomar M, Alvarez-Lerma F, Riera A, Diaz MT, Torres F, Agra Y, et al. Impact of a national multimodal intervention to prevent catheter-related bloodstream infection in the ICU: the Spanish experience. *Crit Care Med* 2013;**41**:2364—72.
21. Salama MF, Jamal W, Al Mousa H, Rotimi V. Implementation of central venous catheter bundle in an intensive care unit in Kuwait: effect on central line-associated bloodstream infections. *J Infect Public Health* 2016;**9**:34—41.
22. Sacks GD, Diggs BS, Hadjizacharia P, Green D, Salim A, Malinowski DJ. Reducing the rate of catheter-associated bloodstream infections in a surgical intensive care unit using the Institute for Healthcare Improvement Central Line Bundle. *Am J Surg* 2014;**207**:817—23.
23. Furuya EY, Dick AW, Herzig CT, Pogorzelska-Maziarz M, Larson EL, Stone PW. Central line-associated bloodstream infection reduction and bundle compliance in intensive care units: a national study. *Infect Control Hosp Epidemiol* 2016;**37**:805—10.
24. Tang HJ, Lin HL, Lin YH, Leung PO, Chuang YC, Lai CC. The impact of central line insertion bundle on central line-associated bloodstream infection. *BMC Infect Dis* 2014;**14**:356.

25. Lin KY, Cheng A, Chang YC, Hung MC, Wang JT, Sheng WH, et al. Central line-associated bloodstream infections among critically-ill patients in the era of bundle care. *J Microbiol Immunol Infect* 2017;**50**:339–48.
26. Tang HJ, Liu WL, Lin HL, Lai CC. Epidemiology and prognostic factors of candidemia in cancer patients. *PLoS One* 2014;**9**: e99103.
27. Kullberg BJ, Arendrup MC. Invasive candidiasis. *N Engl J Med* 2015;**373**:1445–56.
28. Leblebicioglu H, Ozturk R, Rosenthal VD, Akan OA, Sirmatel F, Ozdemir D, et al. Impact of a multidimensional infection control approach on central line-associated bloodstream infections rates in adult intensive care units of 8 cities of Turkey: findings of the International Nosocomial Infection Control Consortium (INICC). *Ann Clin Microbiol Antimicrob* 2013;**12**:10.
29. Hermon A, Pain T, Beckett P, Jerrett H, Llewellyn N, Lawrence P, et al. Improving compliance with central venous catheter care bundles using electronic records. *Nurs Crit Care* 2015;**20**:196–203.
30. Walz JM, Ellison 3rd RT, Mack DA, Flaherty HM, McIlwaine JK, Whyte KG, et al. The bundle "plus": the effect of a multidisciplinary team approach to eradicate central line-associated bloodstream infections. *Anesth Analg* 2015;**120**:868–76.
31. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011;**52**:e162–93.
32. Chen XX, Lo YC, Su LH, Chang CL. Investigation of the case numbers of catheter-related bloodstream infection overestimated by the central line-associated bloodstream infection surveillance definition. *J Microbiol Immunol Infect* 2015;**48**: 625–31.