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CLINICAL AND EPIDEMIOLOGICAL STUDY

Risk factors associated with long-term prognosis of patients with *Staphylococcus aureus* bacteremia

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Abstract
Objective To estimate risk factors associated with long-term outcome (i.e., 1-year survival) in patients with *Staphylococcus aureus* bacteremia (SAB).
Methods and materials This was a retrospective study in which the microbiological laboratory data records of patients admitted to the University Hospital of Regensburg between January 2004 and June 2005 were examined to identify those patients with blood cultures positive for *S. aureus*. Corresponding clinical records for all patients were reviewed using a standardized questionnaire. Of the 119 patients identified with SAB, 80 were available for the >1-year follow-up.
Results Crude 1-year mortality was 47.5; 30- and 90-day mortality was 28.8 and 37.5%, respectively. In-hospital mortality was 28.8%. There were no significant differences in 1-year survival in terms of age, gender, antibiotic resistance, and mode of acquisition (nosocomial vs. community-acquired). A significantly better survival was observed with an identifiable focus present, if the chosen empiric antibiotic therapy was adequate or if the body mass index of the patient was >24.
Conclusion In summary, in this patient cohort, considerable additional mortality due to SAB beyond 30 or 90 days was present. Our results suggest that long-term survival data should be taken into account in outcome studies involving patients with *S. aureus* bacteremia.

Keywords *Staphylococcus aureus* · Bacteremia · Outcome · Mortality

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Introduction

Staphylococcus aureus bacteremia (SAB) is a leading cause of both nosocomial and community-acquired bloodstream infections and associated with a high morbidity and mortality [1] that have been attributed to secondary complications (e.g., endocarditis, metastatic organ infections) and underlying comorbidities.

To date, several studies have addressed risk factors influencing the outcome of patients with SAB [2–8]. Most of these studies evaluated either short-term mortality (30–60 days) or in-hospital mortality, and only a few studies [2, 3] focused on long-term outcome (i.e., 1 year). Since multiple comorbidities are frequently present in patients with SAB and significant additional mortality after 30 days has been reported [2, 3], it would appear important to include long-term outcome after hospital discharge into the survival calculations.

Previous studies have identified several prognostic factors for patients with SAB. Among these are malignant disease, pneumonia, age >60 years, diabetes mellitus, renal failure, severity of disease, inappropriate treatment, and a non-eradicable focus [2, 4–6, 8]. However, several studies have led to conflicting results and failed to identify an increased mortality for patients with methicillin-resistant *S. aureus* (MRSA) or inadequate empirical therapy, respectively [4, 8, 9]. The goal of the study reported here was to estimate the long-term outcome (based on 1-year

crude mortality) of patients with SAB related to various risk factors, including underlying comorbidity, age, and treatment modalities. We therefore reviewed episodes of SAB among patients admitted to our hospital during a randomly chosen 18-month period.

Patients and methods

Patients with SAB at the University Hospital of Regensburg (a 800-bed tertiary care medical center) between January 2004 and June 2005 were identified retrospectively by reviewing microbiological laboratory data records for blood cultures positive for *S. aureus*. Corresponding clinical records for all patients were reviewed using a standardized questionnaire. Items recorded included sex, age, underlying comorbidities, previous hospitalization, predisposing factors (e.g., concomitant medication, immunosuppression, indwelling catheters), onset of SAB, length of hospital stay, antibiotic therapy, and clinical course. Data on antimicrobial susceptibility were retrieved from the Institute of Medical Microbiology and Hygiene.

Patients were followed-up for day of discharge, recurrent SAB, and survival at day 30, day 90, and 1 year. Data for up to 1 year after discharge were provided by the patients' family doctors who were either sent a questionnaire or interviewed by telephone.

Nosocomial infection was defined as SAB occurring $\geq$48 h after hospital admission. Sepsis, severe sepsis, and septic shock were differentiated according to published criteria and recorded APACHE (Acute Physiology and Chronic Health Evaluation) scores [10]. "Optimal" antibiotic regimens for SAB caused by methicillin-sensitive *S. aureus* (MSSA) were defined as penicillin or first- (or second-) generation cephalosporin (if the corresponding isolate was susceptible), oxacillin, or daptomycin; "adequate" treatment consisted of any other β-lactam-antibiotic the corresponding isolate was susceptible to, vancomycin, or linezolid. For MRSA, vancomycin, daptomycin, and linezolid were considered as optimal therapy. "Inadequate" treatment regimens were considered to be those consisting only of antibiotics for which laboratory tests revealed the corresponding isolate to be resistant to and all regimens containing only orally administered antibiotics.

Data were analyzed using SPSS ver. 16 (SPSS, Chicago, IL). Kaplan–Meier estimates were used to calculate survival curves, and Cox regression analyses for univariate and multivariate analysis were applied to calculate statistical significance. $P < 0.05$ was considered to be significant. No corrections for multiple testings were applied.

The study was performed in concordance with the local Institutional Review Board's requirements for retrospective research and did not require patients' consent.

Results

Patients

A total of 119 patients with SAB were identified retrospectively. Of these, the records and questionnaires from 39 patients either provided insufficient data or the patients were lost to follow-up; in both cases, the patients were excluded from the analysis. The patient group excluded from the analysis did not differ significantly from the initial cohort in terms of demographic characteristics. Of the remaining 80 patients, 22 (27.5%) were female and 58 (72.5%) were male. The mean age was 65 years (range 20–87); 45 patients (56.3%) were >65 years and 18 (22.5%) were >75 years.

Only three patients were without any documented comorbidities, of which the most frequent were cardiac disease (48 cases; 60%), diabetes mellitus (27; 33.8%), renal insufficiency (26; 32.5%), malignant disease (17; 21.3%), occlusive vessel disease (16; 20.0%), chronic liver disease (15; 18.8%), cerebral dysfunction (12; 15.0%), and chronic pulmonary disease (10; 12.5%). One patient was human immunodeficiency virus-positive, and one had received a solid organ transplant (Table 1).

Table 1 Underlying comorbidities on day 0 (day of onset of bacteremia)

Comorbidity	Number of patients ($n = 80$)	Percentage of total
Cardiac disease	48	60.0
Diabetes mellitus	27	33.8
Renal insufficiency	26	32.5
On hemodialysis	3	3.8
Cerebrovascular disease/cerebral dysfunction	25	31.3
Malignant disease	17	21.3
Malignant disease (solid)	12	15.0
Malignant disease (bone marrow)	5	6.3
On chemotherapy	7	8.8
Occlusive vessel disease	16	20.0
Liver disease	15	18.8
Orthopedic/vascular implant, pacemaker, artificial heart valve	12	15.0
Pulmonary disease	10	12.5
Chronic alcoholism	9	11.3
Other autoimmune disease	4	5.0
Chronic skin disease	2	2.5
Rheumatoid arthritis	2	2.5
HIV/AIDS	1	1.3
Solid organ transplantation	1	1.3

Staphylococcus aureus bacteremia

Twenty-two patients (27.5%) presented with community-acquired SAB whereas 58 patients (72.5%) had nosocomial bacteremia. Fifty-eight patients (72.5%) were classified as having primary bacteremia and 22 (27.5%) as having secondary bacteremia (with the most frequent sources being previous abscess formation or skin/soft tissue infection followed by surgical wounds, spondylodiscitis, and infections of the respiratory tract).

Among the 48 patients with primary nosocomial bacteremia, 46 (95.8%) had indwelling catheters. The most frequent types were peripheral venous catheters (40 cases; 83.3%), central venous catheters (24; 50.0%), and urinary catheters (17; 35.4%).

Nine patients developed secondary manifestations (mostly metastatic infections), with four diagnosed with endocarditis according to the modified Duke criteria [11]. Overall, 45 patients fulfilled the criteria for sepsis (56.3%), 11 patients qualified as having severe sepsis (13.8%), and another four had septic shock (5.0%). The mean APACHE score was 20.9 (range 9–40), and mean C-reactive protein was 143 mg/l (range 2–384). Eleven (14%) patients required mechanical ventilation, and eight patients (10%) suffered from acute kidney failure. The average length of hospital stay after diagnosis of SAB was 18.5 days, and the average overall hospital stay was 26.9 days.

Of 80 the patients on day 0, 77 were still being treated on day 3, two had died, and one had been discharged. On day 7, 69 were still hospitalized, six had died, and five had been discharged. Overall in-hospital mortality and 30-day mortality were 28.8% (23 patients), 90-day mortality was 37.5% (30 patients), and 1-year mortality was 47.5% (38 patients).

Risk factors associated with mortality

No significant differences in 30-day or 1-year mortality were found between female and male patients. There was a slight trend towards a better outcome in patients <65 years compared to those >65 years (1-year survival 60.0 vs. 46.7%, respectively; $P = 0.41$), but the differences were not statistically significant (Fig. 1a). No significant differences in 1-year survival were found between patients with nosocomial versus community-acquired infection (53.4 vs. 50%, respectively; $P = 0.86$). There was also no relevant difference associated with primary or secondary bacteremia (1-year survival 51.7 vs. 54.5%, respectively; $P = 0.95$). However, outcome was significantly better when there was a suspected focus (e.g., indwelling catheter) compared to an unknown focus, as reflected by both the 30-day mortality (4.5 vs. 42.8%, respectively; $P = 0.002$) and 1-year mortality [26.1 vs. 62.9%, respectively; $P = 0.015$, hazard ratio 2.97, 95% confidence interval (CI) 1.24–7.09; Fig. 1c]. Similarly, patients who had their venous catheters removed on day 0 or day 1 of bacteremia showed a trend towards a better outcome compared to those who had them removed later or not at all (1-year survival 69.2 vs. 42.3%, respectively; $P = 0.051$; Fig. 1d). Finally, a lower body mass index (i.e., BMI <24 kg/m^2) was associated with a significant higher mortality (1-year survival 33.3 vs. 59.3%, respectively; $P = 0.04$, hazard ratio 2.0, 95% CI 1.03–3.89; Fig. 1f). We did not observe a higher mortality in patients with obese BMI (subgroup analyses for BMI >30, >35, and >40 kg/m^2; data not shown). However, in the patient cohort, there were only two patients with a BMI >40 kg/m^2 and six patients with a BMI >35 kg/m^2.

Antibiotic therapy

The rate of MRSA among all isolates was found to be 21.3%; no cases of community-acquired MRSA were identified. Penicillin resistance was identified in 70% of MSSA. Patients with MSSA tended to have a better outcome than those with MRSA (1-year survival 57.1 vs. 35.3%, respectively; $P = 0.15$), but the differences were not statistically significant (Fig. 1b). Only nine patients (11.3%) received therapy classified as "optimal" from day 0, an additional 51.3% were on "adequate" therapy, leaving 30 patients (37.5%) with either inadequate or no therapy on the day of onset of bacteremia. Once the microbiological results were available, 27 patients (33.8%) were finally placed on optimal therapy and 50 patients (62.5%) on adequate therapy. The average duration of antibiotic therapy was 13.9 days (range 2–67 days). Patients whose empiric therapy at onset of bacteremia was active against the corresponding *S. aureus* isolate had a significantly better outcome after 1 year (1-year survival 65.2 vs. 35.3%, respectively; $P = 0.022$, hazard ratio 2.1, 95% CI 1.11–4.05; Fig. 1e). Subgroup analyses of 1-year survival related to "adequate" versus "non-adequate" antibiotic therapy with MSSA or MRSA separately showed no significant differences (data not shown).

Multivariate analysis

Multivariate analysis was performed with parameters related to *S. aureus* infection and identified only malignant disease and inadequate antibiotic therapy on day 0 of bacteremia as a significant predictive factor for 1-year mortality. A subgroup analysis with patients who survived the first 14 days after diagnosis of bacteremia identified only malignant disease and a BMI of <24 kg/m^2 as significant risk factors (Table 2).

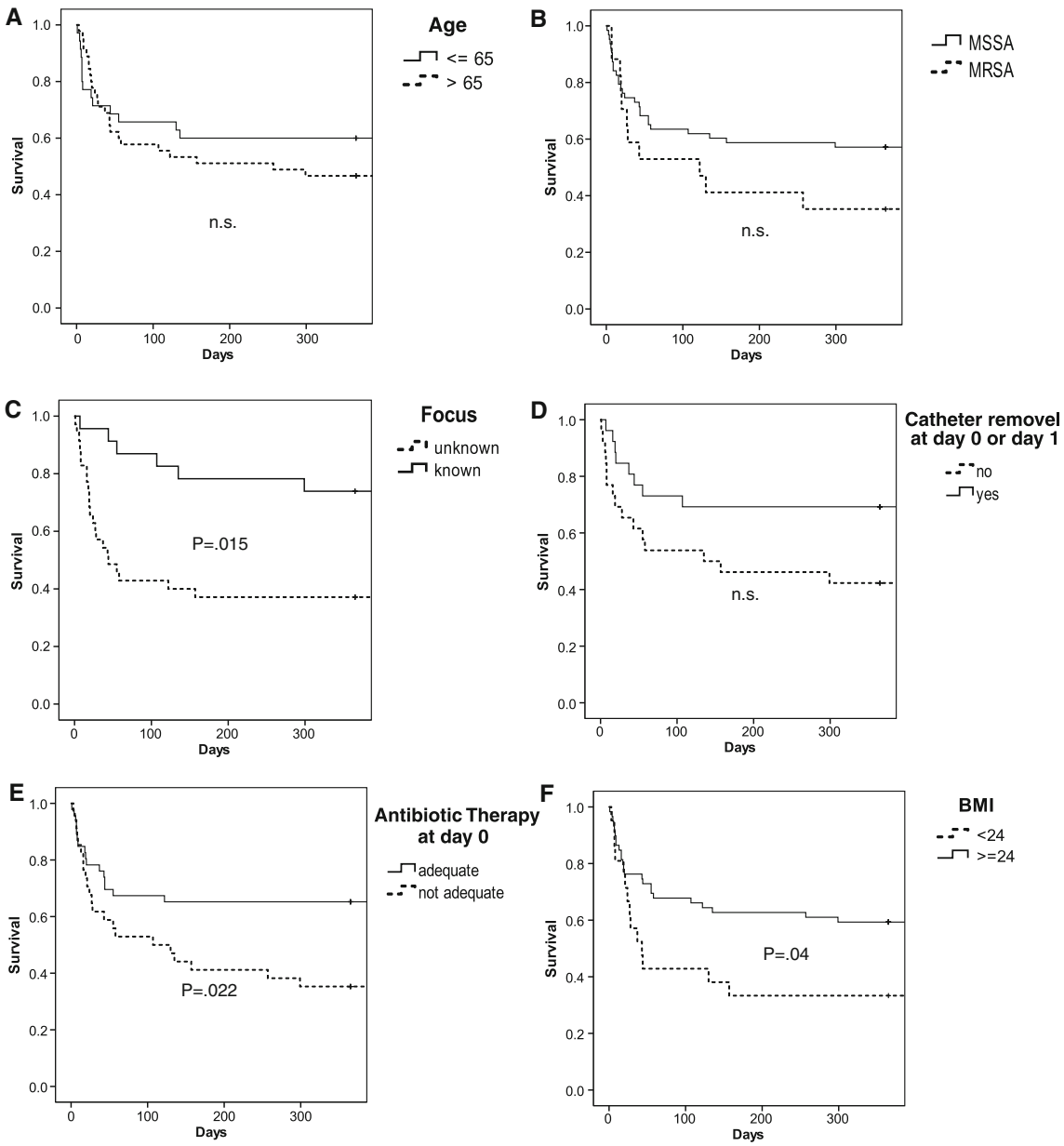

Fig. 1 Cumulative survival (Kaplan–Meier survival curves) based on age (**a**), methicillin-sensitive *Staphylococcus aureus* (*MSSA*) vs. methicillin-resistant *S. aureus* (*MRSA*) (**b**), identifiable suspected focus (**c**), catheter removal on day 0 or day 1 (**d**), adequate versus non-adequate antibiotic therapy at day 0 (**e**), and body mass index (*BMI*) (**f**)

Discussion

We retrospectively examined all cases of SAB identified through laboratory records that were treated at our institution during an 18-month period. Of the 119 cases identified, concise clinical data and 1-year follow-up data were obtainable for 80 patients. The 29% in-hospital mortality for patients with SAB reported here was high compared to the 16.2–23.2% reported in other studies [2–4, 8, 12]. However, selected cohorts of patients with SAB may have even higher mortality rates (e.g., a 38% in-house mortality was reported with underlying malignancies [9]). This high mortality rate may partially be attributable to common occurrence of underlying diseases in this patient population [13, 14]. Most of the patients in our study had a variety of comorbidities, with the most frequent being cardiac disease, diabetes mellitus, renal insufficiency, and malignant disease; these incidences are comparable to the baseline characteristics reported from other (larger) cohorts [2–5]. Another possible contributory factors is an increased carrier rate, especially among hemodialysis patients or insulin-injecting diabetic patients [15, 16]. The total lack of

Table 2 Multivariate analysis of risk factors for long-term survival (Cox regression analysis)

Risk factor	*n*	HR	95% CI	*P*
All patients				
Unknown focus	57/80	2.33	0.95–5.71	n.s.
BMI <24 kg/m^2	21/80	1.45	0.71–2.99	n.s.
Age ≥65 years	45/80	1.44	0.73–2.86	n.s.
Inadequate therapy at day 0	46/80	2.19	1.10–4.33	0.025
MRSA	17/80	1.14	0.54–2.41	n.s.
Malignant disease	17/80	2.69	1.31–5.54	0.007
Patients who survived ≥14 days				
Unknown focus	45/67	1.88	0.67–5.26	n.s.
BMI <24 kg/m^2	17/67	2.46	1.06–5.68	0.035
Age ≥65 years	40/67	2.32	0.88–6.15	n.s.
Malignant disease	14/67	4.24	1.78–10.1	0.001
Antibiotic therapy <14 days	34/67	1.24	0.53–2.87	n.s.

HR Hazard ratio, *CI* confidence interval, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *S. aureus*, *BMI* Body mass index, *n.s.* non-significant

A subgroup of patients who survived through day 14 was analyzed separately to correct for the influence of short duration of antibiotic therapy

intravenous drug users in our cohort may be explained by their low prevalence in the area served by our institution.

The short-term outcome in our study falls within the range of values from other studies: the 30-day mortality (29%) is slightly higher in our study (19.7–23.2% in other studies, [2, 8, 17]), whereas the in-hospital mortality (28.8%) is comparable to previously reported values (17.2–32.7%, [3, 4, 7, 12]). Overall 1-year mortality was found to be 47.5%, which is higher than that reported in the only other study reporting 1-year survival rates to date (37.6%, [2]). The surplus mortality during the year after hospital discharge, namely, almost another 20%, reflects the severity of disease and comorbidities in this patient population. These findings strongly support the inclusion of long-term survival into future studies of SAB.

The majority (72.5%) of all patients with SAB were male, which is in agreement with results from other studies [2–6]. However, the reason for this distorted gender distribution remains to be determined. Higher age (>60 years) has been reported to be an independent risk factor for higher mortality among patients with SAB [2–4, 6]. We observed a trend towards a better outcome in the patient group <65 years, but the total number of cases may have been too small to find significant differences. A separate analysis for patients <75 years and <60 years also showed no significant differences in long-term outcome (data not shown).

The fact that cases of nosocomial SAB outnumbered those with community-acquired SAB and that primary bacteremia was more frequent than secondary bacteremia is in concordance with previous studies [4, 8]. The long-term outcome of patients with nosocomial versus community-acquired SAB was comparable. Central venous catheters are a major risk factor for the development of SAB [13]. Bacteremia without preceding or underlying *S. aureus* infection and suspected catheter-related blood stream infection (CRBSI) was rated as primary infection for purposes of this study. We found a significantly better outcome for those patients with a suspected focus for their primary bacteremia. This may be explained by the fact that removal or treatment of the suspected focus was possible in most of these cases.

The rate of 21% MRSA in our study reflects the increasing prevalence of MRSA observed in German hospitals. In some studies, infection with MRSA has been reported as an independent risk factor associated with the outcome after SAB [5], whereas others have failed to detect significant differences [6, 8, 9]. Although we found a trend towards a better outcome with methicillin-susceptible isolates, thereby supporting the role of MRSA as an independent risk factor, our study cohort may again have been too small to detect a significant difference and to control for relevant confounding factors (e.g., more severe comorbidities). However, we were able to show a trend towards a better outcome for those patients who received an optimal or adequate antibiotic therapy at the day of the onset of bacteremia (i.e., empirical therapy). This emphasizes the need for a quick initiation of adequate antibiotic therapy and prompt catheter removal when SAB is suspected.

Whereas some authors have demonstrated higher mortality among patients with an obese BMI and sepsis or bacteremia [18, 19], we found a comparable outcome between obese and non-obese patients. It has to be noted, however, that the total number of obese patients (BMI >30 kg/m^2) in our cohort was small. Overall, patients with a BMI of >24 kg/m^2 had a significantly better outcome. Although obesity is associated with a higher risk for infections, several studies have found no additional mortality in obese ICU patients [20–22]. On the contrary, in the Intensive Care Unit, mortality in overweight and obese patients with septic shock is lower than that in patients with a normal weight or who are underweight [23]. This result might reflect the impact of nutritional status, serious comorbidities, or the contribution of factors released by adipose tissue to the host response.

Although this study has several limitations (e.g., impossibility to attribute mortality to previous *S. aureus* bacteremia, small sample size, etc.), several risk factors associated with the long-term outcome of patients with *S. aureus* bacteremia were identified, and significant additional mortality beyond 30 days was found. Among

our patient cohort, the 1-year survival rate was significantly better in patients with an identifiable focus, who received adequate antibiotic therapy from the onset of bacteremia, and who presented with a BMI of ≥24.

Conflict of interest None.

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