MAJOR ARTICLE

Impact of an Evidence-Based Bundle Intervention in the Quality-of-Care Management and Outcome of *Staphylococcus aureus* Bacteremia

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(See the Editorial Commentary by Liu on pages 1234–6.)

Background. *Staphylococcus aureus* bacteremia (SAB) is associated with significant morbidity and mortality. Several aspects of clinical management have been shown to have significant impact on prognosis. The objective of the study was to identify evidence-based quality-of-care indicators (QCIs) for the management of SAB, and to evaluate the impact of a QCI-based bundle on the management and prognosis of SAB.

Methods. A systematic review of the literature to identify QCIs in the management of SAB was performed. Then, the impact of a bundle including selected QCIs was evaluated in a quasi-experimental study in 12 tertiary Spanish hospitals. The main and secondary outcome variables were adherence to QCIs and mortality. Specific structured individualized written recommendations on 6 selected evidence-based QCIs for the management of SAB were provided.

Results. A total of 287 and 221 patients were included in the preintervention and intervention periods, respectively. After controlling for potential confounders, the intervention was independently associated with improved adherence to follow-up blood cultures (odds ratio [OR], 2.83; 95% confidence interval [CI], 1.78–4.49), early source control (OR, 4.56; 95% CI, 2.12–9.79), early intravenous cloxacillin for methicillin-susceptible isolates (OR, 1.79; 95% CI, 1.15–2.78), and appropriate duration of therapy (OR, 2.13; 95% CI, 1.24–3.64). The intervention was independently associated with a decrease in 14-day and 30-day mortality (OR, 0.47; 95% CI, .26–.85 and OR, 0.56; 95% CI, .34–.93, respectively).

Conclusions. A bundle orientated to improving adherence to evidence-based QCIs improved the management of patients with SAB and was associated with reduced mortality.

Keywords. *Staphylococcus aureus*; intervention; bacteremia; bloodstream infections; clinical management.

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Staphylococcus aureus is an important human pathogen and one of the leading causes of both nosocomial and community-onset bloodstream infections worldwide [1]. *Staphylococcus aureus* bacteremia (SAB) causes significant morbidity, mortality, and healthcare costs; complications are frequent, and mortality ranges from 20% to 40% [2–5]. Importantly, some aspects of clinical management have been associated with better outcomes [6–8]. Thus, previous studies showed that adherence to specialized advice is associated with improved management and, in some of them, even reduced mortality [9–15]. In these studies, the management and outcomes of patients with SAB who were treated following the recommendations of infectious diseases specialists were compared with those of patients for whom specialized consultation was not sought or where the recommendations provided were not followed. The recommendations provided by specialists in these studies were not structured and/or had not been prioritized in accordance with an evidence-based procedure.

Table 1. Preintervention and Intervention Activities Performed on Patients With *Staphylococcus aureus* Bacteremia in the Participating Hospitals

Period	Activities
Preintervention	Early report (verbal or written) of Gram stain results was provided for all patients with positive blood cultures by clinical microbiologists in 6 of the 12 participating centers. Seven centers had an active "bacteremia program" in which unsolicited consultation for all SAB cases of BSI were provided by infectious diseases subspecialists; neither the recommendations provided nor the follow-up procedures were structured, but were done at the discretion of the infectious diseases subspecialist. Adherence to recommendations was not prospectively measured.
Intervention	1. The intervention was explained to the different services in specific educational sessions. An informative letter was also sent to all heads of services before the intervention period started. 2. Specific recommendations, based on the 6 selected quality-of-care indicators, were specifically provided at least 3 days per week by an infectious diseases specialists from the day *S. aureus* was identified from blood culture until the patient was discharged or died. The recommendations were discussed with the attending physician and were also provided in a structured form which was added to the charts (Supplementary Figure 1), and signed by the infectious diseases specialist at each visit. Adherence to the recommendations was at the discretion of attending physician. 3. The form also included a summary of the rationale for the intervention, which served as educational material.

Abbreviations: BSI, bloodstream infection; SAB, *Staphylococcus aureus* bacteremia.

At present, many tertiary hospitals develop active "bacteremia programs," in which infectious diseases specialists and clinical microbiologists provide early unsolicited advice for the management of patients with bacteremia. Despite this, the specific difficulties inherent to management of SAB may need additional interventions. The objectives of this study were (1) to identify evidence-based quality-of-care indicators (QCIs) for the management of SAB; and (2) to evaluate the impact of an intervention based on a bundle of selected QCIs aimed at improving the management and outcome of patients with SAB.

METHODS

Identification of Quality-of-Care Indicators for the Management of SAB

A systematic review of the literature was performed to identify the best evidence on aspects related to the clinical management of SAB that had a significant influence in prognosis. Studies were retrieved from the PubMed database using the following search terms: *Staphylococcus aureus* OR *S. aureus*, AND *bacteremia* OR *bloodstream infection* OR *sepsis*, AND *outcome* OR *complication* OR *mortality* OR *death* OR *recurrence*. Observational and randomized studies were selected if the 2 following criteria were fulfilled: the predictors or risk factors for outcome determinants (including rates of clinical cure, microbiological cure, mortality, complications or recurrence) were studied, and accepted methods for control of confounding were used in the case of observational studies (including multivariate or stratified analysis or matching). The studies were reviewed by 2 investigators (L.E.L.-C. and J.R.-B.). The variables independently and consistently (eg, they were found in at least 2 studies) related to outcome and amenable to clinical intervention were selected as QCIs; for each of them a formula to measure the level of adherence to the indicator was defined.

Intervention: Study Design and Setting

The intervention study was performed in 12 tertiary hospitals in Spain; 8 of them are teaching hospitals, and 10 have >500 beds. There are infectious diseases services or units in all 12, and active transplantation programs in 4. A quasi-experimental design, before (from January through June 2010) and during the implementation of the intervention (from July to December 2010), was used; in one hospital where the intervention was piloted, the preintervention and intervention periods were from March 2008 to August 2009, and from September 2009 to May 2011, respectively. All episodes of SAB involving admitted patients >17 years of age were considered eligible. Patients were detected through daily review of microbiology reports. Only 1 episode per patient (the first) was included, unless a later episode was separated from the previous one by an interval of >3 months without evidence of recurrence from a deep-seated

Table 2. Definitions of Quality-of-Care Indicators for *Staphylococcus aureus* Bacteremia Selected After Systematic Review of the Literature

Quality-of-Care Indicator	Definition	Formula	References in Supplementary Data
Follow-up blood cultures	Performance of control blood cultures 48–96 h after antimicrobial therapy was started regardless of clinical evolution	Patients in whom follow-up blood cultures were collected ×100/patients alive at 96 h	[9–11] [14] [15] [21]
Early source control	Removal of nonpermanent vascular catheter whenever the catheter was suspected or confirmed as the source of SAB, or drainage of an abscess in <72 h	Patients in which the amenable source was removed in <72 h ×100/patients with source amenable of removal/ drainage	[9–11] [13]
Echocardiography in patients with clinical indications	Performance of echocardiography in patients with complicated bacteremia (see definition in Methods) or predisposing conditions for endocarditis	Patients with echocardiography ×100/ patients with complicated bacteremia or predisposing condition for endocarditis, alive at least 96 h	[9] [10] [12–15] [71–75]
Early use of intravenous cloxacillin for MSSA as definitive therapy	Definitive therapy with intravenous cloxacillin (at least 2 g every 6 h or adjusted based on renal function in renal failure) in cases of methicillin-susceptible strains (allergic patients excluded). Treatment should be started within the first 24 h after methicillin sensitivity was available. For hemodialysis patients, cefazolin 2 g after each hemodialysis session was acceptable	Definitive therapy with intravenous cloxacillin ×100/nonallergic patients with methicillin-susceptible isolates	[9] [13] [79] [81]
Adjustment of vancomycin dose according to trough levels	Measurement of trough levels of vancomycin in patients treated for at least 3 d with this antibiotic and adjustment of dose in order to achieve plasma trough levels between 15 and 20 mg/L in survivors	Patients with trough level of vancomycin determined and dose adjusted ×100/ patients treated with vancomycin for at least 3 d	[24] [59] [76–80]
Treatment duration according to the complexity of infection	Duration of antimicrobial therapy of at least 14 d for uncomplicated bacteremia and 28 d for complicated bacteremia. Sequential oral treatment with fluoroquinolone plus rifampin, trimethoprim-sulfamethoxazole, or linezolid was considered accepted in selected cases	Patients with appropriate duration of therapy ×100/patients alive at 14 or 28 d in cases of uncomplicated or complicated bacteremia, respectively	[10] [12–14] [21] [78]

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.

infection. Patients who died in the first 48 hours (who were not subject to intervention) and those patients receiving palliative care for terminal conditions were excluded.

The intervention and the activities performed during the preintervention period are summarized in Table 1. The intervention consisted of a set of written recommendations according to the 6 aspects selected as QCIs provided in a structured form by an infectious diseases specialist at each hospital. All patients were followed until discharge or death and were assessed for survival and recurrence on days 30 and 90 during a visit to the outpatient clinic or by phone call. Patient data were collected by a nonblinded investigator in each of the participating hospitals.

The study was approved by the ethics committee of the Hospital Universitario Virgen Macarena, which waived the need to obtain written informed consent from the patients on the understanding that the intervention was aimed at improving quality of care according to evidence-based standard of care.

Variables and Definitions

The main outcome variable of the quasi-experimental study was adherence to the 6 QCIs selected, measured as the proportion of cases in which the recommended action was performed. As secondary outcome variables, 14- and 30-day all-cause mortality and the 90-day recurrence rate were considered. Explanatory variables included demographics, type and severity of underlying conditions, acquisition type of SAB, source of infection, severity of systemic inflammatory response syndrome at presentation [16], susceptibility to methicillin, antimicrobial therapy, support therapy, and outcome [17]. We used the Charlson comorbidity index to measure the severity of chronic underlying conditions [18], validated as predictive of mortality among patients with SAB [3]. Acute severity of illness was assessed using the Pitt bacteremia score, measured retrospectively on the day before SAB was diagnosed, which has also been validated as a predictor for mortality in SAB [17]. Type of acquisition was classified as community-associated, healthcare-associated, or

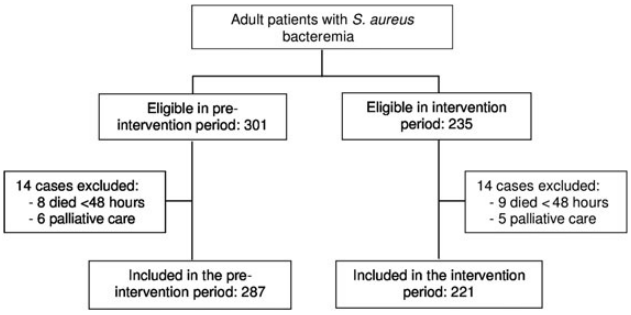

Figure 1. Flow chart of patients included in the multicenter quasi-experimental study.

nosocomial, following Friedman criteria [19]. Primary sources of SAB were defined according to the Centers for Disease Control and Prevention [20], and evaluated in consensus by 2 investigators in each on the participant centers. Sources of SAB associated with high mortality in previous studies were classified as high-risk sources; these included endocarditis, endovascular infections other than catheter-related, central nervous system infections, intra-abdominal infections, and respiratory tract infections [21, 22]. We considered empirical antibiotic treatment as appropriate if at least 1 active drug according to in vitro susceptibility results had been initiated in the first 12 hours after the blood culture was obtained. Persistent SAB was defined as the isolation of *S. aureus* in blood cultures obtained from peripheral veins for ≥3 days despite active antimicrobial therapy according to susceptibility testing. For the purpose of clinical decisions, SAB was considered as complicated if any of the following criteria were present: persistent bacteremia; development of endocarditis or metastatic foci; presence of Janeway lesions, Osler nodes, or other cutaneous or mucosal lesions suggestive of acute systemic infection (including petechiae, vasculitis, infarcts, ecchymoses, pustules, Roth spots, or conjunctival hemorrhage) in the absence of a firm alternate explanation [2]; presence of any permanent prosthetic device; any device-related infection where the device could not be removed in the first 3 days; and SAB in patients under chronic hemodialysis [2, 23–28]. We included the variable "unfavorable clinical course" to reflect the clinical situation in the same day the intervention was started (typically, 48 hours after the blood cultures were taken); it was defined as worsening or lack of evident improvement in the signs of sepsis [16] with regard to the situation the day the blood cultures were taken. Cure was defined as the absence of all signs and symptoms of infection and a negative blood culture at the end of antibiotic therapy [29]. Recurrence was defined as the isolation of *S. aureus* with the same susceptibility pattern from blood cultures or from a deep-seated focus in the following 3 months after clinical cure had been reached.

Microbiological Studies

The recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology were followed for performing, processing, and interpreting the blood cultures [30, 31]. Susceptibility testing was performed using accepted methods at each hospital.

Statistical Analysis

Crude comparisons were performed using the χ^2 or Fisher exact tests for percentages, as appropriate, and the Mann-Whitney *U* test for continuous variables. Relative risks with 95% confidence intervals (Cis) were calculated for the crude analysis of adherence to the indicators in the preintervention and intervention periods. Multivariate analyses were performed using logistic regression. Variables were selected using the backward stepwise procedure; *P* values <.2 and <.1 were used as cutoffs for including and deleting variables in the models, respectively. The predictive ability of the models was studied by the area under the receiver operating characteristic curves. Effect modifications between the exposure of interest and other variables were investigated. The software used for the analysis was the SPSS v17.0 package.

RESULTS

Systematic Review and Definition of Quality-of-Care Indicators

The search strategy retrieved 2828 articles. After reviewing the abstracts, 184 articles were fully reviewed and 81 were selected according to the preestablished criteria (see references in Supplementary Data). Six aspects of clinical management from 16 articles showing an impact on outcome were selected as QCIs (Table 2): performance of follow-up blood cultures; early source control; performance of echocardiography in patients with specific criteria; early use of intravenous cloxacillin in cases of methicillin-susceptible *S. aureus* (MSSA) (or cefazolin in patients under hemodialysis) as definitive therapy in nonallergic patients; adjustment of vancomycin dose according to trough levels; and provision of an appropriate duration of therapy according to the complexity of infection. The definitions of QCIs and the formulas used to measure them are shown in Table 2.

Analysis of the Impact of Intervention

During the study period, 536 episodes of SAB were diagnosed in adult patients admitted to the participating hospitals and were considered eligible for the study; 28 cases were excluded (Figure 1), so that 287 episodes were finally included in the preintervention period and 221 in the intervention period. The baseline demographics and clinical characteristics of the patients in both periods are shown in Table 3. The proportion of vascular catheter–related episodes was higher in the intervention

Table 3. Features of the Patients With *Staphylococcus aureus* Bacteremia

Variable	All Patients (n = 508)	Preintervention (n = 287)	Intervention (n = 221)	*P* Value
Median age, y, (IQR)	67 (55–76)	67 (55–75)	66 (56–77)	.63
Female sex	170 (33.5)	89 (31)	81 (36.7)	.18
Comorbidities				
Diabetes mellitus	148 (29.1)	83 (28.9)	65 (29.4)	.90
Chronic pulmonary disease	69 (13.6)	39 (13.6)	30 (13.6)	.99
Hemodialysis	46 (9.1)	21 (7.3)	25 (11.3)	.12
Malignancy	122 (24)	73 (25.4)	49 (22.2)	.39
Chronic liver disease	60 (11.8)	32 (11.1)	28 (12.7)	.59
Immunosuppression	73 (14.4)	42 (14.6)	31 (14)	.84
Intravenous drug abuse	9 (1.8)	7 (2.4)	2 (0.9)	.19
Endocarditis-predisposing condition	72 (14.2)	42 (14.6)	30 (13.6)	.73
Charlson index ≥2	331 (65.3)	191 (66.8)	140 (63.3)	.42
Pitt score >2	110 (21.7)	64 (22.3)	46 (22.2)	.79
Acquisition				
Hospital-acquired infection	292 (57.5)	165 (57.5)	127 (57.5)	.99
Healthcare-related bacteremia	132 (26)	73 (25.4)	59 (26.7)	.74
Source of bacteremia				
Vascular catheter	197 (38.8)	100 (34.8)	97 (43.9)	.04
Unknown source	172 (33.9)	95 (33.1)	77 (34.8)	.68
Skin and/or soft tissue	53 (10.4)	38 (13.2)	15 (6.8)	.02
Respiratory tract	25 (4.9)	13 (4.5)	12 (5.4)	.22
Osteoarticular	31 (6.1)	21 (7.3)	10 (4.5)	.19
High-risk source[a]	32 (6.3)	18 (6.3)	14 (6.3)	.97
Complicated bacteremia	238 (46.9)	140 (48.8)	98 (44.3)	.32
MRSA	102 (20.1)	57 (19.9)	45 (20.4)	.89
Endocarditis (primary and secondary)[b]	22/180 (12.2)	11/83 (13.3)	11/97 (11.3)	.69
Appropriate empirical therapy	125 (80.1)	65 (75.6)	60 (85.7)	.12
Severe sepsis or septic shock	120 (22.4)	71 (24.2)	46 (20.9)	.51
Unfavorable course[c]	179 (35.2)	96 (33.4)	83 (37.6)	.33

Data are expressed as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] High-risk source: endocarditis, nervous central system, abdominal, and respiratory.

[b] Considered only among patients for whom echocardiography was performed.

[c] Considered the day the blood culture results were reported as defined in the Methods.

period, whereas those related to a skin and soft tissue infection were less frequent.

The crude comparison of adherence to QCIs between the preintervention and intervention periods is shown in Table 4. Adherence significantly improved during the intervention period for all QCIs except for adjustment of vancomycin dose according to trough levels. All centers increased the adherence to at least 4 QCIs; a statistically significant improvement (eg, $P < .05$) to at least 2 QCIs was seen in 9 participant centers (it should be noted that the number of cases was low in some centers). The median percentage of improvement for each QCI and interquartile range is shown in Table 4. To control the effect of potential confounders on the effect of the intervention, we carried out multivariate analyses (Table 4). In summary, the intervention was independently associated with improved adherence to follow-up blood cultures (from 61.2% to 80.3% in the different hospitals), source control (from 70.2% to 90.3%), echocardiography in patients with complicated bacteremia (from 52.8% to 73.3%), early cloxacillin in MSSA (from 56.9% to 76.3%), and appropriate duration of treatment depending on clinical complexity (from 72.9% to 85.2%).

Crude analysis showed a higher 14-day mortality rate in the preintervention period than in the intervention period (51/287 [17.8%] vs 25/221 [11.3%], $P = .04$), whereas the difference for 30-day mortality was not statistically significant (64/287 [22.3%] vs 37/221 [16.7%], $P = .12$). Recurrence of SAB at 90 days showed no significant differences (3/287 [1%] vs 2/221 [0.9%]; RR = 0.86; 95% CI, .14–5.13; $P = .87$). Ninety-day

Table 4. Adherence to Quality-of-Care Indicators

Quality-of-Care Indicator	Preintervention Period	Intervention Period	Median Improvement in Percentage of Adherence to QCI (IQR)	Relative Risk for Adherence to CQI (95% CI)	*P* Value	Adjusted OR for Adherence to QCI (95% CI)[a]	*P* Value
Follow-up blood culture	131/214 (61.2)	159/198 (80.3)	25 (5.9–54.4)	1.31 (1.15–1.49)	<.001	2.83 (1.78–4.49)[b]	<.001
Source control	86/122 (70.2)	105/115 (91.3)	22 (10.2–50)	1.29 (1.13–1.49)	<.001	4.56 (2.12–9.79)[c]	<.001
Echocardiography	76/144 (52.8)	74/101 (73.3)	18.8 (0–65.7)	1.38 (1.13–1.68)	.001	2.50 (1.42–4.41)[d]	.002
Early cloxacillin in MSSA	120/211 (56.9)	124/174 (71.3)	11.1 (0–51.1)	1.25 (1.07–1.45)	.014	1.79 (1.15–2.78)[e]	.009
Vancomycin dosing	23/49 (46.9)	30/54 (55.6)	20 (0–54.3)	1.18 (.80–1.73)	.38	1.42 (.65–3.10)[f]	.38
Treatment duration	151/207 (72.9)	161/189 (85.2)	10.2 (2–20.2)	1.16 (1.05–1.29)	.003	2.13 (1.24–3.64)[g]	.006

Data are expressed as No. (%) of patients except otherwise indicated.

Abbreviations: CI, confidence interval; IQR, interquartile range; MSSA, methicillin-susceptible *Staphylococcus aureus*; OR, odds ratio; QCI, quality-of-care indicator.

[a] Adjusted ORs were calculated by multivariate analyses.

The variables included in final models were: [b]Unfavorable clinical course and catheter source; [c]Type of acquisition; [d]Catheter source and Charlson index; [e]Catheter source, Charlson index and type of acquisition; [f]Catheter source; [g]Complicated bacteremia, Charlson index, and catheter source.

mortality was higher in the preintervention group, although without statistical significance (97/287 [33.8%] vs 59/162 [26.7%]; relative risk [RR] = 0.78; 95% CI, .60–1.03; $P = .08$). We then performed specific analyses to evaluate the impact of the intervention on 14-day and 30-day mortality. First, we performed univariate analyses of the association of different variables with mortality (Tables 5 and 6). The variables age ≥60 years, source other than catheter, Pitt score >2, and intervention period were associated with 14- and 30 day mortality. Multivariate analyses are shown in Table 7; the clinical intervention was independently associated with a decrease in 14-day and 30-day mortality after controlling for potential confounders in the multivariate analysis. The results did not significantly change when the variable source was considered as polychotomous (eg, all the sources were included) instead of the dichotomized low/high-risk sources. Including the variable "preintervention bacteremia program" was not associated with mortality and did not influence the impact of the intervention.

DISCUSSION

Our study shows that a bundle intervention aimed at improving the adherence to selected evidence-based QCI indicators in the management of SAB was effective and associated with reduced mortality.

The management of patients with bacteremia is complex. Widely recognized important aspects of management includes providing early adequate support and antimicrobial therapy, identifying potential foci which should be properly and timely controlled, and active workup and follow-up to promptly detect complications [8]. Advice from infectious diseases specialists has been shown to reduce inappropriate treatment and time to first administration of an active drug and to produce better clinical management of sepsis [32, 33]. In the specific case of SAB, some previous studies showed that infectious diseases specialists' consultation was associated with better management and, in some studies, with a better prognosis [9–15]. A summary of the adherence to the 6 QCIs used in this study as reported in previous studies is shown in Supplementary Table 3.

The use of QCIs is useful for evaluating and monitoring different aspects of healthcare procedures. Indicators are quantitative measures that should be sufficiently sensitive, specific, valid, and reliable to evaluate those aspects of care that influence appropriately defined outcomes, and they should be ideally evidence based [34, 35]. Management of SAB is clinically challenging and has been demonstrated as importantly influencing outcome, making it a suitable process for defining QCIs. To our knowledge, QCIs for SAB management had not previously been established using an appropriate methodology; by using a systematic review of the literature we were able to identify key aspects for SAB management that were amenable for designing an intervention.

During the intervention period, adherence to CQI was significantly and independently improved except for adjustment of vancomycin dose according to trough levels, probably due to the lower number of patients in this subset. These results demonstrate that it is possible to improve the clinical management of SAB with an intervention based on quality-of-care indicators. We think that the use of a structured form for making recommendations, which could then be included in the medical records, was crucial to achieving these results; apart from providing clear and structured recommendations, the form was also useful for reminding the infectious diseases specialists of

Table 5. Univariate Analysis of Variables Associated With 14-Day Mortality

Variable	Dead/Exposed, No. (%)	RR (95% CI)	*P* Value
Age			
<60 y	14 (8.1)	Ref	
≥60 y	62 (18.5)	2.26 (1.30–3.92)	.002
Hospital service			
Surgical	8/81 (8.9)	Ref	Ref
Medical	47/355 (13.2)	1.34 (.66–2.72)	.51
ICU	21/72 (29.2)	2.20 (1.40–3.44)	.002
Acquisition			
Hospital-acquired	44/292 (15.1)	Ref	
Community-onset	13/84 (15.5)	1.02 (.58–1.81)	.93
Source			
Catheter	18/197 (9.1)	Ref	Ref
Unknown	33/172 (19.2)	2.09 (1.22–3.59)	.005
Respiratory	10/25 (40)	4.37 (2.28–8.39)	<.001
Skin and/or soft tissue	7/53 (13.2)	1.44 (.63–3.27)	.38
Pitt score			
≤2	38/371 (10.2)	Ref	
>2	31/110 (28.2)	3.63 (2.28–5.78)	<.001
Susceptibility			
MRSA	10/102 (9.8)	Ref	
MSSA	66/406 (16.3)	1.65 (.84–3.10)	.10
Complicated bacteremia			
No	40/270 (14.8)	Ref	
Yes	36/238 (15.1)	1.02 (.67–1.54)	.92
Empirical treatment			
Inappropriate	12/91 (13.2)	Ref	
Appropriate	52/374 (13.9)	1.05 (.58–1.89)	.86
Hospital with "bacteremia program"			
No	26/151 (17.2)	0.81 (.52–1.25)	.35
Yes	50/357 (14)	Ref	
Intervention period			
Preintervention	51/287 (17.8)	Ref	
Intervention	25/221 (11.3)	0.46 (.29–0.72)	.04

Abbreviations: CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; RR, relative risk.

Table 6. Univariate Analysis of Variables Associated With 30-Day Mortality

Variable	Dead/Exposed, No. (%)	RR (95% CI)	*P* Value
Age			
<60 y	17/172 (9.9)	Ref	
≥60 y	84/336 (25)	2.52 (1.55–4.11)	<.001
Hospital service			
Surgical	10/81 (11.3)	Ref	Ref
Medical	62/355 (17.5)	1.41 (.75–2.63)	.26
ICU	29/72 (40.3)	1.76 (1.10–2.82)	<.001
Acquisition			
Hospital-acquired infection	57/292 (19.5)	Ref	
Community-onset	15/84 (17.9)	0.09 (.58–1.12)	.73
Source			
Catheter	30/197 (15.2)	Ref	Ref
Unknown	40/172 (20.3)	1.52 (.99–2.34)	.05
Respiratory	14/25 (56)	3.67 (2.27–5.93)	<.001
Skin and/or soft tissue	13/53 (13.2)	0.86 (.40–1.86)	.71
Pitt score			
≤2	57/371 (15.4)	Ref	
>2	36/110 (32.7)	2.13 (1.48–3.04)	<.001
Susceptibility			
MRSA	18/102 (17.6)	Ref	
MSSA	83/406 (20.4)	0.86 (.54–1.36)	.52
Complicated bacteremia			
No	51/270 (18.9)	Ref	
Yes	50/238 (21)	1.11 (.78–1.57)	.55
Empirical treatment			
Inappropriate	19/91 (20.9)	1.14 (.72–1.80)	.55
Appropriate	68/374 (18.2)	Ref	
Hospital with "bacteremia program"			
No	29/151 (19.2)	1.05 (.71–1.54)	.80
Yes	72/357 (20.2)	Ref	
Intervention period			
Preintervention	64/287 (22.3)	Ref	
Intervention	37/221 (16.7)	0.75 (.42–1.08)	.12

Abbreviations: CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; RR, relative risk.

all the key aspects to consider for the management of patients with SAB in a convenient and timely manner.

The intervention was also associated with lower mortality. The crude association found might be influenced by the different proportion of some variables potentially affecting outcome (confounders), such as the source of SAB. In relation with the source of bacteremia, catheter-related SAB was more frequent in the intervention period; catheter-related bacteremia is usually associated with lower mortality, whereas others such as respiratory tract infections have a higher mortality rate [36]. To control for the effect of source, this variable was included in the multivariate models both as a polychotomous (all the sources) and as a dichotomous variable (low- and high-risk sources); the results were similar and showed that mortality was lower during the intervention period. However, it is possible that it was not the specific way that intervention was performed that caused the reduction in mortality; unmeasured aspects of improved management of the patients may have also had an impact on these results. Whatever the reason, implementing the intervention

Table 7. Multivariate Analyses of Variables Associated With 14- and 30-Day Mortality Among Patients With *Staphylococcus aureus* Bacteremia

Variables	OR (95% CI)	*P* Value
14-day mortality		
Age >60 y	2.97 (1.51–5.87)	.002
Pitt score >2	3.04 (1.74–5.33)	<.001
High-risk source[a]	2.80 (1.32–5.92)	.007
Intervention	0.49 (.28–.87)	.016
30-day mortality		
Age >60 y	3.48 (1.89–6.41)	<.001
Pitt score >2	2.34 (1.40–3.92)	.001
High-risk source[a]	3.11 (1.54–6.26)	.001
Intervention	0.59 (.36–.97)	.04

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]High-risk source includes endovascular sources different than catheter, endocarditis, nervous central system infections, intra-abdominal infections, and respiratory tract infection.

had a positive impact. As in all bundle interventions, it is difficult to identify the impact of individual measures; we hypothesize that all or several measures act synergistically, although more studies would be needed to identify the essential components of the intervention.

Some of the limitations of previous studies include their retrospective nature [11, 14, 15]; that the way the recommendations were provided were not structured [11] or were unspecified [12, 15]; and that they were performed in one center.

Our study has limitations that should be taken into account. It has the inherent limitations of quasi-experimental, before–after designs [37–40]. Although our methodology tried to control for potential confounding factors by using multivariate analysis, it is possible that other unmeasured factors influenced the results. The strengths of our study include its multicenter and prospective design, the use of evidence-based indicators and a structured intervention that can easily be replicated and incorporated into clinical practice, and the control for the effect of confounders.

In conclusion, our results suggest that it is possible to improve the clinical management and outcome of SAB by providing specialized, structured recommendations aimed at improving adherence to evidence-based QCIs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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