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ORIGINAL PAPER

Comparison of patient characteristics, clinical management, infectious specialist consultation, and outcome in men and women with methicillin-sensitive *Staphylococcus aureus* bacteremia: a propensity-score adjusted retrospective study

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Abstract

Background Sex-related treatment inequalities are suggested to explain outcome differences between men and women in *Staphylococcus aureus* bacteremia (SAB). We compared patient characteristics, clinical management, infectious specialist consultation (ISC) and outcome in men and women with SAB.

Methods Multicenter retrospective study of methicillin-sensitive (MS-) SAB patients categorized according to sex and ISC consultation provided within 7 days of diagnosis.

Results Altogether 617 SAB patients were included in the analysis: 62% males and 38% females. Male sex was associated less often to nosocomial bacteremia (OR 0.69, 95% CI 0.50–0.96, $p=0.029$) and more often to alcoholism (OR 2.25, 95% CI 1.31–3.87, $p=0.003$). No sex-related differences were seen in basic or immunologic laboratory tests, illness severity, intensive care unit treatment or thromboembolic events. ISC was provided to most patients (94%) irrespective of sex. No differences were seen in clinical management of men or women: Transthoracic or -esophageal echocardiography (61% vs. 65%), deep infection (77% vs. 72%), infection removal (30% vs. 27%) and anti-staphylococcal antibiotics as first-line treatment (54% vs. 51%). However, male sex was connected to more frequent adjunctive rifampicin treatment (52% vs. 41%, $p=0.025$). No difference in 28- or 90-day mortality (13% vs. 13% and 18% vs. 20%) or SAB relapse (0% vs. 1%) was observed between men and women. Propensity-score adjusted Cox proportional analysis gave no connection of sex to mortality within 90 days.

Conclusion Patient characteristics, clinical management, ISC guidance, bacteremia relapse, and outcome did not differ in men and women with MS-SAB.

Keywords *S. aureus* bacteremia · Infectious specialist consultation · Deep infection foci · Prognosis · Sex

Introduction

Staphylococcus aureus bacteremia (SAB) is associated with considerable morbidity and mortality [1]. Prognosis of SAB is influenced by age and comorbidity [2], severe sepsis [3], endocarditis [4] and methicillin-resistance [5]. However, infectious disease specialist consultation (ISC) improves prognosis of SAB [6]. ISC as a mandatory practice in SAB is advocated by ever more clinicians [7, 8].

The impact of sex on prognosis in severe infections has received much attention. However, reports are conflicting, with female sex connecting to excess mortality in bacteremia [9], whereas sepsis survival studies present poorer outcome in males [10] or no sex-related prognostic differences [11].

Female sex has repeatedly been associated to poorer prognosis in SAB [12–17]. A recent large Danish population-based study confirmed that women had significantly higher mortality in SAB and suggested that female sex should be considered in risk stratification [13]. The connection of female sex to poor outcome in severe infections has been speculated to be due to sex-related dimorphism

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[18] including female sex steroids [19] enhancing immune response with potential subsequent impact on outcome. Studies on healthcare-seeking behavior speculate that women receive antibiotic prescriptions more often which may delay hospital arrival and influence prognosis [20]. Furthermore, studies on sepsis report care inequality for severely ill female patients with delayed empiric antimicrobials [21], less access to mechanical ventilation, hemodialysis [22] or life-supporting treatments [23]. However, prospective studies [1, 24] and ISC guided management reports [4, 6–8] have not reported any sex-related outcome disadvantage in SAB. These contradicting results were evaluated in a recent editorial [25] and explained by limited data on clinical management including incomplete reporting of ISC, lack of knowledge on infection acquisition and inclusion of poly-microbial infections or non-adjustment for co-morbidities [12–17].

The objective of the present study was to compare patient characteristics, clinical management, infectious specialist consultation, bacteremia relapse and outcome in men and women with methicillin-sensitive (MS-) SAB. Inclusion of MS-SAB only enabled each patients to receive proper non-delayed antibiotics from the first day of SAB and thus reducing empirical antibiotic influence.

Materials and methods

Study population

This was a retrospective multicenter study with 90 days follow-up. All adult patients with blood culture positive for *S. aureus* from five university and seven central hospitals in Finland during January to May 1999 and January 2000 to August 2002 were enrolled. Furthermore, as an extension, each adult patient with positive blood culture for *S. aureus* from Helsinki University Central Hospital in Finland in 2006–2007 was included. Bacteremia due to methicillin-resistance (MRSA) was omitted. Two time-periods were included to account for temporary differences in treatment management, personnel practices or other factors difficult to control for studies. The median time-period between blood culture sampling and clinical awareness of *S. aureus* as a causative pathogen was 3 days. Data documentation included: sex, age, co-morbid diseases, illness severity, deep infection identification and eradication and administration route and length of antibiotic therapy and any ISC. Both basic laboratory tests and tests for immunological status were recorded repeatedly. Final statistical analyses were performed by excluding patients who deceased within 3 days to account for the possibility of death before performed ISC. The primary end-point was mortality at 28 and 90 days and secondary end-point defervescence time, SAB relapse and hospitalization duration. No differences in the deep infection foci, antimicrobial treatment or underlying characteristics were observed in patient groups from the two different inclusion periods.

Definitions

McCabe's criteria were applied for classification of comorbid diseases [26]. ISC within 7 days of *S. aureus* bacteremia diagnosis were recorded. Formal ISC was defined as a bedside consultation by the infectious specialist with review of patient records, physical investigation and written directives. Informal ISC was defined as a telephone consultation (or other informal consultation) where the treating physician documented into the patient records directives given by the ISC [27].

Statistical analyses

Categorical variables were compared with Pearson's χ^2 test and non-categorical variables with Mann–Whitney U test. Univariate parameters with $p \leq 0.1$ were accepted for further analyses. The independent prognostic impact of sex was estimated by propensity-score adjusted Cox proportional regression analysis. First, variables with significant statistical connection to sex were identified and interpreted as relevant. Second, a propensity-score adjusted Cox proportional regression analysis was performed to estimate prognostic parameters of 90-days outcome. All tests were two-tailed and $p < 0.05$ regarded significant. Analyses were done with SPSS 12.0 (SPSS Inc. Chicago IL, USA).

Results

Patient characteristics and illness severity

A total of 617 SAB patients were included. Altogether, 384 (62%) were men aged (56.0 ± 17 years, mean ± SD) and 233 (38%) women (58.3 ± 18 years, mean ± SD). Men, compared to women, had less nosocomial bacteremia (OR 0.69, $p = 0.029$) and more alcoholism (OR 2.25, $p = 0.003$), whereas no significant differences were observed in hospitalization preceding SAB or in other underlying conditions (Table 1). No significant differences were seen between sex and PITT bacteremia scores (mean or total scores ≥ 3), severe sepsis, intensive care unit or thromboembolic events (Table 1).

Laboratory parameters

Basic laboratory parameters were recorded for each patient and teichoic acid antibody and antistaphylolysin for

Table 1 Patient demographics, underlying conditions and severity of illness in 617 patients with methicillin-sensitive *S. aureus* bacteremia stratified according to sex

Patient characteristics	Women 233 (38)	Men 384 (62)	OR (95% CI)	*p* value
Demographics				
Age > 60 years	119 (51)	167 (43)	0.74 (0.53–1.02)	NS
Age, years (mean ± SD)[a]	58.25 ± 18.47	56.02 ± 17.30	–	NS
Nosocomial bacteremia	137 (59)	191 (50)	0.69 (0.50–0.96)	0.029
Previous hospitalization[b]	131 (56)	207 (54)	0.91 (0.66–1.27)	NS
Underlying conditions				
Healthy—nonfatal disease[c]	173 (74)	263 (68)	0.75 (0.52–1.09)	NS
Ultimately—rapidly fatal disease[c]	60 (26)	121 (32)	1.33 (0.92–1.91)	NS
Coronary heart disease	54 (23)	91 (24)	1.03 (0.70–1.51)	NS
Chronic pulmonary disease	42 (18)	64 (17)	0.91 (0.60–1.40)	NS
Diabetes mellitus	35 (15)	73 (19)	1.36 (0.86–2.15)	NS
Chronic renal failure	26 (11)	57 (15)	1.39 (0.85–2.28)	NS
Chronic alcoholism	19 (8)	64 (17)	2.25 (1.31–3.87)	0.003
HIV infection	2 (1)	9 (2)	2.78 (0.60–12.9)	NS
Corticosteroids[d]	22 (9)	31 (8)	0.84 (0.48–1.49)	NS
Malignancy				
Hematological	16 (7)	23 (6)	0.86 (0.45–1.67)	NS
Non-hematological	28 (12)	38 (10)	0.80 (0.48–1.35)	NS
Severity of illness				
Severe sepsis[f]	17 (7)	39 (10)	1.44 (0.79–2.60)	NS
PITT score ≥ 3	21 (9)	44 (11)	1.29 (0.75–2.24)	NS
PITT score (mean ± SD)[a]	0.65 ± 1.45	0.89 ± 1.82	–	NS
ICU treatment[e]	44 (19)	80 (21)	0.75–1.70)	NS
Non-invasive ventilation	9 (4)	22 (6)	0.68–3.34)	NS
Inotrope support	9 (4)	23 (6)	0.72–3.49)	NS
Acute dialysis	7 (3)	15 (4)	1.31 (0.53–3.27)	NS
Thromboembolic events[e]	31 (13)	46 (12)	0.87 (0.53–1.45)	NS
Basic parameters[e]				
C-reactive protein				
At blood cultures	175 ± 114	175 ± 107	–	NS
At day 3	136 ± 79	132 ± 83	–	NS
At day 7	73 ± 64	72 ± 55	–	NS
Leucocyte count	13 ± 5.6	14 ± 15	–	NS
Blood glucose	8.4 ± 4.5	8.4 ± 5.1	–	NS
Albumin (liver)	26 ± 5.8	26 ± 7.5	–	NS
Alanine aminotransferase	70 ± 151	88 ± 361	–	NS
Activated partial thromboplastin time	36 ± 4	39 ± 6	–	NS

Values are n (%) and odds ratios (ORs) with 95% confidence intervals (CI) or mean ± standard deviation (SD). Comparisons with Mann–Whitney *U* test

NS non-significant

[a]Mann–Whitney *U* test

[b]Within 2 months prior to SAB

[c]McCabe's classification [26]

[d]Dose ≥ 10 mg/day ≥ 1 month

[e]At blood culture collection

one-third of patients. Parameters relevant for coagulation and immunology were retrieved for only part of patients. Basic parameters of C-reactive protein, leucocyte count, blood glucose, albumin, alanine aminotransferase and activated partial thromboplastin were measured at daily basis during the first 7 days and thereafter once a week. Parameters for

coagulation, i.e., anti-thrombin III, fibrinogen, thrombin time, factor VIII and d-dimer ($N=42$) were recorded at positive blood cultures, at days 7 and 90. Immunoglobulins A, M and G ($N=22$) and complement factors C-3, C-4, Ch100Cl ($N=43$) and interleucin-2 receptor ($N=10$) were recorded once a week and teichoic acid antibody and antistaphylolysin ($N=256$) at day 3 and 21. No sex-related difference for any laboratory test at any time-point was observed. The basic laboratory results are presented in Table 1.

Clinical management

Altogether 94% (582) of patients received ISC. Most patients had formal (bedside) ISC (84%) whereas informal (telephone) ISC was provided to 62 (10%) patients and only 35 (6%) were managed without consultation. No significant difference with respect to sex were observed for presence or absence of ISC (Table 2). Echocardiography was provided to 63% of patients with no significant difference observed between men and women regarding transthoracic- (61% vs. 65%) or trans-esophageal (18% vs. 17%) examinations. Deep infection foci were identified in 75% (464) and endocarditis in 15% (91) of patients without any sex differences (Table 2). Altogether 29% (178) of patients underwent infection focus removal. No significant differences between men and women were noted regarding radiological or surgical infection focus eradication, infected joint lavage or heart valve replacement (Table 2). An intravenous antimicrobial agent effective in vitro against the *S. aureus* blood isolate was provided to each patient from the first day of positive blood culture. Most received anti-staphylococcal penicillin (53%), whereas 37% had cephalosporin as a first-line treatment. No significant difference was observed regarding sex and standard antimicrobial or adjunctive fluoroquinolone antimicrobial therapy. However, rifampicin adjunctive therapy was provided more often to men compared to women (52% vs. 41%, $p=0.025$) (Table 2).

Primary and secondary outcome

The mortality was 13% at 28 days and 19% at 90 days with no significant difference observed between men and women (Table 2; Fig. 1). Furthermore, when analyzing the two time-periods (years 1999–2002 and 2006–2007) separately no differences in outcome were observed between men and women. Patients who deceased within 3 days ($N=12$) were excluded from univariate and Cox proportional regression analysis to allow for death before the possibility of ISC. When comparing patients who died with 3 days no statistically significant differences were observed regarding sex: 8 (67%) were men and 4 (33%) women (OR 1.22). Mean time ($\pm$SD) to defervescence and hospitalization were 6 ± 9 days and 35 ± 30 days with no sex difference (Table 2; Fig. 2). Documentation regarding SAB relapse was retrieved for 430 patients and only 5 (1%) had a SAB relapse within 90-day follow-up. No significant statistical difference was seen between sex and SAB relapse (Table 2). When comparing disease severity and treatment of deceased men and women no differences were observed (Table 3).

Parameters in univariate analysis connecting to 90-day mortality were: age ≥ 60 years (OR 3.74, $p<0.001$), healthy-nonfatal disease (OR 0.15, $p<0.001$), intensive care unit treatment (OR 2.05, $p<0.01$), formal ISC (OR 0.48, $p<0.01$), endocarditis (OR 2.12, $p<0.01$), pneumonia (OR 3.25, $p<0.001$) and adjunctive rifampicin therapy (OR 0.38, $p<0.001$). The independent prognostic impact of sex was estimated by propensity-score adjusted Cox proportional regression. First, variables with significant statistical connection to sex were identified (Tables 1, 2) and interpreted as relevant for the propensity-score assignment: (i) nosocomial bacteremia, (ii) alcoholism and (iii) rifampicin therapy. Second, a propensity-score adjusted Cox proportional regression analysis was performed for 90-day mortality: age ≥ 60 years (HR 2.21, $p<0.01$), healthy-nonfatal disease (HR 0.23, $p<0.001$), intensive care unit treatment (HR 1.60, $p<0.05$), formal ISC (HR 0.58, $p<0.05$), endocarditis (HR 2.51, $p<0.001$), pneumonia (HR 2.42, $p<0.001$) and rifampicin therapy (HR 0.24, $p<0.001$) (Table 4).

The connection of female sex to poor prognosis in SAB has been reported to be accentuated among patients with chronic pulmonary disease or malignancy [13]. As a further analysis we evaluated the connection of sex and outcome by including only patients with (i) chronic pulmonary disease, (ii) malignancy and (iii) patients with McCabe´s classification for severe underlying conditions. However, mortalities at 28 and 90 days did not differ significantly between men and women with chronic pulmonary disease, malignancy or severe underlying illness according to McCabe´s classification.

Discussion

The main observation was that patient characteristics, clinical management, ISC guidance, bacteremia relapse, and outcome did not differ in men and women with MS-SAB. In this setup, sex had no prognostic impact when accounting for prognostic parameters in propensity-score adjusted Cox proportional analysis.

The results in the present study are in contrast with previous nation- [12–14], region- [15] or single center [16] studies connecting female sex to poor outcome in SAB. We observed overall case fatalities of 13% and 19% at 28 and 90 days with no sex-related difference. Furthermore, when analyzing the two time-periods (years 1999–2002 and 2006–2007) separately no differences in outcome were

Table 2 Clinical management with consultations, radiology, infection focus diagnostics and eradication, antimicrobial therapy, time to defervescence, hospitalization time and outcome in 617 patients with methicillin-sensitive *Staphylococcus aureus* bacteremia (SAB) stratified according to sex

Clinical management	Women 233 (38)	Men 384 (62)	OR (95% CI)	*p* value
Consultations and radiology				
Formal (bedside) ISC[a]	194 (83)	326 (85)	1.13 (0.72–1.76)	NS
Informal (telephone) ISC[a]	25 (11)	37 (10)	0.89 (0.52–1.52)	NS
No ISC[a]	14 (6)	21 (5)	0.91 (0.45–1.82)	NS
Transthoracic echocardiography	153 (65)	236 (61)	0.79 (0.56–1.11)	NS
Trans-esophageal echocardiography	41 (17)	71 (18)	1.06 (0.69–1.62)	NS
Whole-body computed tomography	86 (37)	158 (41)	1.19 (0.86–1.67)	NS
Deep infection foci				
Any deep focus	168 (72)	296 (77)	1.30 (0.90–1.89)	NS
Pneumonia	79 (34)	149 (39)	1.23 (0.89–1.74)	NS
Endocarditis	33 (14)	58 (15)	1.08 (0.68–1.71)	NS
Osteomyelitis/septic arthritis	72 (31)	140 (36)	1.29 (0.91–1.82)	NS
Deep-seated abscess	86 (37)	152 (40)	1.12 (0.80–1.57)	NS
Foreign body foci	40 (17)	51 (13)	0.74 (0.47–1.16)	NS
Infection removal[b]				
Infected joint lavage	6 (3)	7 (2)	0.70 (0.23–2.12)	NS
Heart valve replacement	2 (1)	4 (1)	1.22 (0.22–6.69)	NS
Infected foreign body removal	31 (13)	46 (12)	0.89 (0.56–1.44)	NS
Any infection eradication[c]	63 (27)	115 (30)	1.15 (0.80–1.66)	NS
Antimicrobial therapy				
Vancomycin[d]	8 (3)	5 (1)	0.37 (0.12–1.15)	NS
Cephalosporin[d]	87 (37)	144 (37)	1.01 (0.72–1.41)	NS
Staphylococcal penicillin[d]	119 (51)	209 (54)	1.14 (0.83–1.58)	NS
Fluoroquinolone therapy[e]	119 (51)	184 (48)	0.93 (0.60–1.44)	NS
Rifampicin therapy[e]	96 (41)	194 (52)	1.46 (1.05–2.02)	0.025
Aminoglycoside[e]	40 (17)	62 (16)	0.93 (0.60–1.44)	NS
Outcome				
Defervescence (days)	5 ± 8	7 ± 10	–	NS
Hospitalization (days)	35 ± 34	34 ± 29	–	NS
SAB relapse within 90 days[f]	0	5 (1)	–	NS
Mortality within 28 days	30 (13)	50 (13)	1.01 (0.62–1.65)	NS
Mortality within 90 days	47 (20)	69 (18)	0.87 (0.57–1.31)	NS

Values are expressed as *n* (%) and odds ratios (ORs) with 95% confidence intervals (CI) or mean ± standard deviation (SD) and comparisons with Mann–Whitney *U* test

NS non-significant

[a]Infectious specialist consultation

[b]Data retrieved for 430 patients

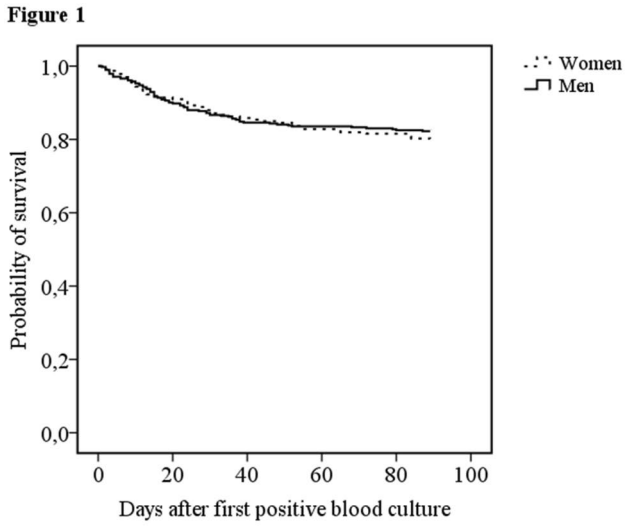
[c]Radiological or surgical

[d]Standard therapy

[e]Adjunctive therapy

[f]Data for 430 patients

observed between men and women. The mortality figures of the present study are considerably lower compared to 30 days case-fatality of 22–38% for males and 26–44% for females [12–16]. In the present study patients who deceased within 3 days were excluded from the final analyzes to allow for death before the possibility of ISC. This naturally might have influenced final results. However, only 12 patients (67% men and 33% women) deceased within the first 3 days and hence it is reasonable to assume that the exclusion of these patients has had only marginal impact on final results. We might have missed some more severe cases but the most likely explanation for the lower mortality is the meticulous localization, identification, and eradication of deep infection focus compared to previous studies [13, 15, 16]. Previous



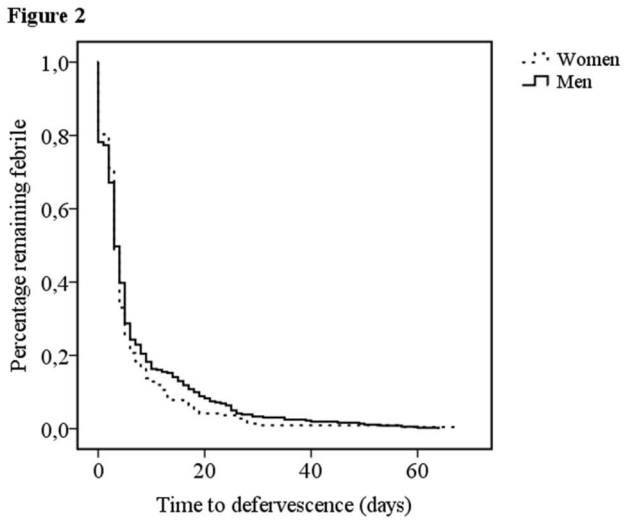


Fig. 1, 2 Kaplan–Meier of 90-days survival and time to defervescence in 617 methicillin-sensitive *S. aureus* bacteremia patients categorized according to sex. Log rank non-significant

studies report female sex as an independent negative prognostic factor in multivariate logistic regression analysis with odd ratios of 1.54–1.59, i.e., closely resembling reported odd ratios of age (1.03), bedridden status on admission (1.54), heart valve disease (1.56) or chronic renal failure (1.92) [12, 15, 16]. In the present study, sex did not connect to 90-day outcome in propensity-score adjusted Cox regression analysis and the hazard ratio of men and women were 0.84 vs. 1.0. Moreover, only 1% of patients presented a SAB relapse within 90 days without any sex difference observed. Previous studies investigating the role of sex in SAB have not documented or reported bacteremia relapse rates [13, 16]. The extensive diagnostics and eradication of deep infection foci in the present study has most likely reduced the degree of observed SAB relapses.

Previous reports present potential mechanisms for the association of female sex to poor outcome in SAB. Parameters such as age, co-morbidity and SAB acquisition are factors with well-known prognostic impact in SAB [1–6]. However, sex-related variation in these parameters have been marginal in earlier reports [13, 16] and one report concluded that age or co-morbidity did not explain outcome differences between men and women [13]. These observations are in line with the present study observing no variations in age or underlying conditions for men and women. However, we observed less alcoholism and more nosocomial SAB in females, nevertheless, when accounting for these variations in propensity-score adjusted analysis no connection of sex to mortality was observed.

Infectious specialist consultation provides evidence for improved clinical management by accelerating diagnostics, localization and eradication of deep infection foci [4, 6–8, 27]. ISC was provided irrespective of sex to 94% of patients and the vast majority (84%) had formal bedside ISC. The present study observed overall deep infection foci occurrence of 75% including endocarditis in 15% and osteomyelitis (or septic arthritis) in 34% of patients. This exceeds previous studies evaluating the prognostic impact of sex in SAB with reports of endocarditis in 9–12% and osteomyelitis in 6–28% of patients [13, 15, 16]. Comparison of deep infection foci is challenging due to lack of [12] or partial reporting [13–17] of infection foci in previous studies. However, most important, ISC improve outcome [4, 6, 27] and ISC as a mandatory practice in SAB is advocated by ever more clinicians [7, 8]. Comparison of ISC guided clinical management is not possible or challenging due to the fact that ISC has been neglected [12–16] or reported incompletely [17] in reports connecting female sex to poor outcome in SAB.

In the present study, standard first-line antibiotic therapies were provided equivalently for men and women and all patients had proper non-delayed antibiotic therapy from the first day of positive blood cultures. This enabled comparison of men and women without the bias from differences in empirical antibiotic therapy. Studies on prognostic impact of sex in SAB have not commented on adjunctive antimicrobial therapies [12–17]. In the present study half of patients received rifampicin or fluoroquinolone adjunctive therapy and rifampicin was provided more often to men compared to women. Adjunctive rifampicin therapy has been associated to a positive prognostic impact among MS-SAB patients with deep infection foci [24]. Corresponding results were achieved also in the present study where 75% of patients had a deep infection diagnosed. However, the ARREST-study, a recent randomized, double-blind, placebo-controlled trial localized deep infection foci in 40% of SAB patients and did not observe any positive influence on prognosis due to adjunctive rifampicin therapy although a small significant reduction in bacteriologically and clinically defined disease

Table 3 Patient characteristics in 116 patients with methicillin-sensitive *S. aureus* bacteraemia who deceased within 90-day follow-up

Patient characteristics	Deceased women 47 (41)	Deceased men 69 (59)	OR (95% CI)	*p* value
Age > 60 years	32 (68)	46 (67)	0.94 (0.43–2.07)	NS
Nosocomial bacteremia	31 (66)	39 (56)	0.67 (0.31–1.45)	NS
Healthy-nonfatal disease[a]	20 (43)	22 (32)	0.63 (0.29–1.36)	NS
Severity of illness				
Severe sepsis[b]	9 (19)	15 (22)	1.17 (0.46–2.95)	NS
PITT scores ≥ 3[b]	12 (26)	16 (23)	0.85 (0.36–2.01)	NS
ICU at bacteremia onset[b]	22 (27)	27 (39)	0.75 (0.35–1.59)	NS
ICU during 7 first days	16 (34)	22 (32)	0.91 (0.41–2.00)	NS
Infectious specialist engagement				
Formal consultation	33 (70)	49 (71)	1.04 (0.46–2.34)	NS
Informal consultation	8 (17)	10 (14)	0.83 (0.30–2.28)	NS
Echocardiography				
Transthoracic	28 (60)	36 (52)	0.74 (0.35–1.57)	NS
Transesophageal	7 (15)	13 (19)	1.33 (0.49–3.62)	NS
Any deep focus	37 (79)	56 (81)	1.16 (0.46–2.93)	NS
Pneumonia	26 (55)	41 (59)	1.18 (0.56–2.50)	NS
Endocarditis	10 (21)	16 (23)	1.12 (0.46–2.73)	NS
Antibiotic therapy				
Staphylococcal penicillin	24 (51)	38 (55)	1.18 (0.56–2.47)	NS
Cephalosporin	16 (34)	25 (36)	1.10 (0.51–2.40)	NS
Fluoroquinolone[c]	23 (49)	27 (39)	0.67 (0.32–1.42)	NS
Rifampicin[c,d]	11 (23)	19 (28)	1.24 (0.53–2.93)	NS

Patients are stratified according to gender. Values are expressed as *n* (%) and odds ratios (ORs) with 95% confidence intervals (CI) unless otherwise stated

NS non-significant

[a]McCabe's classification [26]

[b]At blood culture collection

[c]Adjunctive therapy

[d]For at least 14 days

recurrences was observed [28]. The authors cannot explain why men received more often rifampicin adjunctive therapy in the present study. However, despite inequality in distribution of adjunctive rifampicin therapy between men and women, the propensity-score adjusted Cox proportional analysis, accounting for all prognostic factors, observed no independent prognostic impact of sex.

Reports have proposed that gender dimorphism [18] and female sex steroids [19] may affect immune response with subsequent potential effect on outcome. However, the mean age for female patients in the present study was 58 years (and only 12% of the whole patient coho 0rt were women under the age of 50 years), i.e., most women were presumably of postmenopausal age. However, although postmenopausal age may reduce hormonal influence on immuno-status there might be some relevant differences in sex hormone or steroid levels between men and women. The present study did not record sex hormone or steroid levels. However, we looked for sex differences in laboratory tests including white blood cell count, parameters for coagulation, basic immunoglobulins, complement factors, teichoic acid antibody and antistaphylolysin and could not observe any sex-related differences.

Previous reports on sepsis management have presented alarming results on inequality of clinical management for severely ill female patients including delayed empiric antimicrobial initiation [21] and less access to mechanical ventilation, hemodialysis care [22] or life-supporting treatments [23]. A recent thorough report on sex-related outcome in SAB [13] and a subsequent editorial commentary [26] concluded that non-biological factors, including potential sex-related treatment inequalities, may explain outcome differences between men and women and argued that for the present time female sex is to be viewed as a potential prognostic parameter requiring triage and risk stratification. We did not observe any differences in clinical management, with the exception of adjunctive rifampicin therapy, between men and women.

Table 4 Propensity-score adjusted Cox proportional regression model analysis for 90-day mortality among 605 patients with methicillin-sensitive *S. aureus* bacteremia

Prognostic parameters	PS-adjusted multivariate HR (95% CI)	*p* value
Men	0.84 (0.56–1.27)	NS
Women	1.0	–
Age > 60 years	2.21 (1.41–3.45)	< 0.01
Healthy—nonfatal disease[a]	0.23 (0.15–0.35)	< 0.001
Intensive care unit[b]	1.60 (1.04–2.46)	< 0.05
Formal ISC[c]	0.58 (0.36–0.93)	< 0.05
Endocarditis diagnosis	2.51 (1.56–4.04)	< 0.001
Pneumonia diagnosis	2.42 (1.60–3.66)	< 0.001
Rifampicin therapy[d]	0.29 (0.18–0.47)	< 0.001

Hazards ratio (HR) and 95% confidence intervals (95% CI) are presented. Patients deceased within three first days ($N = 12$) have been excluded

[a]McCabe's classification [26]

[b]At blood culture collection time

[c]Infectious specialist consultation

[d]Adjunctive therapy ≥ 14 days

However, the majority of patients had ISC which is known to improve disease progression and prognosis in SAB [4, 6–8, 27]. Hence, it may be speculated that ISC balances potential sex-related differences in SAB management. However, such conclusions cannot be drawn due to the lack of control groups (without ISC) in the present study.

There are weaknesses in the present study that have to be accounted for when interpreting results. First, differences in patient groups may bias analyses of outcome. However, propensity-score adjustment and data categorization may reduce potential bias [29]. The results were achieved by propensity-score adjustment, hence, author´s view that the results are robust and the risk for statistical bias low. Second, data were collected in years 1999–2002 and 2006–2007 and the question of whether this data is valid to current clinical practice may be raised. However, although clinical management of SAB is continuously developed as new research is published, there are fundamental elements of SAB treatment that have remained unchanged over the years such as the importance of non-delayed onset of proper antibiotic treatment and identification and eradication of infection foci. ISC The authors view that the high presence of ISC in the present study has ensured recording of relevant clinical patient information and hence enabled high standard clinical management of SAB. Hence, the authors view that patient data of the present study is not outdated.

In conclusion, patient characteristics, clinical management, ISC guidance, bacteremia relapse, and outcome do not differ in men and women with MS-SAB.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics statement The trial was approved by the institutional review board of Helsinki University Central Hospital and the ethical committee of Helsinki University Central Hospital.

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