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Course and outcome of *Staphylococcus aureus* bacteraemia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre

C. Kaech[1], L. Elzi[2], P. Sendi[2,3], R. Frei[4], G. Laifer[2], S. Bassetti[2] and U. Fluckiger[2]

[1]Department of Internal Medicine, [2]Division of Infectious Diseases & Hospital Epidemiology, [3]Institute of Clinical Epidemiology and [4]Microbiology Laboratory, University Hospital Basel, Basel, Switzerland

ABSTRACT

Staphylococcus aureus bacteraemia (SAB) is associated with substantial morbidity and mortality worldwide. The charts of adult patients with SAB who were hospitalised in a Swiss tertiary-care centre between 1998 and 2002 were studied retrospectively. In total, 308 episodes of SAB were included: 2% were caused by methicillin-resistant strains; 49% were community-acquired; and 51% were nosocomial. Bacteraemia without focus was the most common type of community-acquired SAB (52%), whereas intravenous catheter-related infection predominated (61%) among nosocomial episodes of SAB. An infectious diseases (ID) specialist was consulted in 82% of all cases; 83% received appropriate antibiotic treatment within 24 h of obtaining blood cultures. Overall hospital-associated mortality was 20%. Community-acquired SAB was associated independently with a higher mortality rate than nosocomial SAB (26% vs. 13%; p 0.009). Independent risk-factors for a fatal outcome were age ($p < 0.001$), immunosuppression (p 0.007), alcoholism ($p < 0.001$), haemodialysis (p 0.03), acute renal failure ($p < 0.001$) and septic shock ($p < 0.001$). Consultation with an ID specialist was associated with a better outcome in univariate analysis ($p < 0.001$). Compared with a previous retrospective analysis performed at the same institution between 1980 and 1986, there was a 140% increase in community-acquired SAB, a 60% increase in catheter-related SAB, and a 14% reduction in mortality. In conclusion, mortality in patients with SAB remained high, despite effective antibiotic therapy. Patients with community-acquired SAB were twice as likely to die as patients with nosocomial SAB. Consultation with an ID specialist may reduce mortality in patients with SAB.

Keywords Bacteraemia, community-acquired, mortality, nosocomial, risk-factors, *Staphylococcus aureus*

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INTRODUCTION

Staphylococcus aureus is a leading cause of both community-acquired and nosocomial bacteraemia [1–7]. Among the general population, 25–40% of individuals carry *S. aureus* in their anterior nares [8–10], and a substantial proportion of *S. aureus* bloodstream infections are endogenous in origin [11]. Of all cases of *S. aureus* bacteraemia (SAB), 40–80% are hospital-acquired [12–20]. In particular, intravenous catheter-related SAB has emerged as a major nosocomial infection problem, because of the increasing use of central venous lines [1,21–24]. A distinctive feature of SAB is the high rate of bacteraemia without focus among patients with community-acquired SAB, ranging from 45% to 85% [13,14,25,26]; most cases of nosocomial SAB have an obvious portal of entry, e.g., intravenous catheters or surgical sites. Endocarditis and secondary foci are common complications of SAB, occurring far more frequently in community-acquired than in nosocomial SAB [12–14, 25–32], and in patients with bacteraemia without focus than in patients with a known focus of SAB [13,28–31]. Despite the availability of effective anti-staphylococcal antibiotics, SAB still has a mortality rate of 20–40% [12–19,27,33,34]. The emergence of methicillin-resistant *S. aureus* (MRSA) has increased further the threat of SAB,

Corresponding author and reprint requests: U. Fluckiger, Division of Infectious Diseases & Hospital Epidemiology, Universitätsspital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
E-mail: uflueckiger@uhbs.ch

as MRSA bacteraemia carries a higher risk of mortality than methicillin-susceptible *S. aureus* bacteraemia [14,17,29,35,36]. The prognosis of SAB can be improved by adequate antibiotic treatment [35,37] and focus removal [12,19,25], whereas age, bacteraemia without focus and septic shock are risk-factors for a fatal outcome [12–18].

The objective of the present study was to analyse retrospectively the clinical, microbiological and therapeutic features of SAB occurring at the University Hospital Basel (Switzerland), with an emphasis on the prognostic impact of appropriate antibiotic therapy and of consulting an infectious diseases (ID) specialist. These results were compared with studies published previously, and especially with a retrospective study on SAB performed previously at the same hospital [13], in order to detect possible changes in the pattern of staphylococcal disease over time.

MATERIALS AND METHODS

Setting and study population

The study was performed at the University Hospital Basel, which is an 800-bed primary- and tertiary-care centre for adult patients, with 26 000 admissions/year. Patients with blood cultures positive for *S. aureus* who were hospitalised during the period 1998–2002 were identified by review of blood culture results from the bacteriology laboratory. All patients considered to have true *S. aureus* bloodstream infection, defined as at least one blood culture positive for *S. aureus* plus a systemic inflammatory response syndrome, were included [38]. Patients with true re-infection could be included several times. Retrospective data collection included age, gender, underlying conditions, place of acquisition, primary focus, consultation with an ID specialist, adequacy and timing of antibiotic treatment, complications, admission to the intensive care unit, and overall hospital mortality.

Definitions

Underlying conditions

Vascular disease was defined as coronary heart disease, stroke, or vascular disease of the extremities. Chronic renal failure was defined as stable elevation of serum creatinine of >180 μmol/L. Immunosuppression included any congenital or acquired quantitative or qualitative deficiency of phagocytic cells, complement, or humoral or cell-mediated immunity. Neutropenia was defined as an absolute neutrophil count <500/μL. Patients infected with human immunodeficiency virus were considered immunosuppressed at any stage of disease. Immunosuppression was also defined as a dose of 25 mg prednisone/day for >1 month, or a cumulative dose of >700 mg prednisone within 3 months before the onset of SAB.

Place of acquisition and primary focus

SAB was considered to be nosocomial if the first positive blood culture was obtained ≥ 48 h after hospital admission, or directly following an invasive procedure performed in hospital, or following haemodialysis. SAB caused by a surgical site infection was also considered to be nosocomial, even if the patient was at home when signs and symptoms of sepsis developed. The primary focus of SAB was determined on the basis of clinical and radiological manifestations and, whenever possible, on the isolation of *S. aureus* from normally sterile sites other than blood. In addition, intravenous catheter-related SAB was defined by evidence of inflammation at the insertion site and/or a catheter-tip culture positive for *S. aureus*, and no evidence of any other focus. Endocarditis was defined according to the modified Duke criteria [39].

Antibiotic therapy

Appropriate antibiotic treatment was defined as therapy with at least one antibiotic to which the microorganism was susceptible, given by an appropriate route and in an appropriate dosage for a sufficient period of time, according to well-accepted published guidelines (e.g., The Sanford Guide to Antimicrobial Therapy [40]). Examples include therapy for 14 days for SAB caused by intravenous catheter-related infection, surgical site infection, and skin/soft tissue infection, and therapy for 28 days for bacteraemia without focus or endocarditis. Trimethoprim–sulphamethoxazole, macrolides, tetracyclines, fluoroquinolone or aminoglycoside monotherapy, ceftriaxone as definitive therapy, and flucloxacillin, amoxycillin–clavulanate and first- or second-generation cephalosporins given orally were considered to be inappropriate regardless of susceptibility. In general, the antibiotic given as soon as the pathogen was known to be *S. aureus* was considered to be the definitive therapy, as MRSA is rare in the institution studied. In the few cases where SAB was caused by MRSA, the antibiotic given as soon as the susceptibility testing results were known was considered to be the definitive therapy.

Complications and outcome

Secondary foci were considered to be either present or absent; the different kinds of secondary foci were not analysed separately. Endocarditis was considered to be a separate entity, not a secondary focus. Acute renal failure was defined as an increase in baseline serum creatinine of $\geq 20\%$. Septic shock was defined according to Bone *et al*. [38]. Disseminated intravascular coagulation was diagnosed if the following three criteria were present (in the absence of other conditions explaining these findings): D-dimers >0.5 mg/L; international normalised ratio >1.5; and thrombocytes $<100\,000$/μL. No attempt was made to determine whether in-hospital death was attributable directly to SAB.

Statistical analysis

Categorical variables were compared using either Pearson's chi-square test or Fisher's exact test, as appropriate. Proportions were compared using the proportions test. Univariate analysis of risk-factors for mortality was with a binary logistic regression model. A stepwise logistic regression model was used to determine the final multivariate model. A p value ≤ 0.05 was considered significant.

RESULTS

Study population and characteristics of patients

Between January 1998 and December 2002, 2547 episodes of bacteraemia occurred at the University Hospital Basel (20.4 episodes/1000 admissions). In total, 341 (13.3%) of these episodes were caused by *S. aureus* (2.7 episodes/1000 admissions), but a hospital chart was unavailable for 33 patients. The remaining 308 patients all had a systemic inflammatory response syndrome and thus fulfilled the inclusion criteria. The demographic characteristics and underlying conditions of these patients are summarised in Table 1. Notably, 31% of the patients with community-acquired SAB were injecting drug-users. There were only six (2%) episodes of MRSA bacteraemia.

Place of acquisition, primary focus of SAB and endocarditis

Of all cases of SAB, 49% were community-acquired and 51% were nosocomial, most often acquired on a surgical ward. Bacteraemia without focus was the most common type of community-acquired SAB (52%), whereas intravenous catheter-related infection predominated (61%) among episodes of nosocomial SAB. Endocarditis accounted for 52 (17%) episodes (Table 2), and was significantly more common in patients with community-acquired SAB than in patients with nosocomial SAB (29% vs. 5%; $p < 0.001$), and also in patients with bacteraemia without focus than in patients with a known focus of SAB (36% vs. 10%; $p < 0.001$; data not shown).

Table 1. Characteristics of patients with *Staphylococcus aureus* bacteraemia

	Community-acquired (*n* = 150)	**Nosocomial (*n* = 158)**
Age (years)		
Mean	54.6	59.1
Median (range)	55 (23–94)	61 (18–92)
Gender, *n* (%)		
Female	55 (37)	48 (30)
Male	95 (63)	110 (70)
Underlying conditions, *n* (%)[a]		
Vascular disease	45 (30)	58 (37)
Diabetes mellitus	37 (25)	37 (23)
Immunosuppression	29 (19)	41 (26)
Malignancy (not in remission)	17 (11)	36 (23)
Injection drug use	47 (31)	4 (3)
Chronic obstructive pulmonary disease	15 (10)	18 (11)
Congestive heart failure (NYHA III/IV)	18 (12)	14 (9)
Alcoholism	14 (9)	17 (11)
Chronic hepatic failure (cirrhosis CHILD B/C)	9 (6)	12 (8)
Chronic renal failure without haemodialysis	7 (5)	14 (9)
Chronic renal failure with haemodialysis	4 (3)	11 (7)

[a]Patients may have more than one underlying condition.

Table 2. Place of acquisition, primary focus and endocarditis in patients with *Staphylococcus aureus* bacteraemia

Acquisition (*n* = 308)	*n* (%)	
Community-acquired	150 (49)	
Nosocomial	158 (51)	
Medical ward	54 (18)	
Surgical ward	72 (23)	
Intensive care unit	32 (10)	
	Community-acquired (*n* = 150)	**Nosocomial (*n* = 158)**
Primary focus, *n* (%)		
Bacteraemia without focus	78 (52)	5 (3)
Skin/soft tissue infection	45 (30)	4 (2)
Bone/joint infection	17 (11)	0
Surgical site infection		
With foreign body	0	17 (11)
Without foreign body	0	20 (13)
Intravenous catheter-related infection	2 (1)[a]	96 (61)
Others	8 (5)	16 (10)
Endocarditis, *n* (%)	44 (29)	8 (5)
On native valve	32 (21)	3 (2)
On artificial valve	12 (8)	5 (3)

[a]Both community-acquired intravenous catheter-related infections were infected port-a-caths.

Antibiotic therapy

An ID specialist was consulted in 253 (82%) cases. Empirical antibiotic therapy was appropriate in 238 (77%) episodes. Definitive antibiotic therapy was appropriate in 258 (88%) episodes. Ten patients died before definitive therapy could be initiated, and the type of definitive therapy was unknown for five patients. The most common empirical therapy was intravenous amoxycillin–clavulanate (118 (38%) patients, including 48 (16%) patients who also received an aminoglycoside). The most common definitive therapy was intravenous flucloxacillin (183 (62%) patients, including 70 (24%) patients who also received an aminoglycoside).

Timing of antibiotic therapy is shown in Table 3. The median time between obtaining blood cultures and starting correct antibiotic therapy was 3.0 h; 83% of all patients received appropriate antibiotic treatment within 24 h of obtaining blood cultures. For 90% of the patients with community-acquired SAB, blood cultures were obtained within 6 h of hospital admission.

Complications and outcome of SAB

Complications and outcome of SAB are shown in Table 4. Secondary foci were significantly more common in patients with community-acquired SAB than in patients with nosocomial SAB (43%

Table 3. Timing of antibiotic therapy for *Staphylococcus aureus* bacteraemia (SAB)

	Time between obtaining blood cultures and start of correct antibiotic therapy (n = 259[a])	Time between hospital admission and obtaining blood cultures (n = 144[b])	Time between hospital admission and start of correct antibiotic therapy (n = 140[b])
Time			
Mean, h	10.7	3.6	11.7
Median, h	3.0 (0.5–93.5)	1.5 (0.5–71)	5.5 (1.0–104)
0–6 h, *n* (%)	170 (66)	129 (90)	81 (58)
6–12 h, *n* (%)	23 (9)	9 (6)	26 (19)
12–24 h, *n* (%)	23 (9)	2 (1)	12 (9)
>24 h, *n* (%)	43 (17)	4 (3)	21 (15)

[a]Data (if available) were analysed for community-acquired and nosocomial SAB.
[b]Data (if available) were analysed for community-acquired SAB and surgical site infection with signs/symptoms of sepsis starting at home.

Table 4. Complications and outcome of *Staphylococcus aureus* bacteraemia (SAB)

	Community-acquired (n = 150)	Nosocomial (n = 158)
Complications, *n* (%)		
Secondary foci	65 (43)	8 (5)
Acute renal failure	44 (29)	26 (16)
Septic shock	20 (13)	11 (7)
Adult respiratory distress syndrome	6 (4)	3 (2)
Disseminated intravascular coagulation	7 (5)	1 (1)
Intensive care unit (ICU) stay caused by SAB, *n* (%)	44 (29)	23 (18; n = 126[a])
Mechanical ventilation caused by SAB, *n* (%)	14 (9)	6 (4)
Overall in-hospital mortality, *n* (%)	38 (26[b]); n = 146[c]	21 (13[b]); n = 156[c]
Time from first positive blood culture to death		
Mean, days	8.8	6.6
Median (range), days	6.0 (1–30)	3.5 (1–26)

[a]Patients who acquired SAB in the ICU (n = 32) were excluded.
[b]p 0.009; total overall hospital mortality was 20%.
[c]The outcome of SAB was unknown for six patients (four community-acquired, two nosocomial).

vs. 5%; p < 0.001), and also in patients with bacteraemia without focus than in patients with a known focus of SAB (53% vs. 13%; p < 0.001; data not shown). Common secondary foci were septic arthritis, spondylodiskitis and skin/soft-tissue seeding. The overall hospital mortality rate was 20%. Patients with community-acquired SAB had a significantly higher mortality rate than patients with nosocomial SAB (26% vs. 13%; p 0.009).

Prognostic factors of SAB

Consultation with an ID specialist was associated in univariate analysis with a better outcome (p < 0.001), but not in multivariate analysis (Table 5). No effect of adequacy or timing of antibiotic therapy on mortality was identified (inadequate empirical therapy: OR 1.1, 95% CI 0.5–2.3, p 0.8; inadequate definitive therapy: OR 0.89, 95% CI 0.8–1.1, p 0.6). Risk-factors in multivariate analysis for a fatal outcome of SAB were age, immunosuppression, alcoholism, haemodialysis, acute renal failure and septic shock (Table 5). Endocarditis was not a risk-factor for mortality (native valve endocarditis: OR 1.4, 95% CI 0.6–3.5, p 0.4; artificial valve endocarditis: OR 1.7, 95% CI 0.5–5.6, p 0.4). Nosocomial SAB was associated independently with a better outcome (Table 5). The following risk-factors for mortality (univariate and/or multivariate analysis) were significantly more frequent for community-acquired SAB than for nosocomial SAB: bacteraemia without focus (52% vs. 3%, p < 0.001); secondary foci (43% vs. 5%, p < 0.001); acute renal failure (29% vs. 16%, p 0.007); septic shock (13% vs. 7%, p 0.06); disseminated intravascular coagulation (5% vs. 1%, p 0.03); intensive care unit stay because of SAB (29% vs. 18%, p 0.05); and mechanical ventilation because of SAB (9% vs. 4%, p 0.05). Of the factors associated in univariate analysis with a better prognosis, intravenous catheter-related SAB was significantly less common among community-acquired episodes of SAB than among nosocomial episodes of SAB (1% vs. 61%, p < 0.001).

DISCUSSION

On comparison of the present study (1998–2002) with a retrospective study by Lautenschlager *et al*. [13] at the same institution during 1980–1986, there was a 23% increase in SAB since the earlier study (2.2 vs. 2.7 episodes/1000 admissions). The total rate of bacteraemia also increased from 16.3 to 20.4 episodes/1000 admissions, with a stable percentage of bacteraemia (13%) being caused by *S. aureus*. The overall higher frequency of SAB was related to a 140% rise in community-acquired SAB (0.5 vs. 1.2 episodes/1000 admissions), whereas the frequency of nosocomial SAB remained essentially stable (1.2 vs. 1.3 episodes/1000 admissions). In particular, there were more injecting drug-users with community-acquired SAB in the present study (0.02 vs. 0.4 episodes/1000 admissions), reflecting an increase in injecting drug-use in the area and/or a rise in infectious complications within this population. It has been shown previously that infections are the main reason for hospitalisation of injecting drug-

Table 5. Prognostic factors in patients with *Staphylococcus aureus* bacteraemia (SAB)[a]

Variable	Univariate analysis OR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
Age (10-year increase)	1.3 (1.2–1.6)	0.001	1.05 (1.02–1.07)	< 0.001
Immunosuppression			4.1 (1.5–11.3)	0.007
Chronic obstructive pulmonary disease	2.8 (1.2–6.1)	0.01		
Congestive heart failure	2.4 (1.0–5.6)	0.05		
Alcoholism	4.6 (2.0–10.1)	< 0.001	11.7 (3.5–39.7)	< 0.001
Chronic hepatic failure	4.5 (1.8–11.6)	0.002		
Chronic renal failure with haemodialysis			6.5 (1.2–34.0)	0.03
Nosocomial SAB	0.4 (0.2–0.7)	0.002	0.2 (0.1–0.5)	0.001
Bacteraemia without focus	2.8 (1.5–5.4)	0.001		
Surgical site infection without foreign body	0.1 (0.01–1.0)	0.05		
Intravenous catheter-related infection	0.1 (0.05–0.4)	< 0.001		
Infectious diseases specialist consulted	0.3 (0.1–0.5)	< 0.001		
Secondary foci	1.9 (1.0–3.7)	0.05		
Acute renal failure	10.0 (5.1–19.6)	< 0.001	4.9 (2.1–11.9)	< 0.001
Septic shock	27.7 (10.9–70.4)	< 0.001	19.5 (6.2–61.6)	< 0.001
Adult respiratory distress syndrome	10.8 (2.6–44.2)	0.001		
Disseminated intravascular coagulation	8.7 (2.0–37.7)	0.004		
Intensive care unit stay caused by SAB	3.8 (2.0–7.5)	< 0.001		
Mechanical ventilation caused by SAB	16.3 (5.5–48.3)	< 0.001		

[a]Only variables for which p was significant are shown.

users in this area [41], with one-third being nasal carriers of *S. aureus* [42]. Compared with the study by Lautenschlager *et al*. [13], there was a 60% increase in intravenous catheter-related SAB (0.5 vs. 0.8 episodes/1000 admissions), and a 14% reduction in overall in-hospital mortality (34% vs. 20%). Possible explanations for the improved prognosis include advances in intensive care treatment during the past two decades, as well as reduced rates of septic shock, adult respiratory distress syndrome and disseminated intravascular coagulation (data not shown), higher rates of intravenous catheter-related SAB, and increased availability of an ID specialist consultation service during the present study period.

A limitation of the present study is the fact that overall hospital mortality rather than specific SAB-related mortality was considered, thereby leading to a possible overestimation of the impact of SAB on fatal outcome. However, this approach was preferred to the bias that would have been created by trying to determine retrospectively whether death was attributable to SAB.

In the present study, significant independent risk-factors for mortality in patients with SAB were age, immunosuppression, alcoholism, haemodialysis, acute renal failure and septic shock. Additional risk-factors reported in previous studies are diabetes mellitus, malignancy, chronic hepatic failure, endocarditis, bacteraemia without focus, pneumonia as the focus of SAB, non-eradicable or non-eradicated foci, inadequate antibiotic therapy, secondary foci and MRSA bacteraemia [12–19,35–37].

In accordance with published studies [12,14,25,43], a significantly higher mortality rate was observed in patients with community-acquired SAB than in patients with nosocomial SAB (26% vs. 13%). Jensen *et al*. [12] and Cunney *et al*. [14] found mortality rates of 40% and 22%, respectively, for community-acquired SAB, compared with 29% and 6% for nosocomial SAB. In the present study, the poorer outcome for community-acquired SAB may be associated with the higher frequency of bacteraemia without focus, secondary foci, acute renal failure, septic shock, disseminated intravascular coagulation, intensive care unit stay and mechanical ventilation, all of which were risk-factors for mortality in univariate and/or multivariate analysis in patients with community-acquired SAB. Furthermore, intravenous catheter-related SAB, which was associated with a better outcome in univariate analysis, was more frequent among episodes of nosocomial SAB. However, nosocomial SAB remained associated independently with a better prognosis following adjustment for these factors, so that the main reason for the better outcome of nosocomial SAB is probably associated with the earlier detection of bloodstream infection in hospital than in the community.

In the present study, consultation with an ID specialist reduced mortality significantly for patients with SAB according to univariate analysis, despite a possible bias regarding the readiness to consult an ID specialist, which was probably greater for critically-ill patients. However, this result may be biased by a deliberate choice not to consult an ID specialist for terminally-ill patients,

or in cases where patients died before consultation with an ID specialist was possible. In a prospective study by Fowler *et al*. [44], consultation with an ID specialist increased the cure rate and decreased the relapse rate significantly, but mortality was not affected. Further prospective studies are needed to elucidate the influence of ID specialists on mortality rates among patients with SAB and with sepsis in general.

Several prospective studies have shown that inadequate antibiotic therapy (empirical only, or empirical and definitive) is a significant risk-factor for mortality resulting from SAB [35,37] or from sepsis in general [45–47], with inadequate therapy being significantly more frequent with MRSA than with methicillin-susceptible *S. aureus* bacteraemia [37,46]. In the present study, inappropriate treatment had no effect on the outcome of SAB. This is probably associated with the fact that most staphylococci at the institution studied have a wide antibiotic susceptibility range, with MRSA being rare. Therefore, treatment with antibiotics considered to be inadequate, despite susceptibility of the isolate, still had some therapeutic efficacy.

Notably, a delay in correct antibiotic therapy for >24 h after obtaining blood cultures was not a risk-factor for a fatal outcome of SAB in the present study. There are several possible explanations: first, the number of patients receiving delayed correct therapy may have been too small to detect a statistically significant difference; second, in many cases, delaying correct therapy meant prescribing inappropriate empirical therapy, which still had some therapeutic efficacy for the reasons mentioned above; and third, patients with SAB and a high risk of death normally appear critically-ill and are therefore likely to receive earlier antibiotic treatment than patients with SAB in a good general condition, thus creating a bias. Lodise *et al*. [34] conducted a retrospective outcome analysis of delayed antibiotic treatment for nosocomial SAB, and reported that a delay in correct treatment beyond a breakpoint as late as 44.75 h after obtaining blood cultures was an independent predictor of infection-related mortality. In contrast, a retrospective study by Fätkenheuer *et al*. [18] did not detect a significant difference in mortality between patients with SAB whose treatment was started >48 h after obtaining blood cultures and patients treated earlier. However, both studies indicated that some patients with *S. aureus* infection can be bacteraemic for several days without their chances of survival being diminished.

In conclusion, *S. aureus* remains a common cause of bloodstream infection, with an increasing frequency of community-acquired SAB and intravenous catheter-related SAB. Despite the availability of effective anti-staphylococcal drugs and the advances in intensive care treatment, mortality in patients with SAB remains high, even at an institution where MRSA has not (yet) emerged as an additional threat. Patients with community-acquired SAB are twice as likely to die as patients with nosocomial SAB, with between one-quarter and one-third of patients not surviving until hospital discharge.

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