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Risk factors and mortality of healthcare-associated and community-acquired *Staphylococcus aureus* bacteraemia

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Abstract

Staphylococcus aureus bacteraemia (SAB) is a leading cause of mortality and morbidity in both nosocomial and community settings. The objective of the study is to explore epidemiological characteristics and predisposing risk factors associated with healthcare-associated (HCA) and community-acquired (CA) SAB, and to evaluate any differences in mortality and efficacy of initial antimicrobial therapy on treatment outcome. We conducted a two-part analysis. First, a triple case–control study in which groups of HCA SAB with onset ≥48 h after hospital admission (HCA ≥48 h), HCA SAB with onset <48 h of hospital admission (HCA <48 h), and CA SAB were compared with controls. Second, a cohort study including all patients with SAB was performed to identify factors associated with in-hospital mortality. SAB was diagnosed in 165 patients over the study period (January 2007 to December 2007). Five variables were independently associated with HCA ≥48 h SAB: presence of central venous catheter, solid tumour, chronic renal failure, previous hospitalization and previous antibiotic therapy. Significant risk factors for HCA <48 h SAB were: Charlson Comorbidity Index ≥3, previous hospitalization, living in long-term care facilities and corticosteroid therapy. Factors independently associated with CA SAB were: diabetes mellitus, HIV infection and chronic live disease. Patients with HCA <48 h SAB were significantly more likely to receive initial inadequate antimicrobial treatment than patients with CA or HCA ≥48 h SAB (44.8% versus 33.3% and 31.5%, respectively). Logistic-regression analysis identified three variables as independent predictors of mortality: presentation with septic shock, infection with methicillin-resistant *S. aureus*, and initial inadequate antimicrobial treatment. More than half of patients with SAB have MRSA strains and presentation with septic shock, and inappropriate empirical therapy was associated with increased mortality.

Keywords: Healthcare-associated, methicillin-resistance, mortality, *Staphylococcus aureus*
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Introduction

Staphylococcus aureus bacteraemia (SAB) is a leading cause of mortality and morbidity in both nosocomial and community settings. Although the mortality rate has declined in some countries as a result of improved quality of care [1], the overall prevalence has increased in line with increasing use of intravascular devices and an expanding 'at-risk' population [1,2].

SAB has been studied in various patient populations meeting selective criteria [3,4]. Notably, the investigation of bacteraemias caused by methicillin-resistant *S. aureus* (MRSA) has become a major focus of interest over the past few years. A number of studies have shown that the characteristics of patients infected with MRSA differ from those of patients with methicillin-susceptible *S. aureus* (MSSA) bacteraemia [5]. Several studies, including one meta-analysis, have suggested that MRSA bacteraemia is associated with a significantly higher mortality rate [5–9]. The proportion of

nosocomial infections caused by MRSA continues to increase in most countries, although with substantial geographical variations [10]. Growing resistance to antibiotics may lead to an increase in inadequate initial antimicrobial treatment (IIAT) of infections.

We performed a prospective study in two Italian hospitals to better understand the epidemiology of SAB. The objectives of the study were to provide a view of epidemiological characteristics and predisposing risk factors associated with healthcare-associated (HCA) SAB in patients hospitalized for 48 h or more (HCA ≥48 h), HCA SAB with onset within 48 h of hospitalization (HCA <48 h), and community-acquired (CA) SAB, and to evaluate differences in mortality and efficacy of initial antimicrobial therapy on treatment outcome.

Materials and Methods

Setting and study design

This study was conducted in two Italian university hospitals that admit *c.* 50 000 patients per year. The microbiology laboratory database was used to identify prospectively patients with SAB who were hospitalized between 1 January 2007 and 31 December 2007; such patients were defined by the presence of at least one positive blood culture and clinical features compatible with systemic inflammatory response syndrome. Each patient was included in the study only once, at the time of the first positive blood culture. Patients were included only if a complete data series could be obtained from their medical records. Cases of polymicrobial bacteraemia were excluded. The distributions of the case and control admissions throughout the study period were similar.

Three case groups were defined: group 1 consisted of patients with HCA ≥48 h SAB, group 2 comprised patients with HCA <48 h SAB, group 3 comprised those with CA SAB. The control group consisted of patients with no positive clinical cultures from any site for *S. aureus* during their hospitalization, and were matched 2 : 1 with the cases according to the following criteria: hospital location (ward), month of admission, and length of hospital stay at the time of matching.

We conducted a two-part analysis. First, a triple case–control study in which 112 patients in group 1, 29 patients in group 2, and 24 patients in group 3 were compared with 224 (group 4), 58 (group 5), and 48 (group 6) control patients, respectively, to determine factors associated with the isolation of HCA ≥48 h, HCA <48 h or CA SAB.

The second part of the analysis was a cohort study including all patients with SAB (group 1 plus group 2 plus group 3), to identify factors associated with in-hospital mortality associated with SAB by using death within 30 days of the first positive blood culture as the outcome and comparing survivors and non-survivors. Patients were compared regarding demographics, medical history, clinical and laboratory findings, and treatment. The impact of underlying diseases was determined by the Charlson Comorbidity Index calculated before the onset of SAB [11], and the overall severity of the patient's illness was rated using the Acute Physiology and Chronic Health Evaluation (APACHE) [12] III score calculated on the basis of available clinical data within the first 24 h following SAB onset. The study was approved by the local ethic committees.

Definitions

Onset of SAB was defined as the date of collection of the first blood culture yielding the study isolate (index culture). The origin of the infection was determined by the date of SAB onset (as defined above) and the date of admission to the two hospitals participating in the study, except if the patient was transferred directly from another hospital; in these last cases, the date of admission to the original inpatient centre was recorded as the date of hospital admission. Infections were defined as HCA ≥48 h if the index blood culture had been collected >48 h after hospital admission and no signs or symptoms of infection had been noted at admission. Infections with onset within the first 48 h of hospitalization were classified as HCA <48 h or CA in accordance with the definitions of the European Centre for Disease Prevention and Control [13].

The source of SAB was defined as an infection caused by a microbial strain identical to the bloodstream isolate, documented by microbiological and physician findings. Septic shock was defined as sepsis associated with organ dysfunction, accompanied by persistent hypotension following volume replacement. An inpatient stay of 2 days or more, during the 12 months preceding the index hospitalization was considered prior hospitalization. The use of any antimicrobial for >48 h during the 3 months preceding the index admission was considered prior antimicrobial therapy. Antibiotic treatment empirically prescribed before *in vitro* susceptibility test results were available was defined as initial antibiotic treatment and considered 'inadequate' (i.e. IIAT) when treatment with an antibiotic possessing *in vitro* activity against the isolated pathogen was absent. No antibiotic therapy or monotherapy with aminoglycosides, trimethoprim, or rifampicin was deemed inadequate.

Microbiology analysis

Identification at species level of isolates and their susceptibility profiles was obtained with the VITEK 2 (Biomérieux Inc., Hazelwood, MO, USA) and Phoenix (Becton Dickinson Microbiology Systems, Sparks, MD, USA) automated systems. Results of susceptibility testing were interpreted in accordance with Clinical Laboratory Standards Institute guidelines [14].

Statistical analysis

Continuous variables were compared by Student's *t* test if normally distributed and the Mann–Whitney *U* test if non-normally distributed. Categorical variables were evaluated using chi-square or the two-tailed Fisher's exact test. The ORs and 95% CIs were calculated to evaluate the strength of any association. All the variables associated with SAB in the univariate analysis ($p \leq 0.10$) were included in a logistic regression model, and a backward stepwise approach was used to identify independent predictors of SAB. Variables were retained in the final model if the p value was ≤ 0.05.

All statistical analyses were performed using the INTERCOOLED STATA program, version 8 for WINDOWS (Stata Corporation, College Station, TX, USA).

Results

Incidence and population characteristics

A diagnosis of SAB was given in 171 of the 111 455 patients hospitalized over the period of the study with an incidence of 38 cases per 100 000 patient-days. Six patients were not included in the analysis because of a lack of sufficient data, resulting in a final number of 165 patients with SAB. The majority of the infections (67.8%, 112/165) were classified as HCA ≥48 h SAB. The remaining 53 were diagnosed within 48 h of admission, but only 24 (14.5%) of these could be classified as CA SAB. The other 29 (17.5%) were HCA <48 h SAB.

Risk factors analysis

The results of a comparison of the case and control groups by univariate analysis are shown in Table 1. The HCA ≥48 h patients were significantly older than controls, and long hospital stays, prior hospitalization, prior antibiotic therapy, previous surgery, and a neutrophil count $<500/mm^3$ were more common in this group. Compared with controls, the HCA ≥48 h patients were more likely to have a Charlson Comorbidity Index ≥3, a central venous catheter, to have undergone invasive procedures, urinary catheterization, nasogastric tube, total parenteral nutrition, previous bacterial infections, solid tumour, diabetes and chronic renal failure.

In univariate analysis HCA SAB was associated with a greater proportion of patients with Charlson Comorbidity Index ≥3, longer hospital stays, prior hospitalization, living in long-term care facilities, presence of central venous catheter, previous bacterial infections, solid tumour, diabetes mellitus, chronic renal failure, HIV infection, and previous radiotherapy and corticosteroid therapy. Compared with controls, CA SAB cases had a significantly greater proportion of younger patients, with higher Charlson Comorbidity Index, with chronic liver diseases, diabetes and HIV infection.

Logistic regression analysis revealed that five variables were independently associated with HCA ≥48 h SAB: presence of central venous catheter, solid tumour, chronic renal failure, previous hospitalization, and previous antibiotic therapy. Significant risk factors for with HCA <48 h SAB were: Charlson Comorbidity Index ≥3, prior hospitalization, provenience from long-term care facilities, to corticosteroid therapy. The variables significantly associated with CA SAB were diabetes, HIV infection, and chronic liver diseases (Table 2).

Antimicrobial resistance and inadequate initial antimicrobial treatment

Methicillin-resistant isolates were identified in 89 of 165 cases (53.9%): the percentage of MRSA was 46% in hospital A and 59% in hospital B. All MSSA and MRSA isolates were susceptible to linezolid, tigecycline, quinupristin-dalfopristin, daptomycin, teicoplanin and vancomycin.

Patients with HCA ≥48 h SAB were significantly more likely to be infected with MRSA isolates than patients with HCA <48 h SAB (68.7% (77/112) versus 41.3% (12/29), p 0.006). None of the patients with CA SAB was infected by MRSA. MRSA isolates were more common in patients hospitalized in intensive-care units and surgical wards than in medical wards (70.8% (17/24) and 70.3% (19/27) versus 46.4% (53/114); p 0.03 and p 0.02, respectively). The main differences between patients with MRSA and MSSA SAB are indicated in Table 3.

Adequate initial antimicrobial treatment was administered to 109 (66.1%) patients within 24 h of hospital admission, and 56 (33.9%) patients received IIAT. Patients with HCA <48 h SAB were statistically more likely to receive IIAT than patients with CA or HCA ≥48 h bacteraemia (44.8% (13/29) versus 33.3% (8/24) and vs. 31.5% (35/112), respectively). Fig. 1 provides the rates of IIAT treatment by pathogen distribution.

Outcome

Thirty days after SAB onset, 35 (21.2%) of the 165 patients had died. The results of the univariate and multivariate

TABLE 1. Univariate analysis of risk factors for nosocomial, healthcare-associated and community-acquired bloodstream infections caused by *Staphylococcus aureus*

	Univariate analysis								
	HCA≥48 h vs Control 1			HCA <48 h vs Control 2			CA vs Control 3		
Variables	HCA≥48 h (*n* = 112)	Control 1 (*n* = 224)	OR (95% CI)	HCA < 48 h (*n* = 29)	Control 2 (*n* = 58)	OR (95% CI)	CA (*n* = 24)	Control 3 (*n* = 48)	OR (95% CI)
Male sex	75 (66.9)	128 57.1)	1.52 (0.92–2.52)	15 (51.7)	32 (55.2)	0.87 (0.32–2.34)	12 (50)	26 (54.2)	0.85 (0.28–2.53)
Age, years, (mean ± SD)	65.9 ± 13.3	62.6 ± 18.1	–	60.7 ± 16.0	60.2 ± 17.9	–	46.8 ± 22.2	59.9 ± 18.6	–*
LOS, days, (mean ± SD)	54.3 ± 49.8	22.8 ± 29.6	–**	37.4 ± 21.8	23.7 ± 24.2	–*	24.1 ± 15.3	21.6 ± 24.1	–
Previous hospitalization[a]	69 (61.6)	67 (29.9)	3.76 (2.27–6.23)**	24 (82.8)	17 (29.3)	11.58 (3.45–44.03)**	0	12 (25)	0 (0–0.50)*
Admission from LTCF	1 (0.9)	7 (3.1)	0.28 (0.01–2.22)	8 (27.6)	3 (5.2)	6.98 (1.46–43.61)*	0	4 (8.3)	0 (0–1.86)
Previous bacterial infections[b]	29 (25.9)	18 (8)	3.99 (2.01–8.06)**	8 (27.6)	9 (15.5)	2.07 (0.60–6.97)	1 (4.2)	9 (18.8)	0.19 (0–1.54)
Comorbidities									
Solid tumour	32 (28.6)	24 (10.7)	3.33 (1.77–6.28)**	10 (34.5)	6 (10.3)	4.56 (1.27–17.20)**	1 (4.2)	5 (10.4)	0.37 (0.01–3.68)
HIV infection	4 (3.5)	11 (4.9)	0.71 (0.16–2.49)	5 (17.2)	2 (3.4)	5.83 (0.86–63.82)*	7 (29.1)	2 (4.1)	9.47 (1.54–98.55)*
Chronic liver disease	15 (13.4)	28 (12.5)	1.08 (0.51–2.21)	7 (24.1)	7 (12.1)	2.32 (0.61–8.71)	9 (37.5)	6 (12.5)	4.2 (1.09–16.6)*
Chronic renal failure	28 (25)	21 (9.4)	3.22 (1.65–6.30)**	10 34.5)	5 (8.7)	5.58 (1.47–23.09)*	4 (16.7)	5 (10.4)	1.72 (0.30–8.90)
Diabetes mellitus	36 (32.1)	29 (12.9)	3.18 (1.76–5.78)**	8 (27.6)	7 (12.1)	2.77 (1.22–10.49)*	10 (41.7)	6 (12.5)	5 (1.32–19.6)
Charlson Comorbidity index ≥3	50 (44.6)	59 (26.3)	2.25 (1.36–3.73)**	14 (48.3)	12 (20.7)	3.58 (1.22–10.49)*	14 (58.3)	10 (20.8)	5.32 (1.61–17.7)*
CVC	71 (63.4)	71 (31.7)	3.73(2.25–6.19)**	18 (62.1)	20 (34.5)	3.11 (1.12–8.74)**	0	15 (31.3)	0 (0–0.37)*
Urinary catheter	76 (67.9)	71 (31.7)	4.55 (2.72–7.63)**	10 (34.5)	18 (31)	1.17 (0.40–3.30)	2 (8.3)	14 (29.2)	0.22 (0.02–1.13)*
Corticosteroid therapy	16 (14.3)	42 (18.8)	0.72 (0.36–1.39)	16 (55.2)	7 (12.1)	8.97 (2.72–30.75)**	7 (29.2)	10 (20.8)	1.56 (0.43–5.46)
Previous antibiotic therapy[a]	61 (54.5)	75 (33.5)	2.38 (1.45–3.88)**	11 (37.9)	57 (98.3)	0.01 (0–0.08)**	6 (25)	29 (60.4)	0.21 (0.06–0.72)*
Apache III score >15	52 (46.4)	87 (38.9)	1.36 (0.84–2.21)	14 (48.3)	22 (37.9)	1.53 (0.56–4.13)	14 (58.3)	20 (41.7)	1.96 (0.65–5.99)

*p <0.05, **p <0.001.
[a]Within 30 days before the onset of bloodstream infection.
[b]Within 3 months of the onset of bloodstream infection.
HCA, healthcare-associated; BSI, bloodstream infection; LOS, length of hospital stay; LTCF, long-term care facility; CVC, central venous catheter; HIV, human immunodeficiency virus.

TABLE 2. Logistic regression analysis of risk factors for bacteraemia caused by *Staphylococcus aureus* stratified by epidemiological category

Variables	p	OR (95% CI)
HCA ≥48 h		
Solid tumour	<0.001	3.95 (2.02–7.72)
Chronic renal failure	<0.001	4.03 (1.92–8.44)
Central venous catheter	<0.001	3.69 (2.15–6.34)
Previous hospitalization	<0.001	3.79 (2.20–6.51)
Previous antibiotic therapy	0.004	2.25 (1.30–3.88)
HCA <48 h		
Admission from LTCF	0.04	6.61 (1.02–42.89)
Previous hospitalization	0.007	5.67 (1.61–19.98)
Charlson Comorbidity Index ≥3	0.01	4.98 (1.38–18.07)
Corticosteroid therapy	0.02	4.78 (1.26–18.12)
Community-acquired		
Diabetes mellitus	0.008	6.21 (1.62–23.77)
HIV infection	0.01	11.03 (1.79–67.76)
Chronic liver disease	0.01	6.00 (1.54–23.37)

HCA, healthcare-associated; LTCF, long-term care facility; HIV, Human immunodeficiency virus.

TABLE 3. Characteristics of the 165 bacteraemia caused by *Staphylococcus aureus* stratified by methicillin resistance

Variables	MRSA (*n* = 89)	MSSA (*n* = 76)	p value
Male sex	59 (66.3)	43 (56.6)	0.20
Age, years (mean ± SD)	65 ± 15	59 ± 18	0.04
Ward at SAB onset			
Medicine	53 (59.6)	61 (80.3)	0.004
Surgery	19 (21.4)	8 (10.5)	0.06
Intensive-care unit	17 (19.1)	7 (9.2)	0.07
Epidemiological category			
Healthcare-associated ≥48 h I	77 (86.5)	35 (46.14)	<0.001
Healthcare-associated <48 h	12 (13.4)	17 (22.3)	0.13
Community-acquired	0 (0.0)	24 (31.5)	<0.001
Previous use of antibiotics[a]	53 (59.6)	25 (32.9)	0.001
Source of bacteraemia			
Central venous catheter	12 (13.5)	11 (14.5)	0.86
Urinary tract	1 (1.1)	2 (2.6)	0.47
Lower respiratory tract	5 (5.6)	2 (2.6)	0.34
Surgical wound	2 (2.3)	2 (2.6)	0.87
Skin and soft tissues	5 (5.6)	5 (6.6)	0.79
Unknown	53 (59.6)	51 (67.1)	0.32
Time to discharge, days (mean ± SD)	33 ± 31	29 ± 22	0.32
Inadequate antimicrobial treatment	39 (43.8)	17 (22.4)	0.004
Apache III >15	42 (47.1)	38 (50)	0.71
Charlson Comorbidity Index ≥3	44 (49.4)	34 (44.7)	0.55
Presentation with septic shock	26 (29.2)	8 (10.5)	0.003
Initial treatment failure	29 (32.6)	8 (10.5)	0.001
30-day mortality	29 (32.5)	6 (7.9)	<0.001

Data are given as number of patients (%) unless stated otherwise.
MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteraemia.
[a]Within 30 days of the onset of bacteraemia.

analyses of risk factors for mortality are shown in Table 4. Logistic-regression analysis identified three variables as independent predictors of hospital mortality: presentation with septic shock, infection caused by MRSA, and IIAT.

Discussion

In this prospective study performed in Italy, we observed an incidence of SAB of 38 per 100 000 patient-days and a

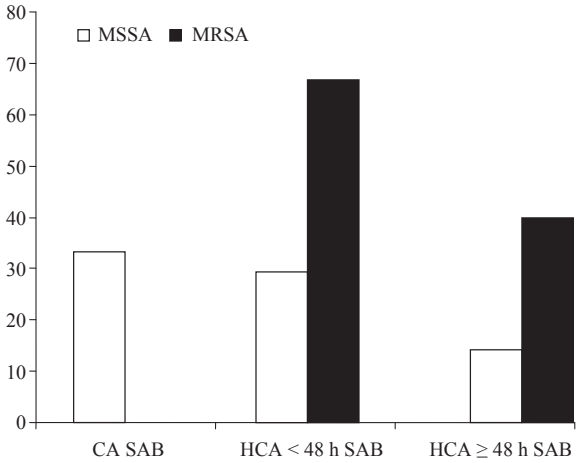

FIG. 1 Inadequate initial antimicrobial treatment (%). Rates of inadequate initial antimicrobial treatment in patients with community-acquired (CA), healthcare-associated ≥48 h (HCA ≥48 h) and healthcare-associated <48 h (HCA <48 h) *Staphylococcus aureus* bacteraemia (SAB) according to methicillin resistance. MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

methicillin-resistance rate of 54%. The percentage of MRSA is higher than that published by the European Antimicrobial Resistance Surveillance System, which for the whole of Italy in 2007 reported an incidence of 7.7 MRSA infections per 100 000 patient-days and a methicillin-resistance rate of 34% [15]. This may be because the two hospitals participating in the study are among the biggest Italian tertiary-care institutions and have large intensive-care units, and patients in this setting accumulate risk factors for methicillin resistance [16]. MRSA was found to be HCA ≥48 h acquired in about 85% of the cases, and the rest of the MRSA acquisition occurred in outpatients, in whom MRSA was considered HCA <48 h (no CA SAB was the result of MRSA). This study confirms previous findings that MRSA rarely causes CA SAB in adults [17]. One of the main findings of this study is that only 13% of patients with MRSA bacteraemia were outpatients with previous healthcare contacts; this proportion is lower than that found in a similar Spanish study [18]. This emphasizes the importance of chronic colonization after MRSA acquisition in healthcare facilities.

There are a number of important observations regarding the epidemiological profile of MRSA bacteraemia in our region. MRSA was responsible for one of the two incidents of SAB reported in 2007 in our Institutions. This finding has important implications for empirical antimicrobial therapy for patients with suspected *S. aureus* infections.

The 21% 30-day in-hospital mortality for patients with SAB reported here was similar to the 16.2–23.2% reported in other studies [19,20]. Our data reveal that the mortality

TABLE 4. Univariate and multivariate analysis of factors associated with 30 days in-hospital mortality among patients with *Staphylococcus aureus*.bacteraemia

Variable	*n* (%) of patients		p value	OR (95% CI)
	Dead (*n* = 35)	Survivors (*n* = 130)		
Univariate analysis				
Male sex	24 (68.5)	78 (60)	0.35	1.45 (0.62–3.57)
Age, years (mean ± SD)	65 ± 28	61 ± 42	0.16	–
Chronic renal failure	11 (31.4)	31 (23.8)	0.36	1.46 (0.57–3.52)
Ward				
Medicine	19 (54.2)	95 (73.1)	0.03	043 (0.18–1.02)
Surgery	8 (22.8)	19 (14.6)	0.24	1.73 (0.58–4.68)
Intensive-care unit	8 (22.8)	16 (12.3)	0.11	2.11 (0.70–5.87)
Epidemiological category				
Healthcare-associated ≥48 h	25 (71.4)	87 (66.9)	0.61	1.23 (0.51–3.15)
Healthcare-associated <48 h	7 (20)	22 (16.9)	0.67	1.22 (0.40–3.36)
Community-acquired	3 (8.6)	21 (16.2)	0.25	0.48 (0.08–1.79)
Methicillin resistance	29 (82.9)	60 (46.2)	<0.001	5.63 (2.09–17.57)
Inadequate antimicrobial treatment	21 (60)	35 (26.9)	<0.001	4.07 (1.74–9.60)
Apache III >15	20 (57.1)	60 (46.1)	0.24	1.55 (0.68–3.56)
Charlson Comorbidity Index ≥ 3	21 (60)	57 (43.8)	0.08	1.92 (0.84–4.45)
Presentation with septic shock	17 (48.6)	17 (13.1)	<0.001	6.27 (2.49–15.68)
Multivariate analysis				
Presentation with septic shock	–	–	0.002	4.14 (1.69–10.14)
Methicillin resistance	–	–	0.006	4.00 (1.47–10.82)
Inadequate antimicrobial treatment	–	–	0.01	2.79 (1.19–6.52)

associated with MRSA bacteraemia is significantly higher than that associated with MSSA bacteraemia (32.5% versus 7.9%, p < 0.001). Several studies have investigated the differences in the mortality rates for patients who have MRSA bacteraemia compared with patients who have MSSA bacteraemia [21,22]. In a recent big multicentre prospective European study when the outcomes from MRSA and MSSA bacteraemia were compared, an effect attributable to methicillin resistance was found for 30-day mortality (OR = 1.8; p 0.04) [8]. In our study the underlying severity of illness in the MRSA group was similar to that in the susceptible group, it may be presumed that bacteraemia by MRSA may have a worse prognosis because of the IIAT. The impact of appropriate empirical therapy against MRSA on survival has been explored in several studies including only patients with bacteraemia; their results were contradictory [23,24]. Other studies have evaluated the importance of empirical therapy in MRSA bacteraemia and IIAT was associated with increased mortality [25,26].

We analysed the influence of IIAT on outcome of SAB. After controlling for the underlying conditions, we found that presentation with septic shock, MRSA and IIAT were associated with increased mortality. In particular, the rates of patients with HCA <48 h SAB who received IIAT were about 60% and 30% for MRSA and MSSA cases, respectively, higher than those found for HCA ≥48 h SAB. Therefore, empirical antibiotic therapy against SA needs to be considered not only for patients with HCA ≥48 h infection where the risk of MRSA is usually higher, but also for patients with HCA <48 h infections, especially if there has been recent contact with healthcare facilities. Early and precise prediction of both *S. aureus* severe infection and methicillin susceptibility is needed to allow for appropriate empirical therapy of MRSA or optimal (beta-lactam) treatment of MSSA infections, avoiding superfluous use of glycopeptides.

As in other studies, all isolates were susceptible to vancomycin, linezolid, daptomycin and tigecycline [27]. We did not detect vancomycin hetero-resistance, in agreement with a recent study from a UK hospital [27].

Our current data support previous observations with respect to risk factors for the acquisition of SAB. However, although several studies have noted a high frequency of chronic comorbid illnesses among patients with SAB, only a few studies have quantified the actual magnitudes of risks [28,29]. The present study adds two main novel observations. First, the distribution and magnitude of comorbidity risk factors for HCA ≥48 h or HCA <48 h SAB are different (Table 2). Second, we identified that admission from a long-term care facility is associated with a 16-fold increased risk for HCA <48 SAB. The spread of MRSA in long-term care facilities increases the reservoir of this organism in the healthcare setting, and residents transferred from long-term care facilities account for a large part of the burden of hospitalized MRSA infections [30,31].

Although we have shown that there are some differences between HCA ≥48 h and HCA <48 h SAB, *S. aureus* infections are predominant in subjects with concomitant medical problems and in those exposed to previous hospitalization. Our experience confirmed the role of previous exposure to antibacterials in promoting acquisition of *S. aureus* infections.

This study has several limitations. First, it was conducted only in two centres; therefore unknown risk factors for

mortality might have been unequally distributed between the different groups. Second, the standard when determining antibiotic efficacy is a randomized controlled trial. Without randomization, physicians and patients select therapies in ways that can introduce substantial confounding. Third, the risks for other treatment factors that may have contributed to adverse outcomes, such as improper dosing and other procedures were not included in the analysis. Finally, the severity of illness was measured within 24 h after the onset of bacteraemia and, therefore, it should not reflect the severity status before the infection onset.

In conclusion, over half of patients with *S. aureus* bloodstream infection in this study have MRSA strains and in these cases presentation with septic shock and inappropriate empirical therapy was associated with increased mortality. Clinicians should be aware that appropriate antimicrobial therapy should be immediately prescribed to reduce the risk of a poor outcome when bloodstream infection caused by *S. aureus* is suspected, in the following settings: patients arriving from long-term care facilities or with previous hospitalization, previous antibiotic exposure and with important comorbidities (e.g. solid tumour, chronic renal failure, diabetes). Our results support prompt initiation of antibiotics targeted against MRSA in cases of suspected hospital and healthcare-associated SAB, especially in patients with signs of severe sepsis.

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Transparency Declarations

In the past 5 years, Matteo Bassetti, MD, PhD, has been a consultant for Astellas Pharma Inc., AstraZeneca, Gilead, Merck Sharp & Dohme Corp., Novartis, and Pfizer Inc., and is on the speaker's bureau of Angelini Pharmaceuticals, Astellas Pharma Inc., AstraZeneca, Gilead, Merck Sharp & Dohme, Novartis, and Pfizer Inc. The other authors declare that they have no competing interests.

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