International Journal of Infectious Diseases 103 (2021) 308–315

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Reduction of 30-day death rates from *Staphylococcus aureus* bacteremia by mandatory infectious diseases consultation: Comparative study interventions with and without an infectious disease specialist

Yoshiro Hadano[a,b,c,*], Tatsuyuki Kakuma[d], Takanori Matsumoto[e], Kazushige Ishibashi[f], Miwako Isoda[f], Hiroshi Yasunaga[g]

[a] *Graduate School of Medicine, Kurume University, Kurume, Japan*
[b] *Department of Infectious Diseases, St. Mary's Hospital, Kurume, Japan*
[c] *Department of Infection Control and Prevention, Tokyo Medical and Dental University Medical Hospital, Tokyo, Japan*
[d] *Biostatistics Center, Kurume University School of Medicine, Kurume, Japan*
[e] *Department of Pharmacy, St. Mary's Hospital, Kurume, Japan*
[f] *Department of Clinical Laboratory, St. Mary's Hospital, Kurume, Japan*
[g] *Department of Cardiovascular Surgery, St. Mary's Hospital, Kurume, Japan*

ARTICLE INFO

Article history:
Received 29 September 2020
Received in revised form 12 November 2020
Accepted 26 November 2020

Keywords:
Staphylococcus aureus bacteremia
Mandatory infectious diseases consultation
Antimicrobial stewardship
Quality-of-care indicators
Japan

ABSTRACT

Objectives: Most Japanese hospitals need to keep to higher *Staphylococcus aureus* bacteremia (SAB) quality-of-care indicators (QCIs) and create strategies that can maximize the effect of these QCIs with only a small number of infectious disease specialists. This study aimed to evaluate the clinical outcomes of patients with SAB before and after the enhancement of the mandatory infectious disease consultations (IDCs).

Methods: This retrospective study was conducted at a tertiary care hospital in Japan. The primary outcome was the 30-day mortality between each period. A generalized structural equation model was employed to examine the effect of the mandatory IDC enhancement on 30-day mortality among patients with SAB.

Results: A total of 114 patients with SAB were analyzed. The 30-day all-cause mortality differed significantly between the two periods (17.3% vs. 4.8%, $P = 0.02$). Age, three-QCI point ≥ 1, and Pitt bacteremia score ≥ 3 were the significant risk factors for 30-day mortality. The intervention was also significantly associated with improved adherence to QCIs.

Conclusion: Mandatory IDCs for SAB improved 30-day mortality and adherence to QCIs after the intervention. In Japan, improving the quality of management in patients with SAB should be an important target.

Introduction

Staphylococcus aureus bacteremia (SAB) is a common and significant infection with high mortality rates. The 30-day all-cause mortality of SAB is 20–30% and has not changed since the 1990s (van Hal et al., 2012). Early identification of SAB is essential to start appropriate treatment, preventing a worse outcome (Khatib et al., 2006). Current guidelines demonstrate the need for immediate intervention and further diagnostic evaluation in patients diagnosed with SAB (Liu et al., 2011; Baddour et al., 2015; Habib et al., 2015). Therefore, the most recent studies have identified evidence-based quality-of-care indicators (QCIs) for the management of SAB and evaluated their impacts. The association between infectious disease specialist (IDS) consultations, and improved outcomes for patients with SAB has been well established (Honda et al., 2010; López-Cortés et al., 2013; Borde et al., 2014; Fries et al., 2014). The IDSs are important in medicine but are rare in Japan. According to a previous report in 2019, there are only 1.2 IDSs per 100,000 population in Japan, compared to 2.8

* Corresponding author at: Department of Infection Control and Prevention, Tokyo Medical and Dental University Medical Hospital, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan.
E-mail address: y-hadano.infe@tmd.ac.jp (Y. Hadano).

https://doi.org/10.1016/j.ijid.2020.11.199

IDSs per 100,000 population in the United States, with only 1491 board-certified IDSs in Japan (Kishida and Nishiura, 2020). Therefore, there are no or limited clinical IDS resources in most tertiary care hospitals, specifically in regional or rural areas in Japan. Moreover, a recent multicenter retrospective observational study in Japanese emergency and critical care departments showed that the adherence rate to QCIs for SAB was extremely low (Miyamoto et al., 2017). Thus, most Japanese hospitals need to keep higher SAB QCIs and create strategies that can maximize the effect of these QCIs with a small number of IDSs. This comparative study aimed to evaluate the clinical outcomes of patients with SAB before and after mandatory infectious disease consultations (IDCs) and the adherence to guidelines in the management of SAB.

Methods

Study design and setting

This retrospective before-and-after study was conducted from April 2015 to September 2016 (pre-intervention period) and from October 2016 to March 2018 (intervention period) at St. Mary's Hospital, a 1097-bed acute tertiary care teaching hospital in Kurume, Japan. In October 2016, one board-certified clinical IDS who had finished a clinical infectious diseases (ID) fellowship in Japan, launched a north-western-style IDC service at St. Mary's Hospital in which ID physicians see patients mainly as consultants without inpatient duties and on an outpatient basis.

During the intervention period, IDCs were mandated for all patients with SAB in St. Mary's Hospital. An IDS and microbiology laboratory technicians performed an every-weekday small meeting at noon and shared information concerning blood culture positive samples. The microbiology laboratory technologist reported the detection of any positive blood culture for *S. aureus* directly to the IDS. An IDS's comment was added in the electronic medical record to all blood culture results positive for *S. aureus*. Based on the evidence-based management approach of SAB, six QCIs were selected for this study: follow-up blood culture, cardiac echocardiography, early source control, optimal antimicrobial therapy, therapy duration of at least 2 weeks intravenously, and therapeutic vancomycin trough level. In addition to this comment, an IDS directly reported and recommended an evidence-based management approach in all SAB cases to the most responsible physicians. An ID doctor was expected to follow up the patient until there was a complete resolution, or the patient was discharged. During this 3-year period, the antimicrobial stewardship team (AST) was functional and monitored for carbapenem or anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics every weekday. Although the AST monitored the vancomycin trough levels during the study period, they did not take a positive approach toward the other QCIs. All episodes of SAB involving admitted cases were reviewed retrospectively by AST members.

Outcome

The primary outcome was the 30-day mortality in patients with SAB between each period. The secondary outcome was pre-specified as adherence to evidence-based guidelines in the management of SAB, as outlined in the internal policy, which was based on published guidelines (Liu et al., 2011; Baddour et al., 2015; Habib et al., 2015). From these indicators, six QCIs were selected for this study: follow-up blood culture on day 4, cardiac echocardiography, appropriate antimicrobial therapy, treatment duration of at least 14 days, early source control, and therapeutic vancomycin trough level. Although data on six QCIs were collected, only three QCIs – follow-up blood culture, echocardiography, and appropriate antimicrobial therapy – were used in data analyses because the other QCIs had missing records. Each QCI was then scored as one if it was implemented and zero otherwise, and the three-QCI scores ranging from 0 to 3 were analyzed.

Data collection

All hospitalized consecutive adult patients ($\geq$18 years) with an episode of SAB, defined as isolation of *S. aureus* from one or more blood culture samples, were included. Only the first episode of SAB during the study period was included, but it was recognized as a separate episode if a patient had another episode of SAB more than 90 days after completing a course of anti-staphylococcal therapy. Patients aged less than 18 years, with allergies for the first-choice treatment, receiving palliative care, not receiving treatment, and who died within 72 h of the day that the blood culture was obtained were excluded.

The following demographic data of the study participants were collected from medical records: age, sex, setting (community-acquired, hospital-onset, and healthcare-associated), requesting department (internal medicine departments or not), microbiological data (methicillin-sensitive *S. aureus* [MSSA] or MRSA), source of bacteremia (catheter-related bloodstream infections, endocarditis, osteomyelitis/arthritis, respiratory tract, skin and soft tissue infection, and other unknown sources), severity of bacteremia based on Pitt bacteremia score, underlying diseases (cardiovascular diseases, chronic lung diseases, chronic kidney diseases, hemodialysis, diabetes, malignant tumor, chronic skin diseases, liver cirrhosis, human immunodeficiency virus [HIV] or acquired immune deficiency syndrome [AIDS], and immunosuppressive therapy), 30-day mortality, and readmission within 90 days after the end of treatment with recurrent SAB. Type of acquisition was classified as community-associated, healthcare-associated, or nosocomial. Acute severity of illness was assessed using the Pitt bacteremia score (Paterson et al., 2004), which was reviewed retrospectively on the day the blood culture was obtained. During the study period, we used routine blood culture bottles (BacT/ALERT FA and BacT/ALERT SN, bioMerieux Inc., Tokyo, Japan). The bacterial species were identified, and minimum inhibitory concentration testing was performed using the MicroScan WalkAway 96 SI System (Beckman Coulter, Tokyo, Japan).

Study definitions

The SAB was characterized by as at least one blood culture positive for *S. aureus* with clinical symptoms and clinically apparent signs. Community-acquired infection was characterized by a positive blood culture obtained at the time of hospital admission or within 48 h after hospital admission in patients not meeting the healthcare-associated infection criteria. Nosocomial infection was characterized by a positive blood culture obtained from patients who had been hospitalized for more than 48 h. Healthcare-associated infection was characterized by a positive blood culture obtained from a patient at the time of hospital admission or within 48 h of admission in cases of attending a hospital or hemodialysis clinic 30 days before SAB diagnosis, hospitalization in an acute care hospital for $\geq$2 days at 90 days before SAB diagnosis, and residing in a nursing home or long-term care facility. Catheter-related bloodstream infections were defined according to the Infectious Diseases Society of America (IDSA) guidelines (Mermel et al., 2009). Infective endocarditis was defined according to the Duke criteria (Durack et al., 1994). Immunosuppressive therapy was defined as a drug used to treat autoimmune diseases within 3 months of SAB onset (i.e. prednisone at a dose of 10 mg prednisone/day for >1 month or

a cumulative dose of >700 mg of prednisone within 3 months of SAB onset) (Asgeirsson et al., 2011).

Recurrence was defined as an identified SAB with the same susceptibility pattern within 90 days of completing a course of anti-staphylococcal therapy.

For the six QCIs, appropriate follow-up blood culture was defined if blood cultures were obtained within 4 days after the first positive blood cultures. This rate of adequate follow-up blood cultures was calculated as the number of patients who were obtained within 4 days after the first positive blood cultures among patients who were alive at 4 days. Completion of transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE) to rule out infectious endocarditis was also assessed. The appropriate treatment duration of antimicrobial therapy was defined as at least 14 days of bacteremia in this study. The duration of antibiotic treatment was considered appropriate if doctors had selected an antibiotic to which the patient's isolate was susceptible. The rate of appropriate treatment duration was calculated as the number of patients with adequate duration of antibiotic therapy among patients who were alive at 14 days in cases of bacteremia. In cases of MSSA bacteremia, cefazolin was recognized as the first-choice and definitive treatment antibiotic because oxacillin and nafcillin were not available in Japan. In cases of central nervous system infections such as meningitis and brain abscess, ceftriaxone, cefepime, carbapenems, and vancomycin are also acceptable. For MRSA bacteremia, vancomycin and daptomycin were recognized as the first-choice antibiotics. Serum trough levels of vancomycin exceeded 15 μg/mL (Steinmetz et al., 2015). Source control was defined as removal of the central venous catheter in the setting of catheter-related bloodstream infection, valve replacement in patients with infective endocarditis, drainage of intra-abdominal abscesses if indicated, and debridement or amputation of skin and soft tissue infections or osteomyelitis.

Statistical analyses

The primary objective of statistical analysis was to evaluate the effect of mandatory IDC by IDS on 30-day mortality rates. The impact of having an IDS was hypothesized to play a multifaceted role in reducing mortality rates. Starting mandatory IDCs referred to as the 'intervention period' may affect the performance of the three QCIs, while the level of Pitt bacteremia score may influence the three QCIs. Pitt bacteremia score and the three QCIs (number of bundle implementations) were considered as risk factors, and patients' age, sex, and other clinical variables were treated as potential confounding variables. To model the multifaceted effects of mandatory IDCs simultaneously after controlling for the confounders, a generalized structural equation model (GSEM) was employed (Kunitake et al., 2020). The Weibull parametric survival model was used to estimate the hazard ratio (HR) for each risk factor as well as the effect of the intervention period and confounders. A logistic regression model was employed to obtain the odds ratios (ORs) indicating the magnitude of interrelationship among risk factors. To determine the confounding variables, a univariate logistic regression model was constructed between the pre-intervention and intervention periods, and the 30-day mortality for each risk factor was obtained from a univariate Cox proportional hazards model. Both factors with $P < 0.2$ were considered as confounding variables. Estimates of model parameters and the path diagram are shown in Figure 3.

Preliminary data analyses were performed before using the GSEM. Categorical data were analyzed using either the chi-squared test or Fisher's exact test and non-categorical data using the Student's *t*-test or Mann–Whitney *U* test as appropriate. The Kaplan–Meier method and log-rank test were used for the intervention period effect. The Cox proportional hazards model was used to estimate the HR of each risk factor on the 30-day mortality in patients with SAB. All tests for significance were two-tailed, and $P < 0.05$ was considered significant. All statistical analyses were performed using the JMP Pro software program (version 14.0, SAS Institute, Cray, NC, USA), Stata/MP 14.0 (StataCorp LP 4,905 Lakeway Drive College Station, TX, USA), and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.6.3). More precisely, it is a modified version of R commander (version 2.6-2) that was designed to add statistical functions frequently used in biostatistics (Kanda, 2013).

Results

A total of 134 patients were screened for inclusion in the study. Based on the exclusion criteria, 20 patients were excluded. The reasons for exclusion are shown in Figure 1. Finally, a total of 114 patients with a first episode of SAB were analyzed, and 50 and 64 patients were included in the pre-intervention and intervention periods, respectively. The baseline demographic data and descriptive information regarding the interventional study are shown in Table 1. During the study period, MRSA bacteremia was observed in 23 patients (46.0%) in the pre-intervention period and 20 patients (31.3%) in the intervention period. There were no significant differences in the underlying diseases between the two groups.

The adherence to QCIs between the pre-intervention and intervention periods is shown in Table 2. In summary, most QCIs significantly improved during the intervention period except for intravenous treatment for 14 days and early source control. The intervention was independently associated with improved adherence to follow-up blood cultures (from 14.0% to 37.5%, $P < 0.01$), TTE/TEE echocardiography (from 52.0% to 75.0%, $P = 0.01$), appropriate antimicrobial therapy (from 56.0% to 75.0%, $P = 0.01$), and appropriate therapeutic vancomycin trough level for MRSA (from 27.8% to 61.1%, $P = 0.01$). The mean of the three-QCI points increased from 1.22 in the pre-intervention period to 1.88 in the intervention period ($P < 0.01$), indicating a significant change in the clinical bundle adherence. The complete rate of the three QCI (three points) between the periods also significantly improved from 8.0% to 28.1% ($P < 0.01$).

The Kaplan–Meier survival curve for patients with SAB stratified by intervention is shown in Figure 2. The 30-day mortality rate was 10.6% (12 patients/114 patients). The 30-day all-cause mortality was also significantly higher in the pre-intervention than the intervention period (17.3% vs. 4.8%, $P = 0.02$). The recurrence within 90 days after treatment did not show any statistical differences between the two periods (14.8% vs. 8.3%, $P = 0.45$). In the sub-analysis of MRSA bacteremia, the 30-day mortality rate was 11.6% (5 patients/43 patients) with a tendency to lower mortality between the periods (17.4% vs. 5.0%, $P = 0.21$).

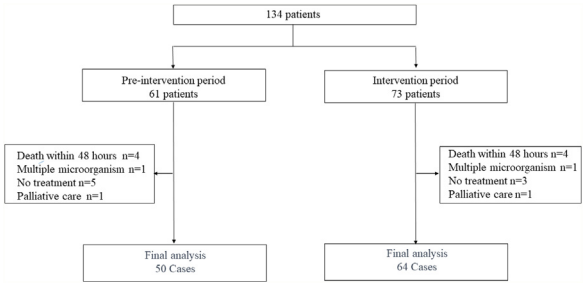

Figure 1. Flow diagram of patients included in the study.

Table 1
Baseline characteristics of patients with *Staphylococcus aureus* bacteremia between the pre-intervention and intervention periods.

Variables	Pre-intervention period		Intervention period		*P*-value
	n = 50	Percent	n = 64	Percent	
Age (years), median (IQR)	68 (55–80)		72 (65–82)		0.14
Sex male	34	68.0	48	75.0	0.41
Setting					0.15
Community-acquired	12	24.0	24	37.5	
Hospital-onset	25	50.0	21	32.8	
Healthcare-associated	13	26.0	19	29.7	
Intensive care unit at the time of blood culture collection	13	26.0	18	28.1	0.80
Pitt bacteremia score, median (IQR)	1 (1–3)		1 (1–3)		0.59
Internal medicine consult	27	54.0	35	54.7	0.94
Microbiology					0.11
MSSA	27	54.0	44	68.8	
MRSA	23	46.0	20	31.3	
Underlying diseases					
Cardiovascular disease	24	48.0	27	42.2	0.54
Chronic lung diseases	11	22.0	12	18.8	0.67
Chronic kidney diseases	19	38.0	24	37.5	0.96
Hemodialysis	9	18.0	12	18.8	0.92
Diabetes	20	40.0	30	46.9	0.46
Malignant tumor	11	22.0	18	28.1	0.45
Chronic skin diseases	11	22.0	15	23.4	0.86
Liver cirrhosis	4	8.0	2	3.1	0.40
HIV/AIDS	1	2.0	0	0	0.44
Immunosuppressive therapy	12	24.0	9	14.1	0.18
Source of bacteremia					0.43
Catheter-related bloodstream infections	13	26.0	12	18.8	
Endocarditis	5	10.0	7	10.9	
Osteomyelitis/arthritis	8	16.0	15	23.4	
Respiratory tract	7	14.0	10	15.6	
Skin and soft tissue infection	4	8.0	10	15.6	
Others and unknown source of bacteremia	13	26.0	10	15.6	

IQR, interquartile range; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

Table 2
Adherence to quality-of-care indicators (QCIs) and three QCI points between the pre-intervention and intervention periods.

Variables	Pre-intervention period		Intervention period		*P*-value
	n = 50	Percent	n = 64	Percent	
Follow-up blood culture on day 4	7/50	14.0	24/64	37.5	<0.01
TTE/TEE echocardiography	26/50	52.0	48/64	75.0	0.01
Appropriate antimicrobial therapy	28/50	56.0	48/64	75.0	0.03
Intravenous treatment for 14 days	30/44	68.2	51/62	82.3	0.09
Early source control	25/33	75.8	35/40	87.5	0.19
Therapeutic vancomycin trough level	5/18	27.8	11/18	61.1	0.04
Three-QCI point (mean)	1.22	0.95–1.49	1.88	1.65–2.10	<0.01
Three-QCI point					<0.01
0	14	28.0	4	6.3	
1	15	30.0	18	28.1	
2	17	34.0	24	37.5	
3	4	8.00	18	28.1	

TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

Tables 3 and 4 show the distribution of risk factors among patients with SAB between the periods and 30-day mortality, respectively. The OR for each risk factor with 95% confidence interval (CI) was obtained from a univariate logistic regression model (Table 3) and the HR with 95% CI for each risk factor was obtained from a univariate Cox proportional hazards model (Table 4). Age and immunosuppressive therapy were considered as confounding variables from these results.

The GSEM was employed to construct a clinical model (Figure 3). This clinical model comprised two components. The first was a survival model to estimate the HR among risk factors and the effect of intervention period and confounders. Age (HR, 1.09; 95% CI, 1.01–1.17), three-QCI point $\geq$ 1 (HR, 0.16; 95% CI, 0.04–0.68), and Pitt bacteremia score $\geq$ 3 (HR, 22.7; 95% CI, 4.6–111.9) were significant risk factors for 30-day survival time. The intervention period (P = 0.08) and immunosuppressive therapy (P = 0.60) had an indirect

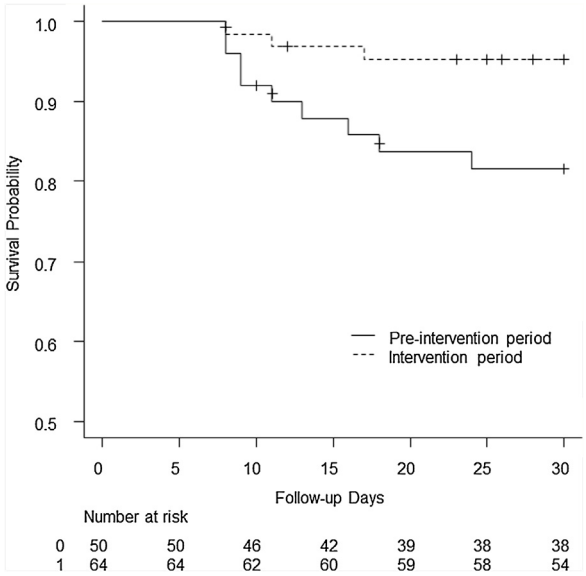

Figure 2. The Kaplan–Meier 30-day survival curves for patients with *Staphylococcus aureus* bacteremia by period.

effect on the 30-day survival time and no direct effects. The associations between risk factors were modeled in the second component. Logistic regression models were employed to evaluate the interrelationships among the risk factors. The odds of three-QCI point ≥ 1 were 6.2 times higher in patients in the intervention period than in patients in the pre-intervention period (95% CI 1.87–20.68). Similarly, the odds of three-QCI point ≥ 1 were 3.9 times higher in patients with Pitt bacteremia score ≥ 3 than with Pitt bacteremia score < 2 (95% CI 1.23–18.99) (Figure 3). All parameter estimates in Table 5 were obtained simultaneously based on GSEM.

Discussion

Our results suggest that mandatory IDCs had better outcomes in patients with SAB for 30-day mortality and improved QCIs in the setting of few IDSs. In addition, adherence to QCIs was generally low, specifically in the pre-intervention period. The association between IDCs and good prognosis of SAB has been well published (Honda et al., 2010; López-Cortés et al., 2013; Borde et al., 2014; Fries et al., 2014; Tissot et al., 2014; Martin et al., 2015; Nguyen et al., 2015; Vogel et al., 2016; Buehrle et al., 2017; Goto et al., 2017; Nagao et al., 2017; Djelic et al., 2018). A meta-analysis showed that bedside IDCs are related to better outcomes, including all-cause 30-day mortality decreasing from 26% to 12% in favor of the IDC group (relative risk, 0.53; 95% CI, 0.43–0.65) (Vogel et al., 2016). Recently Tissot et al. (2014) reported that 'mandatory' IDCs for MRSA bacteremia were associated with better management of patients with MRSA bacteremia and reduced mortality. Martin et al. (2015) also reported on mandatory IDC for patients with SAB, with better adherence to the IDSA guidelines. Automatic notification and IDC for patients with SAB improved adherence to the established QCI (Djelic et al., 2018). Thus, mandating IDCs for all patients with SAB has been shown to improve the rates of guideline-recommended care, including echocardiography, source control, appropriate antimicrobial therapy, and follow-up cultures. The clinical setting of this study was based on a sufficient number of IDCs.

Unfortunately, most tertiary care hospitals in Japan have limited IDS resources, and we need a feasible and sustainable way to achieve a better outcome with few IDSs. In this study, a microbiology conference with microbiology laboratory technicians was organized regularly once every weekday. This is a sustainable burden on the limited IDS resource; nevertheless, 30-day mortality was improved between the periods. Mandatory IDCs may play a role in patient management to achieve a good outcome in patients with SAB in hospitals with limited IDS resources such as most of the tertiary care hospitals in Japan. It is possible that instituting an ID consultation led to increased awareness of the guideline-based management of SAB among the most responsible physicians.

Although the intervention period was not significantly related to 30-day mortality, implementation of three-QCI point and Pitt bacteremia score ≥ 3 were significantly associated with 30-day mortality in the present study. We tried to investigate other cut-off values for Pitt bacteremia. In cases of Pitt bacteremia cut-off score ≥ 2 based on a previous study (Hill et al., 2001), the estimates of model parameters on the factor risk model were as follows: direct effect of 30-day survival time: age (HR, 1.05; 95% CI, 0.99–1.10; P = 0.09), immunosuppressive therapy (HR, 0.87; 95% CI, 0.99–1.10; P = 0.85), intervention period (HR, 0.19; 95% CI, 0.45–0.80; P = 0.02), 3 QCI point ≥ 1 (HR, 0.32; 95% CI, 0.08–1.28; P = 0.11), and Pitt bacteremia score ≥ 2 (HR, 10.0; 95% CI, 2.36–42.6; P = 0.002); for Pitt bacteremia cut-off score ≥ 2, direct effect of three-QCI point ≥ 1: intervention period (OR, 5.42; 95% CI, 0.50–2.89; P < 0.01) and Pitt bacteremia score ≥ 2 (OR, 1.99; 95% CI, −0.54 to 1.91; P = 0.27). This result showed that, the more severe was the SAB status according to the Pitt bacteremia score, the greater was the impact of QCI implementation on 30-day mortality. The overall QCIs in patients with SAB improved during the intervention period. According to previous studies, AST intervention in the management of patients with SAB demonstrated significant adherence to all SAB quality-of-care measures (Wenzler et al., 2017; Smith et al., 2018; Sherbuk et al., 2019). Although antimicrobial stewardship is

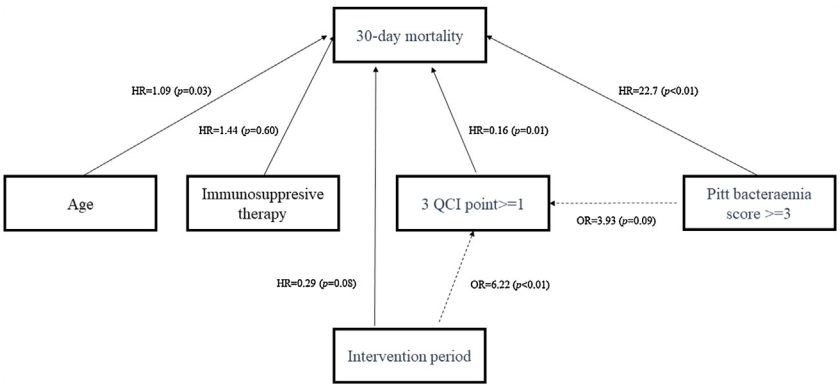

Figure 3. Risk factor model of *Staphylococcus aureus* bacteremia. The solid arrow represents the hazard ratio. The dotted arrow represents the odds ratio. QCIs, quality-of-care indicators.

Table 3
Univariate analysis of influence factors for the intervention period in patients with *Staphylococcus aureus* bacteremia.

Variable	Odds ratio (95% CI)	*P*-value
Age	1.02 (0.99–1.05)	0.14
Sex		
Male	1.41 (0.62–3.23)	0.41
Setting		
Hospital-onset	Ref	
Community-acquired	2.38 (0.98–6.01)	0.06
Healthcare-associated	1.73 (0.70–4.41)	0.23
Susceptibility		
MRSA	0.53 (0.25–1.15)	0.11
Internal medicine consult	1.02 (0.49–2.16)	0.94
Pitt bacteremia score	1.07 (0.84–1.35)	0.58
Underlying diseases		
Cardiovascular disease	0.79 (0.37–1.66)	0.54
Chronic lung diseases	0.82 (0.33–2.07)	0.67
Chronic kidney diseases	0.98 (0.46–2.11)	0.96
Hemodialysis	1.05 (0.41–2.80)	0.92
Diabetes	1.32 (0.63–2.82)	0.46
Malignant tumor	1.39 (0.59–3.37)	0.45
Chronic skin diseases	1.09 (0.45–2.68)	0.86
Liver cirrhosis	0.37 (0.07–2.11)	0.25
Immunosuppressive therapy	0.52 (0.19–1.34)	0.18
Source of bacteremia		
Catheter-related bloodstream infections	0.66 (0.27–1.60)	0.35
Endocarditis	0.87 (0.33–3.95)	0.87
Osteomyelitis/arthritis	1.61 (0.63–4.34)	0.32
Respiratory tract	1.13 (0.40–3.37)	0.81
Skin and soft tissue infection	2.12 (0.66–8.17)	0.21
Others and unknown source of bacteremia	0.53 (0.20–1.32)	0.17

CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 4
Univariate analysis of influence factors for 30-day mortality in patients with *Staphylococcus aureus* bacteremia.

Variable	Hazard ratio (95% CI)	*P*-value
Age	1.03 (0.99–1.09)	0.14
Sex		
Female	Ref	
Male	1.94 (0.62–6.14)	0.27
Setting		
Hospital-onset	Ref	
Community-acquired	1.29 (0.26–6.39)	0.76
Healthcare-associated	3.03 (0.76–12.14)	0.12
Susceptibility		
MSSA	Ref	
MRSA	1.25 (0.40–3.95)	0.71
Internal medicine consult		
No	Ref	
Yes	1.67 (0.50–5.52)	0.39
Pitt bacteremia score	1.52 (1.17–1.93)	<0.01
Underlying diseases		
Cardiovascular disease		
No	Ref	
Yes	1.71 (0.54–5.40)	0.35
Chronic lung diseases		
No	Ref	
Yes	1.96 (0.59–6.50)	0.29
Chronic kidney diseases		
No	Ref	
Yes	0.79 (0.24–2.63)	0.70
Hemodialysis		
No	Ref	
Yes	0.38 (0.05–3.00)	0.30
Diabetes		
No	Ref	
Yes	0.62 (0.19–2.04)	0.42
Malignant tumor		
No	Ref	
Yes	0.54 (0.12–2.48)	0.40
Chronic skin diseases		
No	Ref	
Yes	1.67 (0.50–5.52)	0.39
Liver cirrhosis		
No	Ref	
Yes	1.76 (0.23–13.6)	0.59
Immunosuppressive therapy		
No	Ref	
Yes	2.37 (0.70–7.76)	0.19
Source of bacteremia		
Catheter-related bloodstream infections		
No	Ref	
Yes	0.32 (0.02–1.64)	0.19
Endocarditis		
No	Ref	
Yes	0.76 (0.04–3.89)	0.79
Osteomyelitis/arthritis		
No	Ref	
Yes	0.34 (0.02–1.73)	0.23
Respiratory tract		
No	Ref	
Yes	3.38 (0.90–10.75)	0.07
Skin and soft tissue infection		
No	Ref	
Yes	1.42 (0.21–5.38)	0.67
Others and unknown source of bacteremia		
No	Ref	
Yes	1.29 (0.28–4.32)	0.71

CI, confidence interval; MSSA, methicillin-sensitive *Staphylococcus aureus;* MRSA, methicillin-resistant *Staphylococcus aureus*.

an important aspect of healthcare in all hospitals in Japan, as in other countries, the problem lies in the low adherence rate during the pre-intervention period. The QCIs during the pre-intervention period were significantly low in terms of follow-up blood culture, treatment duration of antimicrobial therapy, and the choice of first-line appropriate antimicrobial therapy. In contrast, the compliance rate of echocardiography was higher than that of other indicators. These results were similar to those of a previous report conducted in emergency and critical care departments in Japan (Miyamoto et al., 2017). According to this previous report and our study, the adherence rate to QCIs for SAB is low in Japan. However, previous survey reports mentioned that the proportion of appropriate knowledge concerning SAB was high in some Japanese institutions such as university hospitals and leading hospitals (Nagao et al., 2017; Moriyama et al., 2019). The adherence to QCIs for SAB may depend on the activity of the AST and ID departments in each hospital. There may be room for improvement because of differences in quality of medical care for SAB between regions and facilities. Because adherence to evidence-based QCIs results in better prognosis, management of SAB should be an important target for interventions to improve the quality of management, specifically in the setting of hospitals with no or limited clinical IDS resources in Japan. Implementation of a hospital-wide protocol for the management of patients with SAB may also be a good aim to improve adherence to the standard of care (Bolhuis et al., 2018).

This study has some limitations. This retrospective study was conducted at a single center, acute tertiary care hospital, and the results may not apply to other settings with different consultation styles, such as university hospitals or cancer centers. Because of the single center and the short-duration nature of the study, the sample size was relatively small. Although the effect of AST cannot rule out to improve adherence to guidelines, another limitation is that we measured the evidence-based factors to manage SAB, but unmeasured factors that were not included may have affected the results. The study duration was 36 months and it is possible that this was insufficient to characterize the effect of this system. The addition of the AST review to mandatory IDC may be associated with improved QCIs in the management of SAB. Finally, there is the potential for changes in practice and microbiologic epidemiology

Table 5
Estimates of model parameters of the factor risk model.

30-day survival	Hazard ratio	95% CI	*P*-value
Age	1.09	1.01–1.17	0.03
Immunosuppressive therapy	1.44	0.37–5.55	0.60
Intervention period	0.29	0.07–1.17	0.08
Three-QCI point $\geq$ 1	0.16	0.04–0.68	0.01
Pitt bacteremia score $\geq$ 3	22.7	4.6–111.9	<0.01
Three QCIs	**Odds ratio**	**95% CI**	***P*-value**
Intervention period	6.22	1.87–20.68	<0.01
Pitt bacteremia score $\geq$ 3	3.93	1.23–18.99	0.09

CI, confidence interval; QCI, quality-of-care indicator.

over time, especially since the proportion of MRSA bacteremia showed a downward trend (a 14.7% reduction from 46.0% to 31.3%) and the mortality in patients with MRSA bacteremia also decreased in this study. Although there are some limitations, other institutions would likely benefit from a similar approach, specifically those that have relatively rare and new IDC services, as in Japan.

Conclusion

In conclusion, mandatory IDCs improved 30-day mortality rate and adherence to evidence-based bundle care and made a difference in mortality due to the intervention even with limited IDS resources. The IDSs should address expanding evidence-based practices for the management of SAB even in the setting of a small number of IDSs, such as most Japanese tertiary care hospitals, using this feasible and sustainable method. In Japan, the quality of SAB management should be improved for better prognosis of SAB. Furthermore, there is an urgent need for IDSs in Japan to appropriately address today's ID threats.

Potential conflicts of interest

The authors declare that they have no conflict of interest.

Funding source

The authors declare that they have no funding sources.

Ethics approval

The study protocol was approved by the Ethical Committee of St. Mary's Hospital (No.17-1212). Data were collected daily as part of standard patient care. Because this was an observational study, informed consent was waived.

Acknowledgements

The authors thank all the clinical staff at St. Mary's Hospital for their dedicated clinical practice and patient care and Dr. Naoya Itoh for his careful supervision.

We would like to thank Editage (https://www.editage.jp) for English language editing.

References

Asgeirsson H, Kristjansson M, Kristinsson KG, Gudlaugsson O. *Staphylococcus aureus* bacteraemia – nationwide assessment of treatment adequacy and outcome. J Infect 2011;62:339–46.

Baddour LM, Wilson WR, Bayer AS, Fowler Jr. VG, Tleyjeh IM, Rybak MJ, et al. American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435–86.

Bolhuis K, Bakker LJ, Keijer JT, de Vries PJ. Implementing a hospital-wide protocol for *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis 2018;37:1553–62.

Borde JP, Batin N, Rieg S, Feik R, Reimling C, Kern WV, et al. Adherence to an antibiotic stewardship bundle targeting *Staphylococcus aureus* blood stream infections at a 200-bed community hospital. Infection 2014;42:713–9.

Buehrle K, Pisano J, Han Z, Pettit NN. Guideline compliance and clinical outcomes among patients with *Staphylococcus aureus* bacteremia with infectious diseases consultation in addition to antimicrobial stewardship-directed review. Am J Infect Control 2017;45:713–6.

Djelic L, Andany N, Craig J, Daneman N, Simor A, Leis JA. Automatic notification and infectious diseases consultation for patients with *Staphylococcus aureus* bacteremia. Diagn Microbiol Infect Dis 2018;91:282–3.

Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994;96:200–9.

Fries BL, Licitra C, Crespo A, Akhter K, Busowski MT, Salazar D, et al. Infectious diseases consultation and the management of *Staphylococcus aureus* bacteremia. Clin Infect Dis 2014;58:598–9.

Goto M, Schweizer ML, Vaughan-Sarrazin MS, Perencevich EN, Livorsi DJ, Diekema DJ, et al. Association of evidence-based care processes with mortality in *Staphylococcus aureus* bacteremia at Veterans Health Administration Hospitals, 2003-2014. JAMA Intern Med 2017;177:1489–97.

Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075–128.

Hill PC, Birch M, Chambers S, Drinkovic D, Ellis-Pegler RB, Everts R, et al. Prospective study of 424 cases of *Staphylococcus aureus* bacteraemia: determination of factors affecting incidence and mortality. Intern Med J 2001;31:97–103.

Honda H, Krauss MJ, Jones JC, Olsen MA, Warren DK. The value of infectious diseases consultation in *Staphylococcus aureus* bacteremia. Am J Med 2010;123:631–7.

Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8.

Khatib R, Johnson LB, Fakih MG, Riederer K, Khosrovaneh A, Shamse, et al. Persistence in *Staphylococcus aureus* bacteremia: incidence, characteristics of patients and outcome. Scand J Infect Dis 2006;38:7–14.

Kishida N, Nishiura H. Accelerating reductions in antimicrobial resistance: Evaluating the effectiveness of an intervention program implemented by an infectious disease consultant. Int J Infect Dis 2020;93:175–81.

Kunitake T, Kakuma T, Ushijima K. Risk factors for lower limb lymphedema in gynecologic cancer patients after initial treatment. Int J Clin Oncol 2020;25:963–71.

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Infectious Diseases Society of America. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:e18–55.

López-Cortés LE, Del Toro MD, Gálvez-Acebal J, Bereciartua-Bastarrica E, Fariñas MC, Sanz-Franco M, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of *Staphylococcus aureus* bacteremia. Clin Infect Dis 2013;57:1225–33.

Martin L, Harris MT, Brooks A, Main C, Mertz D. Management and outcomes in patients with *Staphylococcus aureus* bacteremia after implementation of mandatory infectious diseases consult: a before/after study. BMC Infect Dis 2015;15:568.

Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1–45.

Moriyama Y, Ishikane M, Hayakawa K, Yamamoto K, Akazawa T, Sugiki Y, et al. Comparison of knowledge to antimicrobial stewardship institution policies targeting *Staphylococcus aureus* bacteremia and candidemia between medical doctors and pharmacists in an academic teaching hospital in Japan. J Infect Chemother 2019;25:396–9.

Miyamoto K, Kato S, Kitayama J, Okawa J, Okamoto A, Kamei J, et al. Adherence rate of quality-of-care indicators for *Staphylococcus aureus bacteremia* is extremely low in Japanese emergency and critical care departments: a multicenter retrospective observational study. Acute Med Surg 2017;5:140–5.

Nagao M, Yamamoto M, Matsumura Y, Yokota I, Takakura S, Teramukai S, et al. Complete adherence to evidence-based quality-of-care indicators for *Staphylococcus aureus* bacteremia resulted in better prognosis. Infection 2017;45:83–91.

Nguyen CT, Gandhi T, Chenoweth C, Lassiter J, Dela Pena J, Eschenauer G, et al. Impact of an antimicrobial stewardship-led intervention for *Staphylococcus aureus* bacteraemia: a quasi-experimental study. J Antimicrob Chemother 2015;70:3390–6.

Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. Ann Intern Med 2004;140:26–32.

Sherbuk JE, McManus D, Topal JE, Malinis M. Improved mortality in *Staphylococcus aureus* bacteremia with the involvement of antimicrobial stewardship team and infectious disease consultation. Infect Control Hosp Epidemiol. 2019;40:932–5.
Smith JR, Frens JJ, Snider CB, Claeys KC. Impact of a pharmacist-driven care package on *Staphylococcus aureus* bacteremia management in a large community healthcare network: a propensity score-matched, quasi-experimental study. Diagn Microbiol Infect Dis 2018;90:50–4.
Steinmetz T, Eliakim-Raz N, Goldberg E, Leibovici L, Yahav D. Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. Clin Microbiol Infect 2015;21:665–73.
Tissot F, Calandra T, Prod'hom G, Taffe P, Zanetti G, Greub G, et al. Mandatory infectious diseases consultation for MRSA bacteremia is associated with reduced mortality. J Infect 2014;69:226–34.
van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in *Staphylococcus aureus* bacteremia. Clin Microbiol Rev 2012;25:362–86.
Vogel M, Schmitz RP, Hagel S, Pletz MW, Gagelmann N, Scherag A. Infectious disease consultation for *Staphylococcus aureus* bacteremia — a systematic review and meta-analysis. J Infect 2016;72:19–28.
Wenzler E, Wang F, Goff DA, Prier B, Mellett J, Mangino JE, et al. An automated, pharmacist-driven initiative improves quality of care for *Staphylococcus aureus* bacteremia. Clin Infect Dis 2017;65:194–200.