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Original article

Impact of adherence to individual quality-of-care indicators on the prognosis of bloodstream infection due to *Staphylococcus aureus*: a prospective observational multicentre cohort☆

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ABSTRACT

Objectives: To analyse the adherence and impact of quality-of-care indicators (QCIs) in the management of *Staphylococcus aureus* bloodstream infection in a prospective and multicentre cohort.
Methods: Analysis of the prospective, multicentre international *S. Aureus* Collaboration cohort of *S. Aureus* bloodstream infection cases observed between January 2013 and April 2015. Multivariable analysis was performed to evaluate the impact of adherence to QCIs on 90-day mortality.
Results: A total of 1784 cases were included. Overall, 90-day mortality was 29.9% and mean follow-up period was 118 days. Adherence was 67% (n = 1180/1762) for follow-up blood cultures, 31% (n = 416/1342) for early focus control, 77.6% (n = 546/704) for performance of echocardiography, 75.5% (n = 1348/1784) for adequacy of targeted antimicrobial therapy, 88.6% (n = 851/960) for adequacy of treatment duration in non-complicated bloodstream infections and 61.2% (n = 366/598) in complicated bloodstream infections. Full bundle adherence was 18.4% (n = 328/1784). After controlling for immortal time bias and potential confounders, focus control (adjusted hazard ratio = 0.76; 95% CI, 0.59–0.99; p 0.038) and adequate targeted antimicrobial therapy (adjusted hazard ratio = 0.75; 95% CI, 0.61–0.91; p 0.004) were associated with low 90-day mortality.
Discussion: Adherence to QCIs in *S. Aureus* bloodstream infection did not reach expected rates. Apart from the benefits of application as a bundle, focus control and adequate targeted therapy were independently associated with low mortality. **Francesc Escrihuela-Vidal, Clin Microbiol Infect 2023;29:498**

Introduction

Bloodstream infections are the result of different and heterogeneous types of infection. For more than 20 years, a number of published studies have demonstrated the association between clinical management by infectious diseases specialists and better adherence to clinical quality-of-care indicators (QCIs) [1].

In *Staphylococcus aureus* bloodstream infection (SAB), a systematic review and meta-analysis including 18 studies and 5337 patients showed that clinical management by infectious diseases specialists was associated with lower 30- and 90-day mortality and lower rates of relapse of SAB [2]. Clinical management and outcome of SAB have been well studied, and adherence to five QCIs has been shown to be associated with a favourable prognosis [3]. A structured intervention aimed at improving the implementation of these QCIs, as a bundle, has been shown to provide additional benefits in terms of mortality [4,5]. Surprisingly, their application is heterogeneous and often worse than desired [6,7]. Finally, the specific impact of adherence to each component of the bundle has not been analysed in studies of sufficient sample size. Our objectives were to analyse the rate of adherence and clinical impact of each of these QCIs in a large multicentre international cohort of patients with SAB.

Methods

Design

This analysis forms part of the International *S. Aureus* Collaboration (ISAC) study, a prospective, international cohort study conducted in 11 tertiary care hospitals in five countries: Germany (2 centres), Korea (1), Spain (2), Taiwan (1), and the United Kingdom (5). Data pertaining to all the consecutive cases of SAB between 1 January 2013 and 30 April 2015 were collected. The study protocol was registered in ClinicalTrials.gov in March 2014 (NCT02098850), and details of the methods were also published [8].

Ethical approval

Ethical approval was obtained at each study centre in accordance with local regulations. Informed consent from patients was sought for follow-up visits. At some centres, the study was conducted as part of a service evaluation and informed consent was waived by the Ethics Review Committee or relevant national authority.

Participants

Consecutive adult patients (18 years or older) with clinical signs and/or symptoms of infection and monomicrobial bloodstream infection due to *S. aureus* were prospectively included. Cases where *S. aureus* was isolated together with another pathogen considered to be a skin contaminant such as coagulase-negative staphylococci, diphtheroids and other common skin contaminants, typically isolated from a single blood culture, were also included. Only patients from centres with >25 SAB cases during the study period were included to avoid potential selection bias. Exclusion criteria were SAB in the previous 12 weeks and death within ≤72 hours after the blood culture was taken to reduce immortal time bias because management interventions were not possible in these patients.

Patients were followed for up to 90 days. Whenever possible, survival data were confirmed by the national death register data. Patients lost during follow-up were censored at the date of their last visit or the last known date of interaction with healthcare system (if available).

Variables and definitions

The variables and definitions used in the present study were published previously [8]. Data were prospectively collected by medical staff and reviewed by an infectious disease physician or clinical microbiologist.

Table 1
Characteristics of patients with *Staphylococcus aureus* bloodstream infection ($n = 1784$), univariate analysis of variables associated with 90-day mortality, including quality-of-care indicators and Cox regression model of variables associated with 90-day mortality in the general cohort

	Total (percentage)	Alive	Death	Hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)	p
Age							
<60 y	665 (37.3%)	533 (80.2%)	132 (19.8%)	Ref			
>60 y	1119 (62.7%)	717 (64.1%)	402 (35.9%)	1.81 (1.52–2.15)	0.000	1.51 (1.21–1.90)	**0.000**
Gender							
Female	640 (35.9%)	444 (69.4%)	196 (30.6%)	Ref			
Male	1144 (64.1%)	806 (70.5%)	338 (29.5%)	0.96 (0.83–1.12)	0.666	0.91 (0.76–1.09)	0.301
Charlson							
<2 points	237 (13.3%)	211 (89.0%)	26 (11%)	Ref			
≥2 points	1547 (86.7%)	1039 (67.2%)	508 (32.8%)	2.99 (2.07–4.33)	0.000	1.98 (1.27–3.10)	0.003
Comorbidities							
Chemotherapy	140 (7.8%)	97 (69.3%)	43 (30.7%)	1.02 (0.78–1.32)	0.923	1.16 (0.81–1.66)	0.431
Steroids	115 (6.4%)	75 (65.2%)	40 (34.8%)	1.18 (0.91–1.53)	0.248	1.11 (0.79–1.56)	0.531
Neutropenia	54 (3.0%)	40 (74.1%)	14 (25.9%)	0.86 (0.55–1.36)	0.651	0.71 (0.39–1.31)	0.273
Other immunosuppressions (IS)	105 (5.9%)	72 (68.6%)	33 (31.4%)	1.05 (0.79-1.41)	0.742	1.18 (0.78–1.78)	0.437
Organ/marrow	71 (4.0%)	52 (73.2%)	19 (26.8%)	0.89 (0.60–1.32)	0.599	0.82 (0.48–1.41)	0.476
HIV infection	26 (1.5%)	19 (73.1%)	7 (26.9%)	0.90 (0.47–1.70)	0.831	1.24 (0.58–2.65)	0.588
I.V. drug	86 (4.8%)	71 (82.6%)	15 (17.4%)	0.57 (0.36–0.91)	0.010	1.08 (0.62–1.90)	0.790
Acquisition							
Community	557 (31.2%)	414 (74.3%)	143 (25.7%)	Ref		1.17 (0.96–1.45)	**0.130**
Healthcare	1227 (68.8%)	836 (68.1%)	391 (31.9%)	1.24 (1.05–1.46)	0.009		
Dominant focus of *S. aureus* blood stream infection (SAB)						1.02 (0.99–1.06)	0.245
Catheter	434 (24.3%)	338 (77.9%)	96 (22.1%)	0.68 (0.56–0.83)	0.000		
Skin/soft tissue	522 (29.3%)	383 (73.4%)	139 (26.6%)	0.85 (0.72–1.00)	0.053		
Infective endocarditis (IE)	137 (7.7%)	89 (65.0%)	48 (35.0%)	1.19 (0.93–1.51)	0.175		
Respiratory	136 (7.6%)	71 (52.2%)	65 (47.8%)	1.68 (1.39–2.03)	0.000		
Osteoarticular	248 (13.9%)	191 (77.0%)	57 (23.0%)	0.74 (0.58–0.94)	0.010		
Unknown	307 (17.2%)	179 (58.0%)	129 (42.0%)	1.53 (1.21–1.79)	0.000		
High-risk [a]	273 (15.3%)	160 (58.6%)	113 (41.4%)	1.49 (1.26–1.75)	0.000		
Resistance to methicillin							
Methicillin susceptible *Staphylococcus aureus* (MSSA)	1458 (81.7%)	1043 (71.5%)	415 (28.5%)	Ref			
Methicillin resistant *Staphylococcus aureus* (MRSA)	326 (18.3%)	207 (63.5%)	119 (36.5%)	1.28 (1.09–1.51)	0.005	1.18 (0.96–1.46)	**0.124**
ID evaluation						0.85 (0.68–1.05)	**0.132**
Performed	1455 (81.6%)	1033 (71.0%)	422 (29.0%)	Ref			
Not performed	329 (18.4%)	217 (66.0%)	112 (34.0%)	1.17 (1.00–1.39)	0.072		
Sepsis or septic shock						2.65 (2.04–3.44)	**0.000**
No sepsis or shock	461 (25.8%)	395 (85.7%)	66 (14.3%)	Ref			
Sepsis or shock present	1323 (74.2%)	855 (64.6%)	468 (35.4%)	2.47 (1.95–3.13)	0.000		
Complicated SAB							
Non-complicated	1050 (58.9%)	752 (71.6%)	298 (28.4%)	Ref			
Complicated	734 (41.1%)	498 (67.8%)	236 (32.2%)	1.13 (0.98–1.31)	0.092	1.16 (.97–1.40)	**0.107**
High-risk centre						1.34 (1.12–1.60)	**0.002**
No	1079 (60.5%)	626 (75.7%)	201 (24.3%)	Ref			
Yes	705 (39.5%)	624 (65.2%)	333 (34.8%)	1.43 (1.23–1.66)	0.000		
Adequate empirical antimicrobial therapy						0.75 (0.56–1.00)	**0.050**
Yes	1634 (91.6%)	1152 (92.2%)	482 (90.3%)	Ref			
No	150 (8.4%)	98 (7.8%)	52 (9.7%)	1.18 (0.93–1.48)	0.193		
Quality-of-care indicators							
Follow-up culture							
Not performed	582/1762 (33.0%)	405 (69.6%)	177 (30.4%)	Ref			
Performed	1180/1762 (66.9%)	845 (71.6%)	335 (28.4%)	0.93 (0.80–1.08)	0.410		
Early focus control							
Not performed	839/1342 (62.5%)	603 (71.9%)	236 (28.1%)	Ref	Ref		
Early	416/1342 (31%)	323 (77.6%)	93 (22.4%)	0.79 (0.64–0.98)	**0.033**		
Late	87/1342 (6.5%)	75 (86.2%)	12 (13.8%)	0.49 (0.29–0.84)	**0.006**		
Echocardiography							
Not performed	158/704 (22.4%)	101 (63.9%)	57 (36.1%)	Ref	Ref		
≤7 d	437/704 (62.1%)	316 (72.3%)	121 (27.7%)	0.76 (0.59–0.99)	0.061		
>7 d	109/704 (15.5%)	81 (74.3%)	28 (25.7%)	0.71 (0.49–1.04)	0.097		
Adequate targeted antimicrobial							
No	436/1784 (24.4%)	291 (66.7%)	145 (33.3%)	Ref			
Yes	1348/1784 (75.5%)	959 (71.1%)	389 (28.9%)	0.86 (0.74–1.02)	0.090		
Adequate duration of antimicrobial therapy							
No	341/1558 (21.9%)	274 (80.4%)	67 (19.6%)	Ref			
Yes	1217/1558 (78.1%)	976 (80.2%)	241 (19.8%)	1.01 (0.79–1.28)	1.000		
Adequate duration of antimicrobial therapy (uncomplicated)							
No	109/960 (11.4%)	80 (73.4%)	29 (26.6%)	Ref			
Yes	851/960 (88.6%)	672 (79.0%)	179 (21.0%)	0.79 (0.56–1.11)	0.228		

Table 1 (*continued*)

	Total (percentage)	Alive	Death	Hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)	p
Adequate duration of antimicrobial therapy (complicated)							
No	232/598 (38.8%)	194 (83.6%)	38 (16.4%)	Ref			
Yes	366/598 (61.2%)	304 (83.1%)	62 (16.9%)	1.03 (0.72–1.50)	0.947		

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bloodstream infection. [a]High-risk focus: endocarditis, central nervous system, abdominal and respiratory [4,15].

The primary outcome was overall 90-day mortality, based on previous consensus definitions [9]. The main exposure variables were the proportion of patients with adherence to the different QCI among those in whom each specific QCI was feasible. The QCIs collected included performance of follow-up blood cultures, early focus control, performance of transthoracic or transoesophageal echocardiography, adequate antimicrobial therapy [10], and adequate duration of therapy [11]; their definitions and criteria for being excluded from the denominators for each of them are presented in Table S1. The duration of therapy considered both intravenous and oral antimicrobials. Empirical treatment was considered adequate according to *in vitro* activity of the antimicrobial used. For evaluation of treatment duration and to avoid immortal time bias only patients who survived for at least 10 or 28 days were evaluated in non-complicated and complicated cases, respectively. Landmark times were established for each QCI, and analyses were performed only on those patients alive at day 5 (for performance of follow-up blood cultures and focus control), day 7 (for performance of echocardiography), day 10 (for duration of treatment in patients with uncomplicated SAB) and day 28 (for duration of treatment in patients with complicated SAB). Adherence to treatment duration was considered adequate in patients who died while on treatment if the other QCIs were fulfilled.

Type of acquisition was defined according to Friedman's criteria [12]. Severity of infection on the day the first blood culture was positive was evaluated using the 'Sepsis-related Organ Failure Assessment' score [13]. The focus of bloodstream infection was defined according to the infectious disease physician's evaluation and complementary microbiological results. In complex cases with two or more possible foci, a hierarchical ranking was established to assign the focus (dominant focus), as defined previously [14,15], namely, endocarditis > osteoarticular > pneumonia > other deep focus > surgical wound > skin and soft tissue > central venous catheter > peripheral venous catheter. Persistent bloodstream infection was defined as isolation of *S. aureus* with the same phenotype in follow-up blood cultures after at least 48 hours of treatment with an *in vitro* active intravenous drug. Septic metastases were defined as diagnosis of a distant infection at a previously sterile site.

For clinical decision-making purposes, SAB was considered complicated if any of the following criteria were present: (a) persistent bloodstream infection, (b) endocarditis, (c) metastatic foci or a deep-seated focus such as osteoarticular infection or visceral abscess, (d) and the presence of any device-related infection where the device could not be completely removed within the first 3 days [16,17].

Statistical analysis

Univariate comparisons were performed using the chi-square or Fisher tests for qualitative variables and the Student *t* test or Mann-Whitney U test for continuous variables, as appropriate. Univariate analyses of factors potentially associated with in-hospital (death during index hospitalization) and 90-day mortality, including the QCIs, were performed by univariate Cox regression. The adjusted impact of each QCI on mortality was analysed in a two-step procedure. First, a general Cox regression model was performed to identify variables associated with mortality. Second, variables with a univariate $p < 0.20$ in that model were used to control for their possible confounding effect on the impact of each QCI on mortality. Because the populations for which each QCI could be evaluated were different, to avoid immortal time bias, a model that included

Table 2
Rate of adherence to quality-of-care indicators

Quality-of-care indicator	Adherence	Excluded patients and reasons
Follow-up blood culture	66.9% (1180/1762)	Death occurred before day 5 in 22/1784 patients (1.2%)
Performed		
Early focus control	31% (416/1342)	Focus not amenable to control in 442/1784 patients (24.8%)
Performed early	6.5% (87/1342)	
Performed late	62.5% (839/1342)	
Not performed		
Echocardiography, first 7 d	62.1% (437/704)	Not indicated in 989/1784 patients (55.4%)
Performed before day 7	15.5% (109/704)	Death occurred before day 7 in 81/1784 patients (5.1%)
Performed after day 7	22.4% (158/704)	
Not performed		
Adequate targeted antimicrobial therapy	75.5% (1348/1784)	Death occurred before day 10 in 90/1050 patients (8.6%)
Adequate	72.5% (1057/1458)	
Adequate, MSSA	89.3% (291/326)	
Adequate, MRSA		
Treatment duration in uncomplicated SAB[a]	88.6% (851/960)	Death occurred before day 10 in 90/1050 (8.6%)
Adequate		
Treatment duration in complicated SAB[b]	61.2% (366/598)	Death occurred before day 28 in 136/734 (18.5%)
Adequate		

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bloodstream infection.
[a] Patients who survived for at least 10 days were included.
[b] Patients who survived for at least 28 days were included.

the dichotomous variable 'performance of the rest of the bundle' was built for each QCI. In addition to establishing landmark times, the 'performance of echocardiography' and 'focus control' of QCIs were analysed as time-dependent variables to avoid further immortal time bias. Centres were grouped into low- and high-risk on the basis of their 30-day mortalities using regression tree analysis, and this variable was included in the multivariable analysis to control for the effect of centre [8]. SPSS 18.0 software (IBM SPSS, Chicago, IL, USA) and TreeNet software (Salford Systems) were used for statistical analysis.

Results

During the study period, 2021 eligible cases of SAB were included. Fifty-nine patients from three hospitals were excluded because the hospitals in question recruited fewer than 25 cases over 2 years, 70 were excluded because of SAB in the previous 12 weeks, and 108 because they died in the first 72 hours. Therefore, 1784 cases were included in the final analysis. There were no missing data regarding relevant variables. There were 41 cases lost to 90-day follow-up, with a median time of follow-up of 28.5 days.

Patient characteristics are summarized in Table 1; the median age was 65 years (interquartile range [IQR], 52–77), and 640 (35.9%) were women. The most frequent foci of SAB were skin and soft tissue (522/1784 patients; 29.3%) and vascular catheter infection (434/1784; 24.3%). Endocarditis was diagnosed in 137/1784 cases (7.7%). The focus was unknown in 17.2% of cases (306/1784), and the focus was microbiologically confirmed in 539/1784 (30.2%). Overall, 27% (482/1784) of the patients presented with septic shock and 41.1% (734/1784) had complicated SAB. Empirical treatment was considered adequate in 1634 of 1784 cases (91.6%). In-hospital mortality was 20.9% (372/1784 cases) and 90-day mortality was 29.9% (534/1784 cases); the latter was 32.2% (236/734 cases) in patients with complicated bloodstream infection and 28.4% (298/1049 cases) in those with uncomplicated bloodstream infection. Mean follow-up for surviving patients was 118 days (IQR, 94–187).

Rates of adherence to the QCIs are shown in Table 2. The mean treatment duration in patients with complicated bacteraemia not adhering to the QCI was 16 days (IQR, 13–20). The full bundle was adhered to in 18.4% of cases (328/1784).

In univariate analysis, early or late focus control and adequate targeted therapy were associated with lower in-hospital mortality, whereas only early or late focus control was significantly associated with a protective effect for 90-day mortality. Performance of echocardiography (early or late) and appropriate targeted therapy were nonsignificantly associated with low 90-day mortality (Table 1).

The multivariable analysis is shown in Table 1. The following variables showing $p < 0.20$ for their association with 90-day mortality were potential confounders for the effect of QCI: age ≥60 years old, Charlson index ≥2 points, community acquisition, complicated bloodstream infection, methicillin-resistant *S. aureus* infection, sepsis or septic shock, high-risk centre and adequate empirical therapy. The dominant focus of infection was also included because of its clinical relevance. Multivariable models (one per QCI) were then built to provide an estimate of the impact of each QCI on 90-day mortality, adjusted for the previously identified general mortality predictors (Table 3 and Fig. 1). Focus control (adjusted hazard ratio = 0.76; 95% CI, 0.59–0.99; p 0.038) and adequate targeted antimicrobial therapy (adjusted hazard ratio = 0.75; 95% CI, 0.61–0.91; p 0.004) were associated with low 90-day mortality, whereas follow-up blood cultures before day 5 and adequate duration of therapy were not. The estimate for the

Table 3
Multivariable analysis of variables associated with 90-day mortality in patients with *Staphylococcus aureus* bloodstream infection according to performance of quality-of-care clinical indicators

	Follow-up blood cultures before day 5 ($N = 1762$)		Echocardiography [a] ($N = 704$)		Focus control [a] ($N = 1232$)		Adequate targeted antimicrobial therapy ($N = 1784$)		Duration of therapy ($N = 1217$)	
	Adjusted hazard ratio (aHR) (95% CI)	p	aHR (95% CI)	p	aHR (95% CI)	p	aHR (95% CI)	p	aHR (95% CI)	p
Performance of the quality-of-care indicator	0.89 (0.73–1.09)	0.258	0.73 (0.52–1.01)	0.058	0.76 (0.59–0.99)	**0.038**	0.75 (0.61–0.91)	**0.004**	0.85 (0.63–1.16)	0.307
Performance of rest of the bundle	0.98 (0.80–1.20)	0.826	1.41 (0.99–2.01)	0.058	1.03 (0.82–1.28)	0.816	1.01 (0.82–1.24)	0.948	0.87 (0.66–1.14)	0.315
Age ≥ 60 y	1.54 (1.23–1.92)	**0.000**	1.43 (1.01–2.02)	**0.047**	1.65 (1.25–2.19)	**0.000**	1.51 (1.22–1.88)	**0.000**	1.52 (1.15–2.02)	**0.003**
Charlson index ≥ 2 points	1.97 (1.26–3.06)	**0.003**	1.40 (0.76–2.60)	0.281	1.74 (1.03–2.92)	**0.037**	1.96 (1.27–3.03)	**0.002**	2.41 (1.34–4.32)	**0.003**
Community acquisition	1.17 (.95–1.44)	0.134	1.14 (0.82–1.58)	0.435	1.28 (0.97–1.69)	0.079	1.18 (0.96–1.45)	0.109	1.17 (.89–1.54)	0.260
Focus of infection	1.02 (.99–1.06)	0.257	.95 (.90–1.01)	0.077	1.00 (0.95–1.06)	0.992	1.02 (0.98–1.05)	0.395	1.02 (.97–1.07)	0.519
Complicated bloodstream infection	1.27 (1.05–1.54)	**0.016**	b	b	1.40 (1.11–1.76)	**0.004**	1.21 (1.00–1.45)	0.047	.69 (.52–.91)	**0.007**
Methicillin-resistant *Staphylococcus aureus*	1.15 (.93–1.43)	0.203	1.05 (.75–1.48)	0.763	1.23 (.95–1.60)	0.115	1.24 (1.00–1.53)	0.051	1.05 (.78–1.40)	0.765
Sepsis or septic shock	2.49 (1.92–3.24)	**0.000**	2.56 (1.66–3.94)	**0.000**	2.36 (1.74–3.21)	**0.000**	2.61 (2.01–3.39)	**0.000**	1.87 (1.39–2.52)	**0.000**
High-risk centre	1.29 (1.07–1.56)	**0.007**	1.05 (0.77–1.42)	0.753	1.19 (0.94–1.49)	0.145	1.35 (1.13–1.61)	**0.001**	1.07 (0.84–1.37)	0.584
Adequate empirical therapy	0.76 (0.57–1.02)	0.065	0.88 (0.52–1.47)	0.621	0.73 (0.51–1.05)	0.093	0.78 (0.59–1.04)	0.094	1.03 (0.66–1.59)	0.909
ID evaluation	0.90 (0.71–1.13)	0.371	1.17 (0.74–1.86)	0.508	1.05 (0.77–1.42)	0.760	0.88 (0.71–1.09)	**0.235**	0.97 (0.73–1.30)	0.851

[a] Echocardiography and focus control were analysed as time-dependent variables.
[b] Echocardiography was only considered in complicated cases.

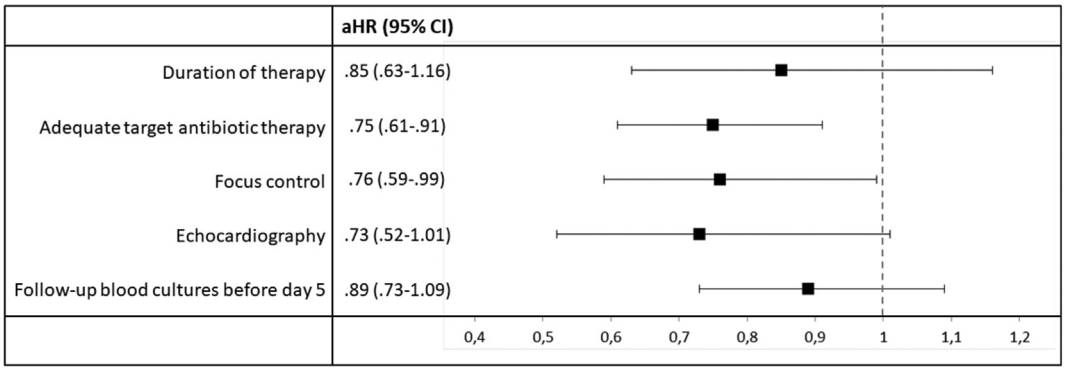

Fig. 1. Multivariable analysis of variables associated with 90-day mortality among patients with *Staphylococcus aureus* bloodstream infection according to performance of quality-of-care clinical indicators. * Multivariable analysis was performed including the following correcting variables: performance of the rest of the bundle, age ≥60 years, Charlson index ≥2 points, community acquisition, focus of infection, complicated bloodstream infection, methicillin-resistant *Staphylococcus aureus*, sepsis or septic shock, high-risk centre, and adequate empirical therapy. A detailed description can be found in Supplementary Table E.

performance of echocardiography did not achieve statistical significance although the upper limit of the confidence interval was close to 1.

Discussion

Management of SAB is highly heterogeneous, even among infectious disease physicians [7,18]. Adherence to a QCI bundle in the management of SAB improves patient management and is associated with low mortality rates [4,19].

Several studies have shown that the involvement of an infectious diseases specialist is associated with improved management and outcomes in patients with SAB [2]; implementation of a multimodal approach to SAB in the form of a 'care bundle' also improves adherence to the current international recommendations for the management of SAB and reduces 14- and 30-day mortality [4,20]. Our aim was to analyse the specific impact on the prognosis of patients with SAB of each QCI in the care bundle.

Adherence to the management recommendations was variable and depended on the QCI in question. Focus control was ultimately performed in only 37.5% of patients in whom it was formally indicated. Adequacy of empirical treatment and duration of treatment in uncomplicated SAB was considered correct in more than 90% of cases. However, no follow-up blood cultures were performed in up to 33% of patients, and almost 40% of complicated SAB cases received less than 28 days of treatment. Overall adherence to the bundle of care was 18.4%. These rates of adherence are significantly lower than those previously reported, although this could also be related to the arbitrary but strict time criteria established when evaluating adherence to each individual QCI. We think that non-adherence to clinical recommendations may be related to insufficient high-quality data supporting certain aspects of SAB management [7], as well as to differences in local practice.

Analysing the impact on outcome of each QCI is challenging for different reasons. First, a particular QCI may not apply to all patients (e.g. focus control is not possible for pneumonia except in the case of empyema). Consequently, we excluded patients from the corresponding QCI for specific analysis of that QCI. Second, they can be applied at different times, which may lead to immortal time bias, although their impact may also depend on how early they are applied. To control for these, we excluded patients who died before a specific landmark time and included them as time-dependent variables when applicable. Finally, the impact of confounders, including adherence to the other QCIs, was also controlled for by multivariable analysis.

Focus control and adequate targeted antimicrobial therapy were independently associated with a low risk of death in our analysis, a result that is clinically sound. The estimate for performing echocardiography was at the borderline of significance, although we only considered it mandatory in patients with complicated SAB. Broad spectrum antibiotics were considered non-adequate when the predefined adequate antimicrobials were not administrated. This could reflect a less than desired adherence to the corresponding QCI.

Although we cannot rule out the influence of residual immortal time bias, echocardiography results may also have some impact with adaptation of certain aspects of treatment depending on the results, particularly in patients diagnosed with endocarditis. Finally, performing follow-up blood cultures and appropriate duration of therapy were not significantly associated with mortality; these interventions might be more closely related to the risk of relapse or late complications. The fact that an independent impact on mortality could not be demonstrated for some QCI should not be interpreted as that they are not needed. Lack of power and correlation with the effect of other QCI may partially explain this. In addition, compliance with indicators such as echocardiography or follow-up blood cultures do not have a direct effect on mortality; however, their results could condition the antibiotic duration or surgical management, situations that do have a prognostic impact.

Our study has several limitations worth noting. We did not collect some data, such as duration of fever, serum vancomycin levels or details of the dosages of antimicrobials. Although the definition of complicated bloodstream infection often includes persistence of fever 72 hours after initiating effective antimicrobial therapy and the presence of an osteoarticular device that cannot be removed within the first 3 days, this information was not available in our database. The absence of follow-up control blood cultures causes underestimation of the true frequency of persistent bacteraemia and consequently of complicated bacteraemia, which may explain the relatively similar 90-day mortality rates between patients with uncomplicated and complicated SAB. Similarly, low adherence to echocardiography performance could have lowered the rate of endocarditis diagnosis. Analysis of focus control was not based on the individual characteristics of each case, but was predefined according to the primary focus of infection [8]. Consequently, the rate of adherence to this QCI may be underestimated owing to the possible inclusion of patients in whom focus control was not indicated. Furthermore, it was not possible to determine the influence of age and comorbidities on

the final decision to perform focus control. Finally, residual immortal time and confounding biases may have occurred despite our best efforts. The strengths of the study are that it is prospective and multicentre, with detailed definitions of adherence to quality-of-care recommendations, and the efforts described above to control for bias.

In conclusion, our results show that QCIs are applied in a heterogeneous manner, and that, beyond their impact as a bundle, some of them seem to have a measurable independent impact on mortality in patients with SAB.

Authors' contributions

F.E.V., J.R.B. and L.E.L.C. conceived the idea for the manuscript and wrote the final draft. All authors participated in the prospective inclusion of cases in the ISAC cohort and contributed to the preparation of the manuscript. All authors have reviewed and approved the final version of the manuscript.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.10.019.

References

[1] Byl B, Clevenbergh P, Jacobs F, Struelens MJ, Zech F, Kentos A, et al. Impact of infectious diseases specialists and microbiological data on the appropriateness of antimicrobial therapy for bacteremia. Clin Infect Dis 1999;29:60–6. https://doi.org/10.1086/520182.

[2] Vogel M, Schmitz RPH, Hagel S, Pletz MW, Gagelmann N, Scherag A, et al. Infectious disease consultation for *Staphylococcus aureus* bacteremia– a systematic review and meta-analysis. J Infect 2015;72:19–28. https://doi.org/10.1016/j.jinf.2015.09.037.

[3] Ten Oever J, Jansen JL, van der Vaart TW, Schouten JA, Hulscher MEJL, Verbon A. Development of quality indicators for the management of *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2019;74:3344–51. https://doi.org/10.1093/jac/dkz342.

[4] 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. https://doi.org/10.1093/cid/cit499.

[5] Pérez-Rodríguez MT, Sousa A, López-Cortés LE, Martínez-Lamas L, Val N, Baroja A, et al. Moving beyond unsolicited consultation: additional impact of a structured intervention on mortality in *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2019;74:1101–7. https://doi.org/10.1093/jac/dky556.

[6] Diallo K, Thilly N, Luc A, Beraud G, Ergonul Ö, Giannella M, et al. Management of bloodstream infections by infection specialists: an international ESCMID cross-sectional survey. Int J Antimicrob Agents 2018;51:794–8. https://doi.org/10.1016/j.ijantimicag.2017.12.010.

[7] Liu C, Strnad L, Beekmann SE, Polgreen PM, Chambers HF. Clinical practice variation among adult infectious disease physicians in the management of *Staphylococcus aureus* bacteremia. Clin Infect Dis 2019;69:530–3. https://doi.org/10.1093/cid/ciy1144.

[8] Nambiar K, Seifert H, Rieg S, Kern WV, Scarborough M, Gordon NC, et al. Survival following *Staphylococcus aureus* bloodstream infection: a prospective multinational cohort study assessing the impact of place of care. J Infect 2018;77:516–25. https://doi.org/10.1016/j.jinf.2018.08.015.

[9] Harris PNA, Mcnamara JF, Lye DC, Davis JS, Bernard L, Cheng AC, et al. Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition. Clin Microbiol Infect 2017;23:533–41. https://doi.org/10.1016/j.cmi.2016.10.023.

[10] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 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. https://doi.org/10.1093/eurheartj/ehv319.

[11] Thorlacius-Ussing L, Sandholdt H, Nissen J, Rasmussen J, Skov R, Frimodt-Møller N, et al. Comparable outcomes of short-course and prolonged-course therapy in selected cases of methicillin-susceptible *Staphylococcus aureus* bacteremia: a pooled cohort study. Clin Infect Dis 2021;73:866–72. https://doi.org/10.1093/cid/ciab201.

[12] Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791–7. https://doi.org/10.7326/0003-4819-137-10-200211190-00007.

[13] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10. https://doi.org/10.1001/jama.2016.0287.

[14] Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG, Hellmich M, Hopkins S, et al. *Staphylococcus aureus* bloodstream infection: a pooled analysis of five prospective, observational studies. J Infect 2014;68:242–51. https://doi.org/10.1016/j.jinf.2013.10.015.

[15] Smit J, Rieg SR, Wendel AF, Kern WV, Seifert H, Schønheyder HC, et al. Onset of symptoms, diagnostic confirmation, and occurrence of multiple infective foci in patients with Staphylococcus aureus bloodstream infection: a look into the order of events and potential clinical implications. Infection 2018;46:651–8. https://doi.org/10.1007/s15010-018-1165-x.

[16] Fowler VG, Olsen MK, Corey GR, Woods CW, Cabell CH, Reller LB, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. Arch Intern Med 2003;163:2066–72. https://doi.org/10.1001/archinte.163.17.2066.

[17] Jung N, Rieg S. Essentials in the management of *S. aureus* bloodstream infection. Infection 2018;46:441–2. https://doi.org/10.1007/s15010-018-1130-8.

[18] Fowler VG, Sanders LL, Sexton DJ, Kong L, Marr KA, Gopal AK, et al. Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. Clin Infect Dis 1998;27:478–86. https://doi.org/10.1086/514686.

[19] 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. https://doi.org/10.1007/s15010-014-0633-1.

[20] 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. https://doi.org/10.1007/s15010-016-0946-3.