



# Should all adjunctive corticosteroid therapy be avoided in the management of hemodynamically stable *Staphylococcus aureus* bacteremia?

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**Abstract** The purpose of this study was to examine the prognostic impact of corticosteroids in hemodynamically stable *Staphylococcus aureus* bacteremia (SAB). There were 361 hemodynamically stable methicillin-sensitive SAB patients with prospective follow-up and grouping according to time-point, dose and indication for corticosteroid therapy. To enable analyses without external interfering corticosteroid therapy all patients with corticosteroid therapy equivalent to prednisone >10 mg/day for  $\geq 1$  month prior to positive blood culture results were excluded. Twenty-five percent (92) of patients received corticosteroid therapy of which 11 % (40) had therapy initiated within 1 week (early initiation) and 9 % (31) had therapy initiated 2–4 weeks after (delayed initiation) positive blood culture. Twenty-one patients (6 %) had corticosteroid initiated after 4 weeks and were not included in the analyses. A total of 55 % (51/92) received a weekly prednisone dose >100 mg. Patients with early initiated corticosteroid therapy had higher mortality compared to patients treated without corticosteroid therapy at 28 days (20 % vs. 7 %) (OR, 3.11; 95%CI, 1.27–7.65;  $p < 0.05$ ) and at 90 days (30 % vs. 10 %) (OR, 4.01; 95%CI, 1.82–8.81;  $p < 0.001$ ). Considering all prognostic markers, early initiated corticosteroid therapy predicted 28-day (HR, 3.75; 95%CI, 1.60–8.79;  $p = 0.002$ ) and

90-day (HR, 3.10; 95%CI, 1.50–6.39;  $p = 0.002$ ) mortality in Cox proportional hazards regression analysis. When including only patients receiving early initiated corticosteroid therapy with prednisone  $\geq 100$  mg/week the negative prognostic impact on 28-day mortality was accentuated (HR 4.8,  $p = 0.001$ ). Corticosteroid therapy initiation after 1 week of positive blood cultures had no independent prognostic impact. Early initiation of corticosteroid therapy may be associate to increased mortality in hemodynamically stable SAB.

## Introduction

*Staphylococcus aureus* is one of the most common bacteremic pathogens and associated with considerable mortality of 12–32 % in recent studies [1, 2]. The prognosis of *Staphylococcus aureus* bacteremia (SAB) is dictated by severe underlying conditions such as immunosuppression and corticosteroid therapy [3–6], severe sepsis and septic shock [4, 7], deep infection foci such as endocarditis [1, 8] and methicillin-resistance [1, 9]. Recently, over 70 % of SAB patients have had deep infection foci diagnosed [3, 8].

Hemodynamic instability, i.e. severe sepsis or septic shock, is encountered in 10–38 % of SAB patients [4, 7]. The role of corticosteroids in the management of severe sepsis and septic shock is continuously debated. Experimental studies have related the potential therapeutic impact of corticosteroids in severe infections to various molecular mechanisms such as prevention of release of interleukin-1 [10] or tumor necrosis factor [11] from mononuclear cells. The first clinical studies in 1976 suggested improved survival with high dose corticosteroid [12] but subsequent randomized-controlled trials failed to confirm these results [13–16]. In the late 1990s and early 2000s prolonged low-dose hydrocortison treatment improved survival in several studies [17, 18], including a meta-analysis

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[19]. However, further studies with severe sepsis or septic shock have demonstrated that corticosteroids do not affect 28-day mortality whereas long course treatment with low dose corticosteroids may reduce 28-day all-cause mortality [20], and a recent meta-analysis associated high-dose corticosteroid treatment to an indifferent or higher mortality probability and low-dose corticosteroid treatment to a lower mortality probability [21].

Corticosteroids may be used in hemodynamic stable SAB patients for various reasons although their impact on patient outcome has not been studied. In bacteremic patients underlying conditions such as rheumatic diseases or chronic pulmonary diseases may necessitate corticosteroid therapy due to exacerbation or non-suitability of other treatment options [4, 6, 22–24]. Corticosteroids may be needed in the management of neurosurgical procedures like subdural hematoma [25, 26] in which operative treatment may predispose patients to SAB. There are also SAB-related indications for corticosteroid treatment such as epidural abscesses, to relieve myeloid compression [27], or SAB-induced immune complex glomerulonephritis [28]. It has not been evaluated how common the use of corticosteroids during SAB treatment is and how it affects outcome in hemodynamic stable patients.

The objective of this study was to investigate the indications, initiation time-point, dose and prognostic impact of adjunctive corticosteroid therapy in hemodynamic stable SAB patients. The inclusion of methicillin-sensitive *S. aureus* strains only enabled a study setting without the impact of differences in empirical antibiotic therapy.

## Materials and methods

### Settings and study population

This was a prospective multicenter study including adult patients with at least one positive blood culture for *S. aureus* from five university and seven tertiary care central hospitals in Finland [22]. To enable thorough analyses without any external interfering corticosteroid therapy, all patients with corticosteroid therapy equivalent to prednisone  $\geq 10$  mg/day for  $\geq 1$  month prior to positive blood culture and all patients with severe sepsis or septic shock receiving systemic corticosteroid as part of sepsis therapy at blood culture collection time-point were excluded. Further exclusion criteria were: age  $< 18$  years, pregnancy, breastfeeding, imprisonment, epilepsy, bacteremia 28 days prior to the study, polymicrobial bacteremia and meningitis [22, 29]. No cases of methicillin-resistant *S. aureus* (MRSA) were accepted (N=6). There was a three-day median time-period between blood culture sampling and study inclusion. Data collection included the following parameters: age, gender, SAB acquisition, underlying diseases and McCabe's classification, length and administration

route of antibiotic therapy and any corticosteroid therapy. Documentation of infection foci were based on clinical suspicion or verified by bacteriological, pathological or radiological findings. Laboratory findings, radiological investigations and time to defervescence (axillary temperature below 37.5 °C) were recorded. Primary endpoint was mortality at 28 or at 90 days. Secondary endpoints were prevalence of deep infection foci and time to defervescence.

### Antibiotic therapy

The standard antibiotic therapy was a semisynthetic penicillin. Patients with contradictions for penicillin were provided with cefuroxime, clindamycin or vancomycin. Furthermore, fluoroquinolone and rifampicin served as additional antibiotic therapy. Length of antibiotic therapy was considered proper when administered intravenously for at least 28 days for a deep infection focus and 14 days in the absence of any deep infection. Detailed information on antimicrobial therapy indications, dosage and administration routes has been provided earlier [29, 30].

### Follow-up time period

The prospective follow-up time for the study was 90 days. No patients were lost during the follow-up. Patients that were transferred to other hospitals during the study were followed by direct communication with hospital staff and by thorough patient record retrieval. A follow-up visit at the outpatient polyclinic was arranged for each patient who was not hospitalized at 90 days.

### Definitions

Healthcare-associated (HA) SAB was defined as bacteremia with the first positive blood culture for *S. aureus* obtained  $\geq 48$  hours after hospital admission or when the patient had remained in a long-term care facility or undergone hemodialysis within the preceding two months. McCabe's criteria were used to classify underlying diseases [31]. Deep infection foci were defined as pneumonia, endocarditis, purulent arthritis, osteomyelitis, deep-seated abscess and foreign-body infections. Severe sepsis was classified as sepsis in combination with hypotension, hypoperfusion, or organ failure and septic shock as sepsis with arterial hypotension despite adequate fluid resuscitation [32].

### Corticosteroid therapy

Corticosteroid therapies were started on a clinical basis and were documented and altered into equivalent doses of prednisone. Therapy was grouped according to (1) onset time-point, (2) cumulative weekly dosage and (3) indication for therapy.

Initiation time-point was grouped into (i) early initiation (therapy onset within the first week of positive blood culture), (ii) delayed initiation (therapy onset within 2–4 weeks after positive blood culture) and (iii) late initiation (therapy onset past 4 weeks of positive blood culture).

### Statistical analysis

Categorical variables were compared with Pearson's  $X^2$  test and non-parametric data were analyzed with Mann-Whitney U-test. Odds ratios (OR) with 95 % confidence intervals (CI) were calculated. Univariate factors with  $p < 0.05$  were accepted for Cox proportional hazards regression model analysis of factors predicting mortality, and hazard ratios (HR) with 95 % confidence intervals (CI) were calculated. The Kaplan-Meier method was applied for survival estimates. Analyses were done using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed and  $p < 0.05$  was considered as significant.

## Results

### Patient characteristics

Altogether 430 patients with SAB were included. When accounting for pre-bacteremic corticosteroid use and patients with severe sepsis or septic shock, 69 patients were excluded and 361 hemodynamically stable methicillin-sensitive SAB patients were accepted for the study (Fig. 1).

### Adjunctive corticosteroid therapy

Ninety-two (25 %) of 361 SAB patients received corticosteroid therapy of whom 40 (11 %) had the therapy initiated within one week (early initiation) and 31 (9 %) within 2–4 weeks (delayed initiation). Furthermore, in 21 (6 %) patients the corticosteroid treatment was initiated after 4 weeks (late initiation) of positive blood culture and these patients were not included in the analyses. Altogether 269 (75 %) patients were treated without corticosteroid therapy (Fig. 1 and Table 1). The weekly mean cumulative corticosteroid dose ( $\pm$  standard deviation) was  $276 \pm 436$  mg prednisone during the first week and weekly corticosteroid doses of at least 100 mg were received by 26/92 (65 %) patients during the first week and by 12/92 (39 %) patients during weeks 2 to 4.

Indications for corticosteroid therapy were recorded from the patient records and in detail analyzed for patients with early initiated corticosteroid therapy (Table 2). In 7 (17 %) patients the indication could not be reliably retrieved. The most common indication was the suspicion or diagnosis of an immunological phenomenon including 30 % of patients, either (i) activation of an earlier diagnosed autoimmune

disease (e.g. ankylosing spondylitis), (ii) a reactive process (e.g. reactive arthritis) or (iii) the suspicion of an immunological defect. Among 20 % of patients, early initiated corticosteroid therapy was due to an exacerbation of a pulmonary disease or due to a pleural effusion. In 17 % of cases, corticosteroid therapy was initiated early due to epidural-, para-spinal- or pre-sacral abscesses; however, this did not impact mortality. Altogether 6 (16 %) patients had corticosteroid therapy initiated early due to purulent pericarditis (8 %) or due to a neurosurgical procedure (8 %) (Table 2).

The basic characteristics between patients with early, delayed and no corticosteroid therapy are compared in Table 1. No significant differences regarding age, gender, SAB acquisition and chronic diseases according to McCabe's classification were observed except for rheumatoid arthritis which occurred significantly more often among patients with delayed initiation of corticosteroid as compared to no corticosteroid treatment (10 % vs. 1 %,  $p < 0.01$ ). However, the total amount of patients with rheumatoid arthritis was only 8 (2 %).

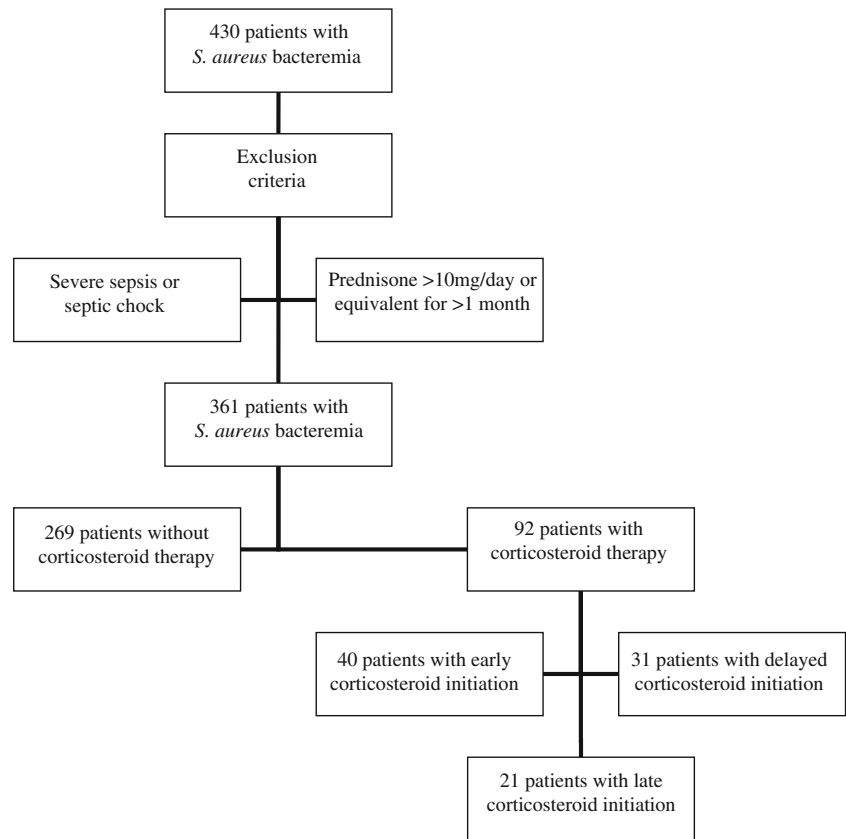
### Antibiotic therapy

An intravenous antibiotic therapy effective in vitro against the *S. aureus* blood isolate was provided to each patient from the day of positive blood culture. Altogether 272 (75 %) patients received anti-staphylococcal penicillin (cloxacillin), 69 (19 %) received cefuroxime and 8 (2 %) received vancomycin (Table 1). No significant difference was observed regarding the distribution of anti-staphylococcal penicillin or cefuroxime between the corticosteroid groups whereas vancomycin therapy was provided significantly more often to patients receiving early (10 %) or delayed (6 %) corticosteroid therapy as compared to patients treated without corticosteroid therapy (1 %) ( $p < 0.01$ ). Clindamycin as antibiotic therapy was received by only 5 (1 %) patients (data not shown). Fluoroquinolone as additional antibiotic was provided to 205 (57 %) and rifampicin to 210 (58 %) patients with no significant difference between the corticosteroid groups (Table 1).

### Deep infection foci and defervescence

Altogether 297 (82 %) patients had a deep infection focus diagnosed (Table 1). The vast majority of deep infection foci (76 %) were diagnosed within three days after the positive blood culture and verified by bacteriological, radiological or pathological findings whereas a few pneumonia cases ( $N = 5$ ) were diagnosed through clinical suspicion only. Patients with early initiated corticosteroid therapy, as compared to patients treated without corticosteroid therapy, had significantly more often pneumonia (60 % vs. 30 %,  $p < 0.001$ ) and osteomyelitis (48 % vs. 32 %,  $p < 0.05$ ). When comparing patients with delayed initiation of corticosteroid therapy to patients treated without corticosteroid therapy no significant difference was

**Fig. 1** Study profile. Originally, 430 methicillin-sensitive *S. aureus* bacteremia were recruited. Patients with corticosteroid therapy equivalent to prednisone  $\geq 10$  mg/day for  $\geq 1$  month prior to positive blood culture and all patients with severe sepsis or septic shock were excluded ( $N = 69$ ). No cases of methicillin-resistant *S. aureus* were included ( $N = 6$ ). Corticosteroid therapy: Early initiation, i.e. initiation within week 1 of positive blood cultures for *S. aureus*; Delayed initiation, i.e. initiation within week 2–4 of positive blood cultures for *S. aureus*; Late initiation, i.e. initiation within week 5–12 of positive blood cultures for *S. aureus*



observed in the occurrence of deep infection foci. No differences in invasive eradication of deep infection foci, i.e. abscess punctuation, surgical focus removal or infected joint lavage, were observed between the groups either (Table 1).

## Mortality

No significant differences in time to defervescence were observed between the groups (Table 1). The total case fatality in 361 patients at 28 days was 8 % and at 90 days 12 %. Patients with early initiated corticosteroid therapy, as compared to patients treated without corticosteroid therapy, had significantly higher mortality at 28 days (20 % vs. 7 %,  $p < 0.05$ ) and at 90 days (30 % vs. 10 %,  $p < 0.001$ ). No difference in mortality was seen between patients with delayed initiation of corticosteroid therapy and patients treated without corticosteroid therapy (Table 1, Fig. 2).

Mortality was analyzed according to indications for early corticosteroid therapy (Table 2). Patients with corticosteroid therapy initiated due to a complicated pulmonary disease had the highest 90-day mortality (63 %) whereas the corresponding mortality was seemingly lower for patients with corticosteroid due to purulent pericarditis (33 %), craniotomy (33 %) or an immunological phenomenon (17 %). Patients with unrecorded indication for corticosteroid treatment had a high mortality of 43 %. No mortality was observed among patients

receiving corticosteroid therapy due to epidural-, para-spinal- or pre-sacral abscesses (Table 2).

The prognostic impact of early and delayed corticosteroid therapy was evaluated by univariate analysis and Cox proportional hazards regression analysis (Table 3). In univariate analysis, parameters for 28-day positive prognostic impact were McCabe's healthy-nonfatal underlying conditions (OR 0.16,  $p < 0.001$ ) and rifampicin therapy  $> 14$  days (OR 0.27,  $p = 0.003$ ), whereas age  $> 60$  years (OR 11.1,  $p < 0.001$ ), alcoholism (OR 3.52,  $p = 0.003$ ), endocarditis (OR 2.47,  $p = 0.03$ ), pneumonia (OR 2.93,  $p = 0.004$ ) and early initiated corticosteroid therapy (OR 3.39,  $p = 0.005$ ) were found as negative prognostic parameters. Delayed initiation of corticosteroid therapy had no prognostic impact in 28-day univariate analysis. In Cox proportional hazards regression analysis parameters with positive prognostic impact were McCabe's healthy-nonfatal underlying conditions (HR 0.30,  $p = 0.002$ ) and rifampicin therapy  $> 14$  days (HR 0.24,  $p = 0.003$ ), whereas age  $> 60$  (HR 10.1,  $p < 0.001$ ), alcoholism (HR 3.25,  $p = 0.008$ ), endocarditis (HR 4.49,  $p < 0.001$ ) and early initiated corticosteroid therapy (HR 3.75,  $p = 0.002$ ) were negative prognostic parameters (Table 3). When repeating univariate and Cox proportional hazards regression analysis for 90-day prognostic parameters the results resembled those of 28-day prognostic parameters with the exception of chronic renal failure (HR 2.78,  $p = 0.007$ ), malignancy (HR 2.37,  $p = 0.028$ )

**Table 1** Characteristics of 340 hemodynamically stable patients with methicillin-sensitive *S. aureus* bacteremia (SAB) categorised according to initiation time-point of adjunctive corticosteroid therapy

Variable	No corticosteroid (n=269)	Early initiation <sup>a</sup> (n=40)	Delayed initiation <sup>b</sup> (n=31)	Early initiation vs. no corticosteroid		Delayed initiation vs. no corticosteroid	
				OR (95 % CI)	p-value	OR (95 % CI)	p-value
General characteristics							
Age > 60 years	126 (47)	21 (53)	18 (58)	1.25 (0.65–2.44)	NS	1.57 (0.74–3.34)	NS
Male gender	168 (62)	27 (68)	14 (45)	1.25 (0.62–2.53)	NS	0.50 (0.23–1.05)	NS
Nosocomial bacteremia	139 (52)	16 (40)	19 (61)	0.62 (0.32–1.23)	NS	1.48 (0.69–3.17)	NS
Underlying diseases							
Healthy-nonfatal <sup>c</sup>	208 (77)	29 (73)	21 (68)	0.77 (0.37–1.64)	NS	0.62 (0.28–1.38)	NS
Ultimately-rapidly fatal <sup>c</sup>	61 (33)	11 (28)	10 (32)	1.29 (0.61–2.74)	NS	1.62 (0.73–3.63)	NS
Rheumatoid arthritis	4 (1)	1 (3)	3 (10)	1.70 (0.19–15.6)	NS	7.10 (1.51–33.3)	<0.01
Connective tissue disease	11 (4)	3 (8)	2 (6)	1.90 (0.51–7.14)	NS	1.62 (0.34–7.66)	NS
Chronic kidney disease	34 (13)	2 (5)	5 (16)	0.36 (0.08–1.58)	NS	1.33 (0.48–3.69)	NS
Chronic lung disease	37 (14)	10 (25)	5 (16)	2.09 (0.94–4.63)	NS	1.21 (0.44–3.34)	NS
Malignancy	31 (12)	6 (15)	6 (19)	1.36 (0.53–3.49)	NS	1.84 (0.70–4.84)	NS
Diabetes	65 (24)	14 (35)	5 (16)	1.69 (0.83–3.43)	NS	0.60 (0.22–1.64)	NS
HIV-infection	8 (3)	0	0	—	—	—	—
Injection drug use	31 (12)	5 (13)	2 (6)	1.10 (0.40–3.01)	NS	0.53 (0.12–2.33)	NS
Antibiotic therapy							
Cloxacillin <sup>d</sup>	206 (77)	27 (68)	23 (74)		NS		NS
Cefuroxime <sup>d</sup>	55 (20)	5 (13)	4 (13)		NS		NS
Vancomycin <sup>d</sup>	2 (1)	4 (10)	2 (6)		<0.01		<0.01
Fluoroquinolone <sup>c</sup>	154 (57)	20 (50)	21 (68)		NS		NS
Rifampicin <sup>e</sup>	154 (57)	23 (58)	17 (55)		NS		NS
Rifampicin > 14 days <sup>e</sup>	124 (46)	15 (38)	14 (45)		NS		NS
Infection diagnostics							
Any deep infection focus <sup>f</sup>	210 (78)	38 (95)	28 (90)	5.34 (1.25–22.8)	<0.05	2.62 (0.77–8.93)	NS
Pneumonia <sup>f</sup>	82 (30)	24 (60)	13 (42)	3.42 (1.73–6.78)	<0.001	1.65 (0.77–3.52)	NS
Endocarditis <sup>f</sup>	39 (14)	5 (13)	8 (26)	0.84 (0.31–2.28)	NS	2.05 (0.86–4.91)	NS
Septic arthritis <sup>f</sup>	33 (12)	6 (15)	5 (16)	1.26 (0.49–3.24)	NS	1.38 (0.49–3.83)	NS
Osteomyelitis <sup>f</sup>	85 (32)	19 (48)	11 (35)	1.96 (1.00–3.83)	<0.05	1.19 (0.55–2.60)	NS
Any deep abscess <sup>f</sup>	113 (42)	22 (55)	16 (52)	1.69 (0.87–3.29)	NS	1.47 (0.69–3.10)	NS
Abscess drainage	67 (25)	15 (38)	11 (35)	1.81 (0.90–3.63)	NS	1.66 (0.76–3.64)	NS
Surgical focus removal	59 (22)	13 (33)	11 (35)	1.71 (0.83–3.53)	NS	1.96 (0.89–4.32)	NS
Infected joint lavage	8 (3)	0	0	—	—	—	—
Outcome							
Time to defervescence <sup>g</sup>	4.32 ± 5.39	4.15 ± 6.12	4.35 ± 3.16	—	—	—	NS
Mortality within 28 days	20 (7)	8 (20)	2 (6)	3.11 (1.27–7.65)	<0.05	0.86 (0.19–3.86)	NS
Mortality within 90 days	26 (10)	12 (30)	3 (10)	4.01 (1.82–8.81)	<0.001	1.00 (0.29–3.52)	NS

Originally, altogether 430 SAB patients were identified. Patients with corticosteroid therapy equivalent to prednisone  $\geq 10$  mg/day for  $\geq 1$  month prior to positive blood culture and all patients with severe sepsis or septic shock receiving systemic corticosteroid as part of sepsis therapy at blood culture collection time-point were excluded (N = 69). Twenty-one patients had corticosteroid therapy initiated 4 weeks past positive blood culture and these were not included in the analysis. Data are no. (%) of patients unless otherwise specified. NS non-significant

<sup>a</sup> Corticosteroid therapy initiation within week 1 of positive blood culture for *S. aureus*

<sup>b</sup> Corticosteroid therapy initiation within week 2–4 of positive blood culture for *S. aureus*

<sup>c</sup> According to McCabe and Jackson [31]

<sup>d</sup> Standard antibiotic therapy

<sup>e</sup> Additional antibiotic therapy

<sup>f</sup> Diagnosed within 90 days time

<sup>g</sup> Time given in days (mean  $\pm$  SD)



**Table 2** Categorization of 40 hemodynamically stable patients with *S. aureus* bacteraemia (SAB) according to indication for adjunctive corticosteroid therapy started within a week after positive blood culture

Indication for corticosteroid use	Patient number (n = 40)	3-day mortality	28-day mortality	90-day mortality
1. Purulent pericarditis	3 (8)	0	0	1 (33)
2. Craniotomy	3 (8)	0	0	1 (33)
3. Epidural, para-spinal or pre-sacral abscess	7 (17)	0	0	0
4. Complicated pulmonary disease <sup>a</sup>	8 (20)	0	5 (63)	5 (63)
5. Activation of autoimmune disease <sup>b</sup>	12 (30)	0	1 (8)	2 (17)
6. Other indication	7 (17)	0	2 (29)	3 (43)

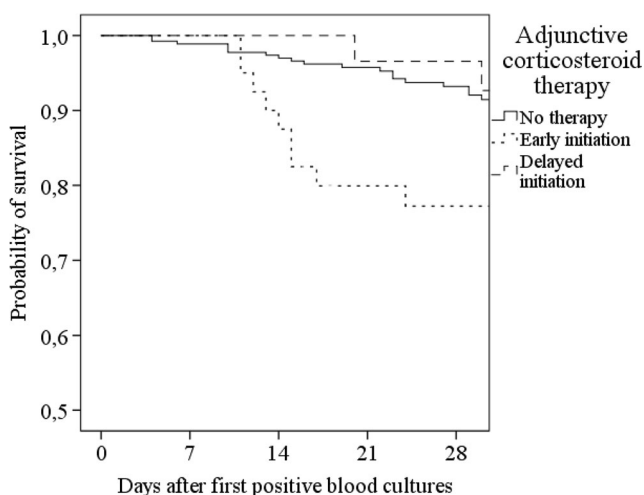
Data are number (%) of patients

<sup>a</sup> Chronic obstructive pulmonary disease, asthma bronchial or pulmonary obstruction.

<sup>b</sup> Earlier diagnosed autoimmune disease

and delayed initiation of corticosteroid therapy (HR 2.32,  $p=0.014$ ) associating to negative prognosis in univariate analysis (data not shown).

As a further investigation, we performed a Cox proportional hazards regression analysis including only patients with chronic pulmonary disease or SAB related pneumonia (N=164). The results of this analysis closely resemble those of Table 3 with a 90-day negative prognostic impact due to early initiated corticosteroid therapy (HR 2.94,  $p=0.008$ ). This prognostic impact was further accentuated when including only patients receiving early initiated corticosteroid therapy with a minimum of prednisone 100 mg/week (HR 4.65,  $p<0.001$ ).



**Fig. 2** Kaplan-Meier analysis of 28-day survival of 340 *Staphylococcus aureus* bacteremia patients categorized according to corticosteroid therapy (log-rank 0.04). Patients with corticosteroid therapy equivalent to prednisone  $\geq 10$  mg/day for  $\geq 1$  month prior to positive blood culture and all patients with severe sepsis or septic shock at blood culture collection time-point were excluded (N=69). No cases of methicillin-resistant *S. aureus* were included (N=6). Corticosteroid therapy: Early initiation, i.e. within week 1 of positive blood culture for *S. aureus*; Delayed initiation within weeks 2–4 of positive blood culture; Late initiation within weeks 5–12 of positive blood culture

## Discussion

The main finding of our study was a significantly poorer outcome among SAB patients receiving early initiated corticosteroid therapy as compared to those treated without corticosteroid therapy or with corticosteroid therapy at a later stage. Patients treated with early initiated corticosteroid therapy had a more than 3-fold higher hazard ratio for a fatal outcome when adjusting for all prognostic factors.

Parameters with indisputable prognostic impact in SAB are immunosuppression, severity of illness at blood culture collection time-point and proper antibiotic therapy [4, 22, 33]. Immunosuppressive therapy (including corticosteroid therapy) prior to positive blood culture is known to deteriorate the prognosis of SAB [3–6, 22]. SAB patients suffering from severe sepsis or septic shock present with high mortality [4, 7, 22] and systemic corticosteroids are widely applied as sepsis therapy despite controversial results in large clinical trials. Furthermore, prognosis of SAB is impaired by delayed proper antibiotic therapy [33]. MRSA is connected to delayed effective antibiotic therapy and poorer outcome [6, 9, 34] and vancomycin therapy is known to increase the risk for persistent and recurrent SAB and to impair prognosis as compared to beta-lactam antibiotic therapy [35, 36]. In the present study patients with early corticosteroid therapy received significantly more often vancomycin therapy as compared to patients treated without corticosteroid therapy or patients with delayed corticosteroid therapy. However, altogether only 8 (2 %) patients received vancomycin therapy and the low n-number did not allow for reliable statistical analyses. Thus, we were not able to evaluate the prognostic impact of vancomycin treatment among patients with corticosteroid therapy.

This study excluded patients with corticosteroid therapy equivalent to prednisone  $\geq 10$  mg/day for  $\geq 1$  month prior to positive blood culture results and included only hemodynamically stable patients. No MRSA cases were included and all patients were provided with an effective antibiotic therapy from the time-point of the first positive blood culture and only

**Table 3** Cox proportional hazards regression model for prognostic factors of 28-day mortality in *S. aureus* bacteremia patients (N = 340)

Variable	Univariate analysis OR (95 % CI)	p-value	Multivariate analysis HR (95 % CI)	p-value
Age > 60 years	11.1 (3.31–37.4)	<0.001	10.1 (2.93–34.8)	<0.001
Nosocomial bacteremia	0.96 (0.45–2.02)	NS		
Healthy-nonfatal underlying disease <sup>a</sup>	0.16 (0.08–0.36)	<0.001	0.30 (0.14–0.65)	0.002
Alcoholism	3.52 (1.45–8.57)	0.003	3.25 (1.36–7.79)	0.008
Any malignancy	2.42 (0.97–6.02)	NS		
Rifampicin therapy > 14 days <sup>b</sup>	0.27 (0.11–0.67)	0.003	0.24 (0.09–0.61)	0.003
Endocarditis	2.47 (1.07–5.70)	0.03	4.49 (1.94–10.4)	<0.001
Pneumonia	2.93 (1.37–6.30)	0.004		
Corticosteroid, early initiation <sup>c</sup>	3.39 (1.39–8.25)	0.005	3.75 (1.60–8.79)	0.002
Corticosteroid, delayed initiation <sup>d</sup>	0.74 (0.17–3.28)	NS		

Originally altogether 430 SAB patients were identified. Patients with corticosteroid therapy equivalent to prednisone  $\geq 10$  mg/day for  $\geq 1$  month prior to positive blood culture and all patients with severe sepsis or septic shock at blood culture collection time-point were excluded (N = 69). Patients were grouped according to time-point of corticosteroid treatment initiation: 40 patients had early corticosteroid initiation, 31 patients had delayed corticosteroid initiation and 21 patients had late corticosteroid initiation. Patients with late corticosteroid initiation were not included in the analyses. Hazards ratio (OR) and 95 % confidence intervals (95 % CI) are presented. NS non-significant

<sup>a</sup> According to McCabe and Jackson [31]

<sup>b</sup> Additional antibiotic therapy

<sup>c</sup> Corticosteroid therapy initiation within week 1 of positive blood culture for *S. aureus*

<sup>d</sup> Corticosteroid therapy initiation within week 2–4 of positive blood culture for *S. aureus*

2 % received vancomycin. Hence, we were able to analyze the impact of corticosteroid therapy in hemodynamically stable SAB without any external interfering corticosteroid therapy and without any bias or delay in proper antibiotic therapy onset.

However, our study has several weaknesses which have to be taken into account when the results are interpreted. Although the patients were followed prospectively they were not randomized according to corticosteroid treatment. Complicated pulmonary diseases and pneumonia in association with SAB has been described as a powerful parameter for poor outcome [3, 22, 37, 38]. This was observed also in the present study as patients with early corticosteroid treatment due to pulmonary complications demonstrated very high (63 %) mortality rates.

It may be argued that patients with early initiated corticosteroid therapy had a more severe form of SAB, including a more pessimistic prognosis initially, and thus were more prone to receive corticosteroid therapy at an early phase. To further investigate this argument a Cox proportional hazards regression analysis was performed including only patients with chronic pulmonary disease or SAB related pneumonia and within this subgroup of patients early initiated corticosteroid therapy had an evident negative prognostic impact which was further accentuated when including only patients receiving early initiated corticosteroid therapy with a minimum of prednisone 100 mg/week. Another major bias is the low number of patients with early corticosteroid therapy in the various

indication groups not making it possible to analyze them with statistical testing. However, as corticosteroids are not generally indicated for SAB treatment, randomized studies would not be ethically justifiable. We think that our study, despite its weaknesses, has a clear message to clinicians to overweigh the indications of corticosteroid treatment carefully in the early treatment of SAB.

Various attempts were made to control reasons for the differences in outcome between patients with early and delayed initiation of corticosteroid therapy and patients treated without corticosteroid therapy. Differences in age, bacteremia acquisition, underlying conditions or antibiotic therapy did not explain the poorer prognosis. Patients with deep infection foci, including pneumonia and osteomyelitis, were more prone to receive early initiated corticosteroid therapy as compared to patients treated without corticosteroid therapy. Parameters with independent prognostic impact have been identified in earlier studies, e.g. age > 60–65 years [1, 38], severe underlying diseases [1, 36], adjunctive rifampicin therapy [30], chronic alcoholism [4, 22] and endocarditis [1, 22]. When controlling for all of these parameters early initiated corticosteroid therapy remained an independent prognostic marker for 28 and 90 days fatal outcome.

The exclusion of patients with corticosteroid therapy prior to SAB diagnosis and the inclusion of only hemodynamically stable patients have inevitably influenced the results as immunosuppressive therapy, severe sepsis and septic shock associate to high mortality [4, 7, 22, 33]. Furthermore, each

patient was provided with a formal infectious disease specialist consultation which is known to improve treatment results and prognosis [1, 3, 39]. Altogether, these factors have most probably contributed to an overall lower mortality of only 8 % at 28 days and of 12 % at 90 days as compared to earlier studies presenting 28–30 days and 90 days mortality figures of 16–26 % [5, 38–40] and 12–32 %, respectively [1, 2]. However, although the overall mortality in the present study was low, a negative prognostic impact due to early corticosteroid treatment was evident.

In conclusion, our data suggests that in hemodynamical stabile SAB early initiation of corticosteroid therapy may be associated to poor outcome as compared to delayed initiation of corticosteroid therapy or no corticosteroid therapy. The authors encourage caution regarding early use of corticosteroids in the management of hemodynamical stabile SAB patients.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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