APMIS JOURNAL OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY

APMIS 127: 515–528

DOI 10.1111/apm.12955

Changes in hemostasis parameters in nonfatal methicillin-sensitive *Staphylococcus aureus* bacteremia complicated by endocarditis or thromboembolic events: a prospective gender-age adjusted cohort study

ERIK FORSBLOM,[1] AINO LEPÄNTALO,[2] ULLA WARTIOVAARA-KAUTTO,[2] EEVA RUOTSALAINEN[1] and ASKO JÄRVINEN[1]

[1]Division of Infectious Diseases, Inflammation Center, University of Helsinki and Helsinki University Hospital ; [2]Department of Hematology, University of Helsinki and Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland

Forsblom E, Lepäntalo A, Wartiovaara-Kautto U, Ruotsalainen E, Järvinen A. Changes in hemostasis parameters in nonfatal methicillin-sensitive *Staphylococcus aureus* bacteremia complicated by endocarditis or thromboembolic events: a prospective gender-age adjusted cohort study. APMIS 2019;127:515–528.

The aim of this study was to examine the changes in hemostasis parameters in endocarditis and thromboembolic events in nonfatal methicillin-sensitive *Staphylococcus aureus* bacteremia (MS-SAB) – a topic not evaluated previously. In total, 155 patients were recruited and were categorized according to the presence of endocarditis or thromboembolic events with gender-age adjusted controls. Patients who deceased within 90 days or patients not chosen as controls were excluded. SAB management was supervised by an infectious disease specialist. Patients with endocarditis (N = 21), compared to controls (N = 21), presented lower antithrombin III at day 4 ($p < 0.05$), elevated antithrombin III at day 90 ($p < 0.01$), prolonged activated partial thromboplastin time at days 4 and 10 ($p < 0.05$), and enhanced thrombin–antithrombin complex at day 4 ($p < 0.01$). Thromboembolic events (N = 8), compared to controls (N = 34), significantly increased thrombin–antithrombin complex at day 4 ($p < 0.05$). In receiver operating characteristic analysis, the changes in these hemostasis parameters at day 4 predicted endocarditis and thromboembolic events ($p < 0.05$). No differences in hemoglobin, thrombocyte, prothrombin fragment, thrombin time, factor VIII, D-dimer or fibrinogen levels were observed between cases and controls. The results suggest that nonfatal MS-SAB patients present marginal hemostasis parameter changes that, however, may have predictability for endocarditis or thromboembolic events. Larger studies are needed to further assess the connection of hemostasis to complications in SAB.

Key words: Endocarditis; hemostasis; infectious specialist consultation; staphylococcus aureus bacteremia; thromboembolic events.

Erik Forsblom, Division of Infectious Diseases, Inflammation Center, Helsinki University Hospital, P.O. Box 340, 00029, HUS Helsinki, Finland. e-mail: erik.forsblom@helsinki.fi

Staphylococcus aureus is a major cause of severe bacteremia, and Staphylococcus aureus bacteremia (SAB) is associated with mortality reaching 15%–30%

(1–3). Management guided by infectious specialists and non-delayed proper antimicrobial treatment improve outcome (4–6). Endocarditis and thromboembolic events are feared complications associated with negative prognostic impact. Studies report endocarditis in 4%–20% of SAB patients (1–5) and thromboembolic events due to endocarditis in 47%–61% of SAB patients (7, 8). Thromboembolic events are explained by fragmentation of infective vegetation by blood turbulence (9) and virulence factor of *S. aureus* (e.g. coagulase) promoting the coagulation (10). Thromboembolic events, however, are not uncommon in systemic bacterial infections regardless of endocarditis (11–16).

Severe infections and subsequent inflammatory processes may induce hemostatic alterations ranging from coagulation activation to thromboembolic

Received 31 October 2018. Accepted 4 April 2019

events and life-threatening conditions, for example disseminated intravascular coagulation (17–21). Studies have observed that disturbed hemostatic mechanisms include procoagulant upregulation, physiological anticoagulant downregulation and fibrinolysis suppression (22–24). These results in increased concentrations of acute phase protein fibrinogen and factor VIII (17, 19), prothrombin fragments and thrombin–antithrombin complexes (20, 21) and D-dimer ((18, 25)), but decreased natural anticoagulant antithrombin III (17, 26). Furthermore, *in vitro* studies have shown that bacterial structures, for example peptidoglycan may activate platelets and induce coagulation (27–29). However, although endocarditis and thromboembolic events occur in SAB, systematic studies of hemostasis parameters have not been done previously.

The objective here was to prospectively evaluate hemostasis parameter changes in nonfatal methicillin-sensitive (MS) SAB in two major thrombogenic states, endocarditis or thromboembolic events, and compare them with gender-age adjusted control patients with MS-SAB. A formal infectious disease specialist guidance guaranteed proper clinical management. The inclusion of only MS-SAB cases enabled a study setting where each patient received correct antibiotic therapy from the first day of positive blood culture thus avoiding disturbance from variations in empiric antibiotic therapy.

MATERIALS AND METHODS

Settings and study population

The study prospectively enrolled adult patients with at least one blood culture positive for MS *S. aureus* at Helsinki University Central Hospital during January 1999 to May 1999 and January 2000 to August 2002. Patients with endocarditis or thromboembolic events were identified together with gender-age adjusted control patients without endocarditis or a thromboembolic event. Patients were divided into two groups, the endocarditis group and the thromboembolic events group, and both groups included gender-age adjusted controls and were followed up for 90 days. All patients received formal bedside infectious disease specialist consultation to ensure proper management of SAB. Data recording included age, gender, infection acquisition, previous hospitalizations, underlying diseases with focus on risk factors for endocarditis and thromboembolic events, foreign devices, medication preceding bacteremia, illness severity including intensive care unit (ICU) treatment and length and administration route of antibiotic therapy. Infection foci and thromboembolic events were diagnosed through radiological, bacteriological or pathological investigations. Laboratory results, including 10 different hemostasis parameters, were recorded repeatedly during the 90-day follow-up time. The decision to analyze hemostasis parameters was made on day 90 when it was evident that the patient had survived 90-day follow-up time and could have hemostasis parameters analyzed (from stored blood samples) throughout the whole follow-up time. Hence, patients who died during the 90-day follow-up were excluded. Further exclusion criteria were age <18 years, pregnancy, breast-feeding, bacteremia 28 days prior to study or neutropenia ($<0.5 \times 10^9$/L). No methicillin-resistant SAB was accepted. The trial was approved by The Institutional Review Board of Helsinki University Central Hospital and The Ethical Committee of Helsinki University Central Hospital. A written informed consent was provided by each patient.

Definitions

We classified the severity of background diseases according to McCabe′s criteria (30). The modified Duke criteria were applied for endocarditis (31). Sepsis with hypotension, hypoperfusion or organ failure was defined as severe sepsis, whereas sepsis with arterial hypotension not responding to adequate fluid resuscitation was defined as septic shock (32). The definition of deep infection foci included pneumonia, osteomyelitis, septic arthritis, deep-seated abscess and foreign body infections. Both arterial (myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack and parenchymal embolizations, e.g. splenic thromboembolism) and venous (deep vein thrombosis or pulmonary embolism) complications were recorded.

Blood hemostasis parameters

We recorded hemostasis parameters at three time-points. The median time phase between blood culture collection and reporting of bacteremia pathogen is commonly 3 days. Thus, we decided to record hemostasis parameters at day 4 (i.e. 1-day past positive blood culture report), at day 10 and day 90. Parameters included; (i) prothrombin fragments 1 + 2, (ii) thrombin–antithrombin complex, (iii) factor VIII, (iv) D-dimer, (v) fibrinogen, (vi) antithrombin III, (vii) thrombin time, (viii) activated partial thromboplastin time (APTT), (ix) hemoglobin and (x) thrombocyte levels. Laboratory tests were always collected at 07.00 am. An explicit laboratory methodology has been described previously (33).

Anticoagulation

The decision to commence anticoagulation therapy and the choice of medication and dosage were made by a senior internal medicine specialist in cooperation with the infectious disease specialist. The anticoagulant used was either warfarin or the low-molecular-weight heparin enoxaparine. Warfarin was administered (3 or 5 mg) once a day (at 08.00 am) and the dosage was titrated until an international normalized ratio (INR) of 2–3 was achieved. The INR reference of 2–3 was considered appropriate. The dosage of enoxaparine was 1 mg/kg twice a day (at 08.00 am and at 22.00 pm).

Formal infectious specialist guidance

All patients received formal infectious disease specialist consultation within 7 days of positive blood culture report

including review of patient records, physical examination and written instructions on clinical management. Detailed information on consultations has been provided previously (5).

Antibiotic therapy

The standard antibiotic therapy was a semisynthetic penicillin, cloxacillin (2.0 g q 4 h) intravenously, alternatively cefuroxime (1.5 g q 6 h), ceftriaxone (2.0 g q 24 h), clindamycin (600 mg q 6–8 h), or vancomycin (1.0 g b.i.d.) for patients with contradictions for penicillin. The potential subsequent standard oral therapy was cloxacillin (500 mg q 6 h), cephalexin or cefadroxil (500 mg q 6 h), or clindamycin (300 mg q 6 h). Fluoroquinolone (levofloxacin) or rifampicin served as an additional antibiotic therapy. The dose of levofloxacin was 500 mg (intravenously or orally) once daily for patients under 60 kg and 500 mg b.i.d. for patients over 60 kg in weight. Rifampicin was administered 450 mg (orally or intravenously) once daily for patients under 50 kg and 600 mg once daily for

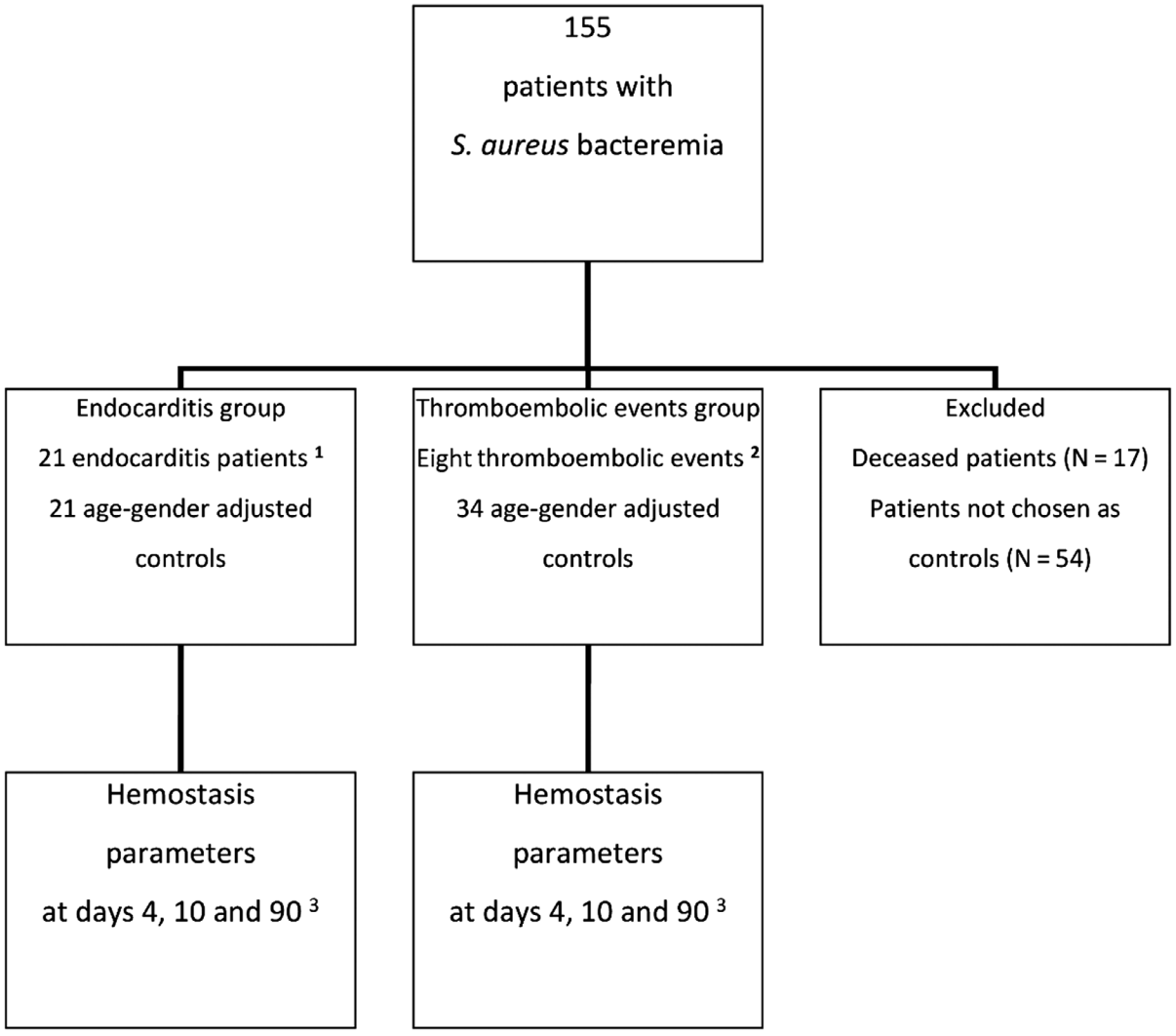

Fig. 1. Study profile. Two groups each including 42 methicillin-sensitive *Staphylococcus aureus* bacteremia (SAB) patients. Hemostasis laboratory parameters were determined at days 4, 10 and 90. Patients with infective endocarditis or thromboembolic events were compared to gender-age adjusted controls patients without endocarditis or thromboembolic events. The management of SAB was overseen by infectious disease specialist at all times. Patients were followed up for 90 days. (1) According to modified Dukes criteria for endocarditis (31). (2) Myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, parenchymal embolization (e.g. splenic thromboembolism), deep vein thrombosis or pulmonary embolism. (3) Hemostasis parameters that is hemoglobin, thrombocytes, prothrombin fragments 1 + 2, thrombin–antithrombin complex, factor VIII, D-dimer, activated partial thromboplastin time, fibrinogen, antithrombin III and thrombin time.

Table 1. Methicillin-sensitive *S. aureus* bacteremia patients categorized according to endocarditis or thromboembolic event

Variables	Infective endocarditis				Thromboembolic events			
	Present (N = 21)	Absent[31] (N = 21)	OR (95% CI)	p-value	Present (N = 8)	Absent[31] (N = 34)	OR (95% CI)	p-value
Demographics								
Male sex	14 (67)	14 (67)	1.00 (0.28–3.61)	NS	5 (63)	23 (68)	0.80 (0.16–3.95)	NS
Age > 60 years	6 (29)	4 (19)	1.70 (0.40–7.20)	NS	2 (25)	8 (24)	1.08 (0.18–6.46)	NS
Weight (kg)								
Mean (± SD)	69 ± 12	79 ± 15	—	NS	71 ± 12	75 ± 15	—	NS
BMI	23 ± 3.8	27 ± 5.3	—	NS	23 ± 3.0	25 ± 5.3	—	NS
Nosocomial infection	8 (38)	12 (57)	0.46 (0.13–1.59)	NS	1 (13)	19 (56)	0.11 (0.01–1.02	<0.05
Previous hospitalization[42]	8 (38)	12 (57)	0.46 (0.13–1.59)	NS	1 (13)	19 (56)	0.11 (0.01–1.02	<0.05
Underlying conditions								
Healthy-nonfatal[53]	15 (71)	18 (86)	0.42 (0.09–1.96)	NS	6 (75)	27 (79)	0.78 (0.13–4.72)	NS
Ultimately rapidly fatal[53]	6 (29)	3 (14)	2.40 (0.51–11.3)	NS	2 (25)	7 (21)	1.29 (0.21–7.80)	NS
Coronary heart disease	6 (29)	2 (10)	3.80 (0.67–21.6)	NS	2 (25)	6 (18)	1.56 (0.25–9.67)	NS
Chronic pulmonary disease	4 (19)	2 (10)	2.24 (0.36–13.8)	NS	1 (13)	5 (15)	0.83 (0.08–8.27)	NS
Chronic liver disease	11 (52)	5 (24)	3.52 (0.94–13.2)	NS	5 (63)	11 (32)	3.49 (0.70–17.3)	NS
Chron. renal failure	3 (14)	3 (14)	1.00 (0.18–5.63)	NS	2 (25)	4 (12)	2.50 (0.37–16.9)	NS
Diabetes mellitus	5 (24)	3 (14)	1.88 (0.39–9.12)	NS	3 (38)	5 (15)	3.48 (0.63–19.4)	NS
HIV positive	2 (10)	1 (5)	2.11 (0.18–25.2)	NS	1 (13)	2 (6)	2.29 (0.18–28.8)	NS
Predisposing factors[64]								
Hypertension	5 (24)	9 (43)	0.42 (0.11–1.57)	NS	1 (13)	13 (38)	0.23 (0.03–2.09)	NS
Heart arrhythmia[75]	5 (24)	1 (5)	6.25 (0.66–59.0)	NS	1 (13)	5 (15)	0.83 (0.08–8.27)	NS
Injective drug use	11 (52)	5 (24)	3.52 (0.94–13.2)	NS	5 (63)	11 (32)	3.49 (0.70–17.3)	NS
Previous ACH/Stroke	1 (5)	3 (14)	0.86(0.72–1.02)	NS	1 (13)	3 (9)	0.91 (0.82–1.01)	NS
Previous endocarditis	3 (14)	0	—	NS	1 (13)	2 (6)	2.29 (0.18–28.9)	NS
Foreign devices/bodies[86]								
Any surgical procedure	6 (29)	2 (10)	3.80 (0.67–21.6)	NS	3 (38)	5 (15)	3.48 (0.63–19.4)	NS
Any foreign device/body	6 (29)	6 (29)	1.00 (0.26–3.82)	NS	1 (13)	11 (32)	0.29 (0.03–2.74)	NS
Central venous catheter	3 (14)	4 (19)	0.71(0.14–3.64)	NS	1 (13)	6 (18)	0.79 (0.67–0.94)	NS
Orthopedic device/body	1 (5)	2 (19)	0.48 (0.04–5.68)	NS	1 (13)	2 (6)	2.29 (0.18–28.8)	NS
Prosthetic heart valve	5 (24)	0	—	<0.05	0	5 (15)	—	NS
Preceding medication[42]								
Statin	2 (10)	3 (14)	0.63 (0.09–4.23)	NS	0	5 (15)	—	NS
Aspirin	2 (10)	3 (14)	0.63 (0.09–4.23)	NS	1 (13)	4 (12)	1.07 (0.10–11.1)	NS
β-Blocker	8 (38)	5 (24)	1.97 (0.52–7.49)	NS	2 (25)	11 (32)	0.69 (0.12–4.03)	NS
Corticosteroid	12 (57)	7 (33)	2.68 (0.76–9.34)	NS	5 (63)	14 (41)	2.38 (0.49–11.6)	NS
Severity of illness								
Septic shock[97]	0	0	—	—	0	0	—	—
ICU[97]	7 (33)	1 (5)	10.0 (1.10–90.6)	<0.05	2 (25)	6 (18)	1.56 (0.25–9.67)	NS
ICU[108]	12 (57)	1 (5)	26.6 (2.99–237)	<0.001	2 (25)	6 (18)	1.56 (0.25–9.67)	NS
ICU mean (days ± SD)[108]	2.57 ± 3.2	0.1 ± 0.2	—	<0.001	3.3 ± 3.9	0.85 ± 2.0	—	NS
Deep infection foci[108]								
Pneumonia	14 (67)	8 (38)	3.25 (0.92–11.5)	NS	7 (88)	15 (44)	8.87 (0.98–80.1)	<0.05
Deep abscesses	13 (62)	11 (52)	1.48 (0.43–5.05)	NS	5 (63)	19 (56)	1.32 (0.27–6.41)	NS
Osteomyelitis—septic arthritis	11 (52)	6 (29)	2.75 (0.77–9.86)	NS	4 (50)	13 (38)	1.62 (0.34–7.60)	NS
Foreign body infection	8 (38)	2 (10)	5.85 (1.07–32.1)	<0.05	2 (25)	8 (24)	1.08 (0.18–6.46)	NS
Endocarditis subgroup								
Left-sided native	5 (24)	0	—	—	—	—	—	—
Right-sided native	8 (38)	0	—	—	—	—	—	—
Prosthetic valve	8 (38)	0	—	—	—	—	—	—
Antibiotic/anticoagulation								
Antistaphylococcal penicillin[119]	17 (81)	11 (52)	3.86 (0.97–15.4)	NS	7 (88)	21 (62)	4.33 (0.48–39.4)	NS
Cephalosporin[119,1210]	3 (15)	7 (33)	0.33 (0.07–1.53)	NS	1 (12)	9 (26)	0.39 (0.04–3.69)	NS
Clindamycin[119]	0	1 (5)	—	NS	0	1 (3)	—	NS
Vancomycin[119]	1 (5)	2 (10)	0.48 (0.04–5.68)	NS	0	3 (9)	—	NS
Fluoroquinolone[1311]	10 (48)	10 (48)	1.00 (0.29–3.36)	NS	5 (63)	15 (44)	2.11 (0.43–10.3)	NS
Rifampicin[1311]	14 (67)	11 (52)	1.82 (0.52–6.33)	NS	6 (75)	19 (56)	2.37 (0.42–13.5)	NS
Monotherapy[1412]	5 (24)	7 (33)	1.60 (0.41–6.19)	NS	1 (12)	11 (32)	3.35 (0.37–30.7)	NS
Combination therapy[1513]	16 (76)	14 (67)	1.60 (0.41–6.19)	NS	7 (88)	23 (68)	3.35 (0.37–30.7)	NS
Anticoagulation[1614,1715]	19 (90)	8 (38)	15.4 (2.81–84.7)	<0.001	6 (75)	21 (62)	1.86 (0.33–10.6)	NS
LWMH	11 (52)	8 (38)	1.79 (0.52–6.11)	NS	5 (63)	14 (41)	2.38 (0.49–11.6)	NS
Warfarin	8 (38)	0	—	—	1 (13)	7 (21)	0.55 (0.06–5.25)	NS

patients over 50 kg in weight. The proper length of therapy was defined as intravenous administration for at least 28 days for deep infection focus and at least 14 days in the absence of deep infection. Rifampicin was administered when there was a suspicion or diagnosis of deep infection foci. Detailed information on antibiotic

Table 1. *(continued)*

Variables	Infective endocarditis				Thromboembolic events			
	Present (N = 21)	Absent[31] (N = 21)	OR (95% CI)	p-value	Present (N = 8)	Absent[31] (N = 34)	OR (95% CI)	p-value
Outcome								
Defervescense								
Mean (days ± SD)[108]	5.8 ± 7.0	3.3 ± 2.4	—	<0.05	4.5 ± 2.9	4.6 ± 5.9	—	NS
≥7 days	7 (33)	1 (5)	10.0 (1.10–90.6)	<0.05	2 (25)	6 (18)	1.56 (0.25–9.67)	NS
Hospital duration (days ± SD)[108]	47 ± 15	30.4 ± 16	—	<0.01	49 ± 13	36 ± 18	—	<0.05

ACH, acute cerebral hemorrhage; NS, nonsignificant; SD, standard deviation.
[1]Gender-age adjusted controls.
[2]Within preceding 3 months.
[3]According to McCabe's classification (30).
[4]For endocarditis or thromboembolic events.
[5]Including atrial fibrillation.
[6]In one year.
[7]At blood cultures.
[8]Within 90-day follow-up.
[9]Standard antibiotic therapy.
[10]Cefuroxime or ceftriaxone.
[11]Additional therapy.
[12]Only standard antibiotic therapy.
[13]Standard and additional antibiotic therapy.
[14]Warfarin or low-weight-molecular heparin (LWMH).
[15]Initiated within days 1–7 of SAB diagnosis.

indications and administration have been provided previously (34, 35).

Statistical analysis

Pearson's chi-squared test was applied for categorical variables and Mann–Whitney *U* test for continuous variables. Univariate analyses and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Receiving operating characteristic (ROC) analyses were used to evaluate the discriminative power of hemostasis parameters at an early phase in predicting endocarditis or thromboembolic events. The area under the curve (AUC) was calculated. Modified power analyses, observing power coefficients and 95% CIs, were applied to estimate the reliability of the patient participant number. A professional statistician was consulted for all analyses. Tests were two-tailed and $p < 0.05$ was considered significant. Analyses were performed with SPSS 12.0 (SPSS Inc. Chicago, IL, USA).

RESULTS

The patient cohort

Altogether 155 patients were enrolled. Two groups were designed including 21 patients with SAB and endocarditis (endocarditis group) and 8 patients with SAB and thromboembolic events (thromboembolic events group). Gender-age adjusted controls included 21 and 34 patients, respectively. Patients who deceased within 90 days (N = 17) and patients not chosen as gender-age adjusted controls (N = 54) were excluded (Fig. 1). Patients for both the groups were included in the chronologic order they were encountered. Subgrouping of the endocarditis patients included: five (24%) cases of native left-sided endocarditis, eight cases (38%) of native right-sided endocarditis and eight cases (38%) of prosthetic valve endocarditis (Table 1). There were altogether eight patients with arterial or venous thromboembolic events recorded: one case of unstable angina pectoris, five cases of stroke, one case of splenic thromboembolism and one case of deep vein thrombosis with subsequent pulmonary embolism. No patients were lost during the follow-up time of 90 days. The median time between blood culture sampling and confirmation of *S. aureus* growth was 3 days.

Demographics and underlying conditions

No differences in demographics, underlying conditions, predisposing factors or medications preceding SAB of patients with endocarditis or thromboembolic events compared to gender-age adjusted controls were observed (Table 1). However, patients with thromboembolic events had less nosocomial SAB and previous hospitalization compared to controls ($p < 0.05$), whereas prosthetic heart valve was more common in patients with endocarditis compared to controls ($p < 0.05$; Table 1).

Severity of illness, deep infections and antimicrobial therapy

Altogether 19% needed ICU treatment at blood culture collection time-point, whereas 31% received ICU treatment during the 90-day follow-up time. The mean ICU duration was 1.3 ± 2.8 days (±SD) (Table 1). There were no cases of septic shock during the 90-day follow-up. Patients with endocarditis were more likely to receive ICU treatment than controls (33% vs 5%; $p < 0.05$), whereas no corresponding trend was seen for patients with thromboembolic events (Table 1). The overall prevalence of deep infection foci in the patient population was 83%. No differences in the occurrence of deep abscess, osteomyelitis or septic arthritis were seen between cases and controls. However, foreign body infections were more common among patients with endocarditis compared to controls (38% vs 10%, $p < 0.05$). Patients with thromboembolic events suffered more often from pneumonia compared to controls (88% vs 44%, $p < 0.05$; Table 1). All patients received an antimicrobial agent effective *in vitro* against the *S. aureus* isolate starting from the day of positive blood culture. Altogether 67% received antistaphylococcal penicillin, 24% cephalosporin, whereas 7% were treated with vancomycin and 2% with clindamycin. Rifampicin was provided to 60% of patients, whereas fluoroquinolone (levofloxacin) was received by 48% (Table 1). No differences in antimicrobial therapy was seen between patients with or without endocarditis or thromboembolic events (Table 1).

Anticoagulation

Within the first week, 64% of patients had anticoagulants initiated, whereas within the 90-day follow-up 74% patients had received anticoagulants (Table 1). Hence, among patients who received anticoagulants, the majority had the anticoagulant initiated within the first week, whereas for a minority the anticoagulant was commenced at a later time-point. Low-molecular-weight heparin was more frequently used than warfarin. Within the first week, 70% received low-molecular-weight heparin and 30% received warfarin. Patients with

Table 2. Hemostasis parameters in methicillin-sensitive *S. aureus* bacteremia according to endocarditis or thromboembolic event

Hemostasis[19] parameters	Normal ranges	Infective endocarditis			Thromboembolic events		
		Present (N = 21)	Absent[20] (N = 21)	p-value	Present (N = 8)	Absent[20] (N = 34)	p-value
Hemoglobin[21]	134–167 g/L	111 ± 17	121 ± 19	NS	124 ± 15	114 ± 19	NS
Thrombocytes[21]	150–360 × 10^9L	190 ± 115	251 ± 108	NS	155 ± 94	235 ± 115	NS
Prothrombin fragments							
Day 4	0–0.35 nmol/L	1.47 ± 0.7	1.9 ± 1.4	NS	1.69 ± 0.6	1.69 ± 1.2	NS
Day 10		1.43 ± 0.8	1.6 ± 1.4	NS	1.77 ± 1.1	1.48 ± 1.2	NS
Thrombin–antithrombin complex							
Day 4	<4 μg/L	6.30 ± 2.4	4.5 ± 2.2	<0.01	6.51 ± 1.9	5.13 ± 2.5	<0.05
Day 10		4.28 ± 1.8	6.8 ± 12	NS	3.79 ± 1.7	5.98 ± 9.5	NS
Factor VIII							
Day 4	52–148%	193 ± 48	203 ± 79	NS	194 ± 61	199 ± 66	NS
Day 10		170 ± 52	169 ± 65	NS	174 ± 73	168 ± 56	NS
D-dimer							
Day 4	< 0.5 mg/L	2.4 ± 1.7	1.9 ± 1.4	NS	1.99 ± 1.9	2.20 ± 1.5	NS
Day 10		2.2 ± 1.9	1.9 ± 1.6	NS	2.01 ± 2.7	2.04 ± 1.6	NS
Fibrinogen							
Day 4	1.7–4.0 g/L	5.4 ± 1.5	6.2 ± 2.2	NS	5.16 ± 1.3	5.91 ± 1.9	NS
Day 10		5.4 ± 1.2	5.2 ± 1.6	NS	5.47 ± 1.7	5.26 ± 1.4	NS
Antithrombin III							
Day 4	84–108%	89 ± 16	104 ± 20	<0.05	88.8 ± 16	98.4 ± 20	NS
Day 10		119 ± 19	114 ± 15	NS	126 ± 22	115 ± 16	NS
Thrombin time							
Day 4	17–25 s	15 ± 1.7	15.8 ± 1.6	NS	14.8 ± 1.4	15.6 ± 1.7	NS
Day 10		17 ± 3.3	17.1 ± 2.5	NS	17.7 ± 4.7	16.8 ± 2.33	NS
Activated partial thromboplastin time							
Day 4	23–33 s	40 ± 6.3	36 ± 3.9	<0.05	37.4 ± 6.9	38.6 ± 5.4	NS
Day 10		45 ± 12	38 ± 5.9	<0.05	48 .0 ± 19	40.2 ± 62	NS

NS, non-significant. Data are mean ± SD. Values of p with Mann–Whitney *U* test.
[1]Hemostasis parameters at days 4 and 10 after diagnosis of methicillin-sensitive *S. aureus* bacteremia.
[2]Gender-age adjusted controls.
[3]Hemoglobin and thrombocyte values for day 4 only.

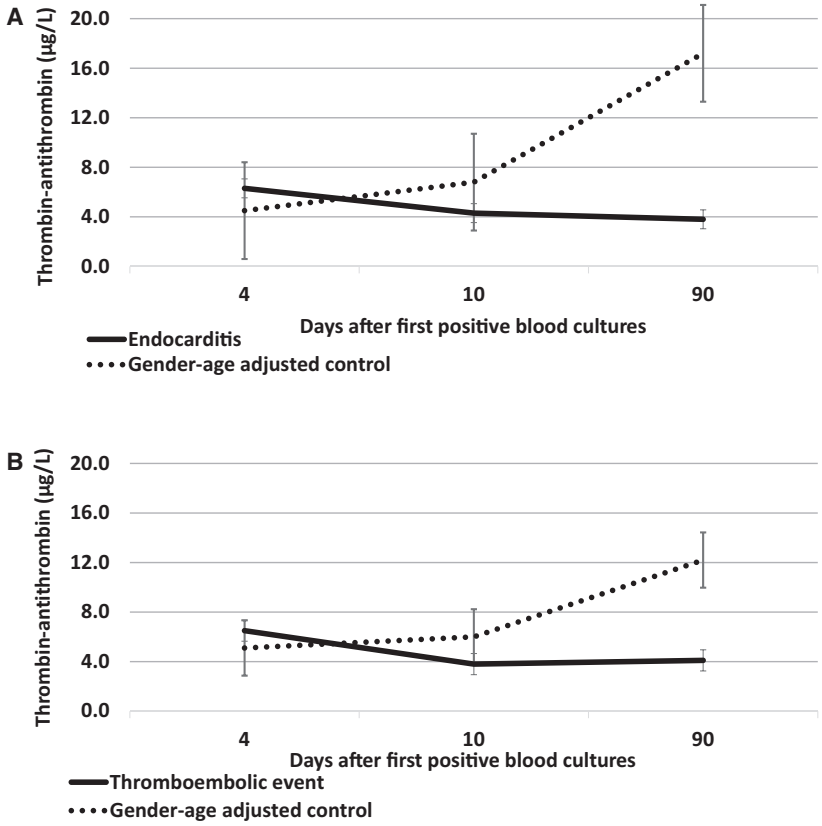

Fig. 2. Graphic presentation of the hemostasis parameters thrombin–antithrombin complex (2A–B), factor VIII (3A–B), D-dimer (4A–B), fibrinogen (5A–B), antithrombin III (6A–B) and activated partial thromboplastin time (7A–B) for patients with diagnosis of endocarditis (N = 21) vs gender-age adjusted controls patients (N = 21) or patients with thromboembolic events (N = 8) vs gender-age adjusted controls patients (N = 34). Follow-up time of 90 days.

endocarditis, compared to controls, received more often anticoagulants (90% vs 38%, $p < 0.001$), whereas no difference was seen between patients with thromboembolic events and their controls (75% vs 62%; Table 1).

Hemostasis parameters

Significant differences between endocarditis patients and controls were found in thrombin–antithrombin complex, antithrombin III and APTT levels (Table 2, Figs 2–7aa–). Thrombin–antithrombin complex at day 4 was higher in patients with endocarditis compared to controls (6.3 ± 2.4 vs 4.5 ± 2.2 µg/L, $p < 0.01$) and in patients with thromboembolic events compared to those without it (6.5 ± 1.9 vs 5.1 ± 2.5 µg/L, $p < 0.05$). This difference was diminished by days 10 and 90 as the concentrations increased in control patients (Table 2, Figs 2–7aa–). The activity of antithrombin III at day 4 was lower and at day 90 higher in patients with endocarditis compared to controls (89 ± 16 vs 104 ± 20%, $p < 0.05$ and 121 ± 19 vs 107 ± 12%, $p < 0.01$), whereas no difference was observed in patients with and without thromboembolic events. APTT was prolonged on days 4 and 10 in patients with endocarditis compared to patients without (40 ± 6.3 s vs 36 ± 3.9 and 45 ± 12 s vs 38 ± 5.9 s, $p < 0.05$) whereas no differences were observed at day 90. However, when comparing patients with thromboembolic events and controls, no differences were seen in APTT (Table 2 and Figs 2–7bb–).

ROC analyses for significant hemostasis changes were performed to evaluate their discriminative power in predicting occurrence of endocarditis or thromboembolic events. Hemostasis parameters with predictable value for endocarditis were antithrombin III at day 4 (AUC 0.71, 95% CI 0.54–0.86, $p < 0.05$), APTT at days 4 and 10 (AUC 0.69, 95% CI 0.53–0.87, $p < 0.05$ and AUC 0.70, 95% 0.54–0.87, $p < 0.05$) and thrombin–antithrombin complex at day 4 (AUC 0.75, 95% CI 0.60–

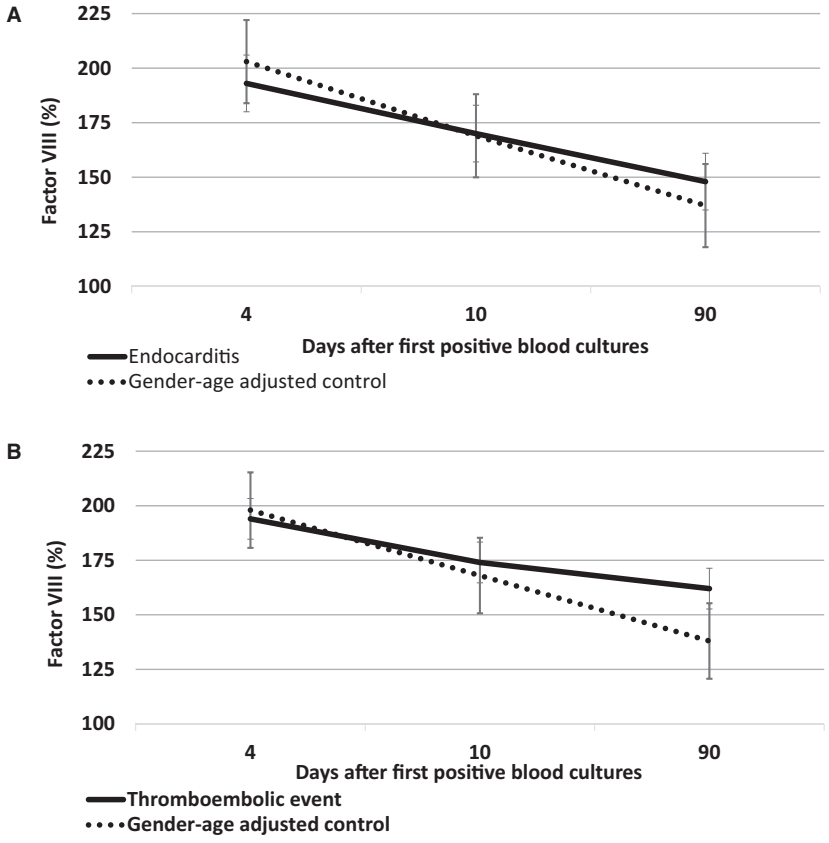

Fig. 3. See Fig. 2 caption.

0.91, $p < 0.01$). Thrombin–antithrombin complex at day 4 was the only predictable value for thromboembolic events (AUC 0.74, 95% CI 0.58–0.89, $p < 0.05$). Prothrombin fragment, thrombin time, factor VIII, D-dimer or fibrinogen levels did not predict endocarditis or thromboembolic events in ROC analyses.

Additional analyses were performed to further evaluate the hemostasis parameter fluctuations in SAB. Patients were categorized according to (i) ICU vs non-ICU treatment, (ii) antibiotic monotherapy (standard antibiotic therapy only) vs combination therapy (standard antibiotic therapy + fluoroquinolone or rifampicin) or (iii) low (<2.0 mg/L) vs high (>2.0 mg/L) D-dimer at day 4. ICU patients, compared to non-ICU patients, had lower thrombocyte count ($p < 0.05$) and lower antithrombin III ($p < 0.05$) at day 4, whereas no other hemostasis parameter changes were observed. No differences in hemostasis parameters were observed when we categorized the whole patient cohort according to mono- or combination antibiotic therapy. Patients with low D-dimer, compared to high D-dimer, had higher antithrombin III at day 4 ($p < 0.05$) and higher activated partial thromboplastin time at day 10 ($p < 0.05$) whereas no other hemostasis parameter changes were observed.

The mean observed power coefficient for hemostasis parameters in the endocarditis group was 0.48 ± 0.29 ($\pm$SD) and most of the 95% CIs were narrow as compared to the width of normal ranges for the hemostasis parameters. For hemostasis parameters in the thromboembolic events group the mean observed power coefficient was 0.14 ± 0.09 ($\pm$SD); however, most of the 95% CIS were wide as compared to the normal ranges for the hemostasis parameters.

Defervescence and hospitalization

The mean defervescense time was longer for patients with endocarditis compared to controls (5.8 ± 7.0 vs 3.3 ± 2.4 days, $p < 0.05$), whereas no corresponding trend was seen for thromboembolic events. The mean hospitalization was 38 days and longer for patients with endocarditis or thromboembolic events as compared to controls (47 ± 15

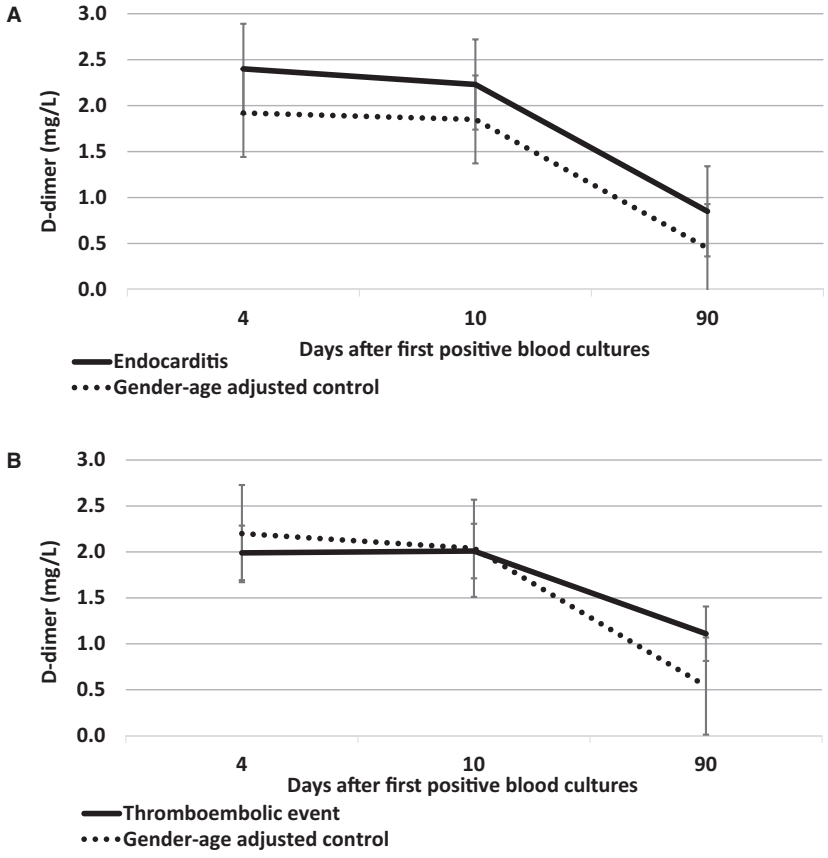

Fig. 4. See Fig. 2 caption.

vs 30 ± 16, $p < 0.01$ and 49 ± 13 vs 36 ± 18 days, $p < 0.05$ respectively).

DISCUSSION

This is the first study to report a systematic and prospective evaluation of hemostasis parameter changes and their association and predictability for endocarditis and thromboembolic events in MS-SAB. Patients with endocarditis, compared to age- and gender-adjusted controls, presented an increased hemostatic activity at an early time-point with lowered levels of antithrombin III and elevated levels of thrombin–antithrombin and prolonged APTT. Patients with thromboembolic events, compared to gender-age adjusted controls, had increased levels of thrombin–antithrombin at an early time-point. The early hemostasis parameter changes also seemed to predict endocarditis or thromboembolic events. However, no cases of septic shock were present, all patients were supervised by an infectious disease specialist including non-delayed proper antimicrobial therapy initiation and deceased patients were excluded. These results suggest the possibility that proper clinical management among surviving MS-SAB patients result in rapid decline of bacterial load, reduced inflammation activity and lower systemic coagulation activation. This may further explain similarities in other hemostasis parameters between the groups, and why some hemostasis parameters did not differ between patients with endocarditis or thromboembolic events as compared to gender-age adjusted controls.

The hemostasis parameters evaluated in previous reports on endocarditis and subsequent thromboembolic events have been prothrombin fragments, a side product of prothrombin to thrombin conversion, and thrombin–antithrombin complex, a complex formed between thrombin and its inhibitor antithrombin III (20, 21). These studies showed that native valve endocarditis due to miscellaneous causative pathogens, in combination with thromboembolic events, elevated levels of both prothrombin fragments and thrombin–antithrombin complex as compared to endocarditis without thromboembolic events or control patients. The authors'

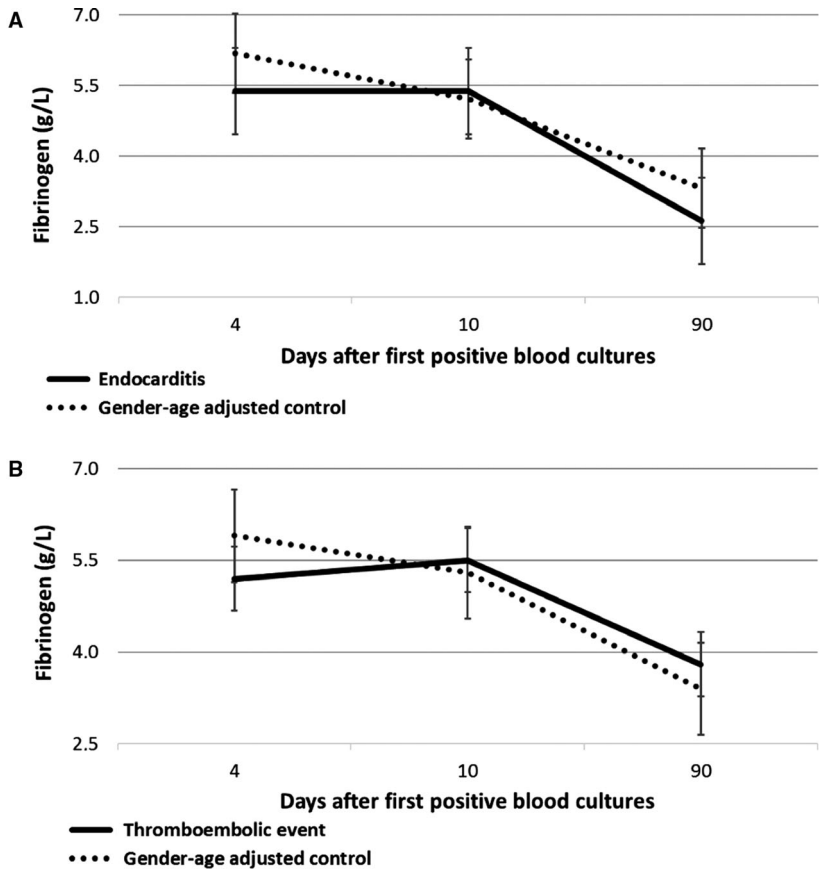

Fig. 5. See Fig. 2 caption.

concluded that endocarditis and subsequent thromboembolic events were associated with impaired fibrinolysis and enhanced systemic activation of coagulation (20, 21). The results of the present study are partly in line with these observations. We recorded elevated thrombin–antithrombin complex at day 4 but no changes were observed in levels of prothrombin fragments in endocarditis or thromboembolic patients as compared to controls. Furthermore, ROC analyses suggested a predictability of day 4 thrombin–antithrombin complex for endocarditis and thromboembolic events. However, differences in study setups may explain these variable results as we included only *S. aureus* as a causative pathogen (20, 21).

Recent studies have shown that elevated D-dimer at a level of 4.0–4.2 mg/L either on admission in infective endocarditis (25) or within hours of blood culture-positive infections (18) were associated with increased in-hospital mortality. The mean D-dimer levels observed in the present study were below these proposed cut-off values and we could not observe any differences in D-dimer levels between MS-SAB patients with and without endocarditis or thromboembolic events in our study.

Antithrombin III is a natural anticoagulant produced by th liver with potential anti-inflammatory properties. Previous reports have shown that in severe infections, for example in critically ill sepsis patients, antithrombin III levels are decreased and antithrombin III has been evaluated as a potential agent for sepsis treatment (17, 26, 36). In the present study, levels of antithrombin III at day 4 were significantly lower and at day 90 significantly higher in patients with endocarditis as compared to controls. Furthermore, in ROC analyses, both at the day 4 and the day 90, the changes were predictable for endocarditis but not for thromboembolic events. The antithrombin III results of the present study are comparable with those of a previous observation for critically ill sepsis patients despite a different patient population (17). Interestingly, we could demonstrate that SAB in combination with endocarditis is severe enough to suppress antithrombin III levels among surviving MS-SAB patients.

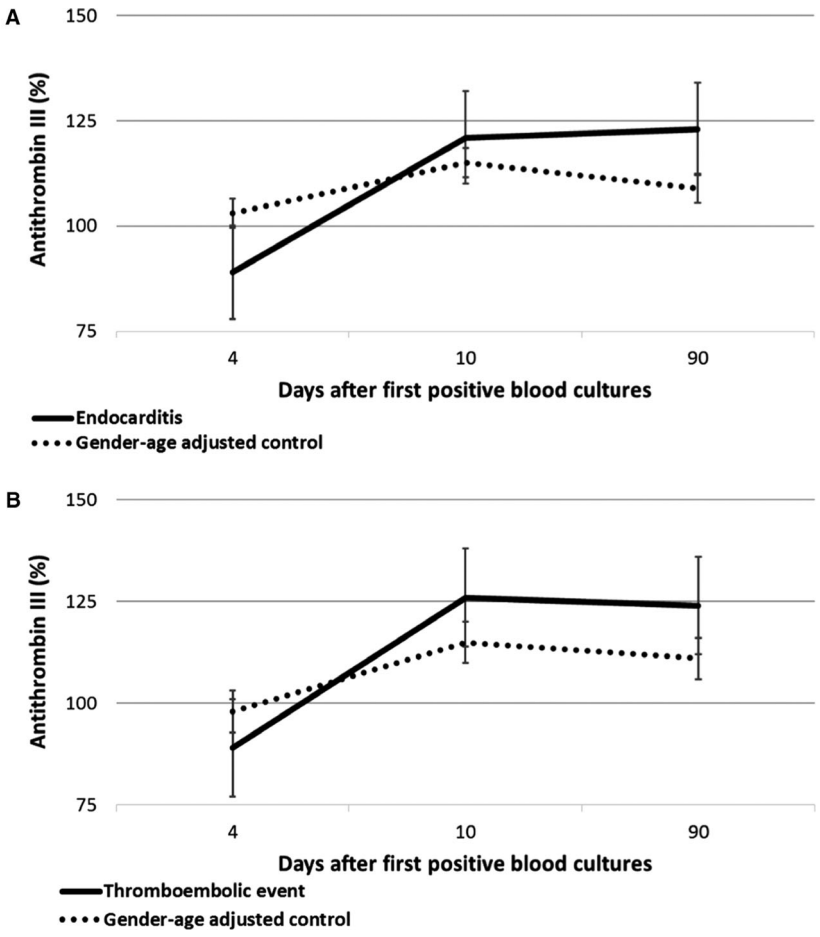

Fig. 6. See Fig. 2 caption.

Fibrinogen and factor VIII are acute phase proteins and natural procoagulants. Studies have showed associations between severe sepsis and elevated levels of fibrinogen and factor VIII (17, 19). Moreover, increased concentrations of factor VIII have been observed in patients with recurrent thromboembolic events (37) and case reports have presented elevated factor VIII levels secondary to endocarditis (38). Factor VIII and fibrinogen levels observed in this study were above baseline references as a sign of upregulation of their production in all SAB patients. However, there were no significant differences between SAB patients with and without complications. Therefore, these hemostasis parameters are not predictive of endocarditis or thromboembolic events in SAB.

APTT, an estimation of intrinsic and common pathway coagulation activity, may be prolonged in severe illnesses such as sepsis (17). The present study observed prolonged APTT, compared to baseline references, for the whole SAB study population. Furthermore, at an early time-point, SAB patients with endocarditis presented longer APTT than controls. Anticoagulation may prolong APTT. Thus, the question may be raised whether the observation of prolonged APTT in this study was due to use of anticoagulation. However, the majority of patients with thromboembolic events had anticoagulation therapy initiated in the first week of SAB and no further prolongation of APTT was observed. Thus, prolongation of APTT in patients with endocarditis seems to be independent of anticoagulation.

To further evaluate hemostasis parameter changes in SAB, additional analyses were performed with patients categorized according to ICU vs non-ICU treatment, antibiotic mono- vs combination therapy and low (<2.0 mg/L) vs high (>2.0 mg/L) D-dimer at day 4. The results from these additional analyses were similar to the main results using categorization according to endocarditis or thromboembolic events. This strengthens the

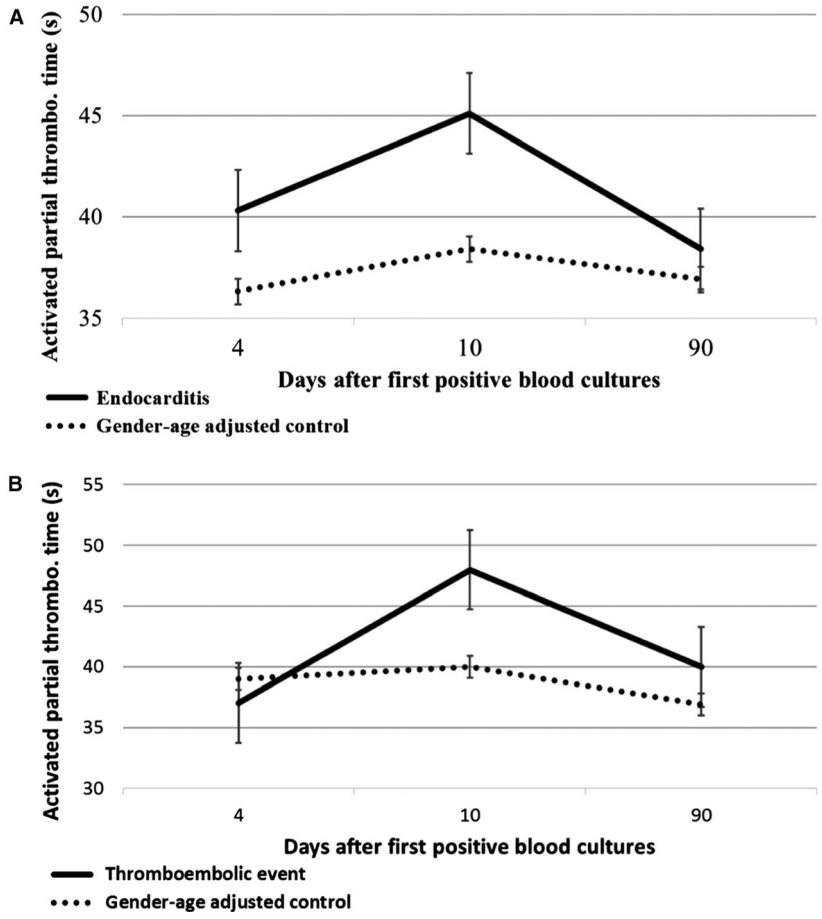

Fig. 7. See Fig. 2 caption.

conclusion that nonfatal MS-SAB patients receiving proper clinical management present only marginal hemostasis parameter changes.

Several studies connect MRSA bacteremia to worse outcome and vancomycin, as compared to beta-lactam antibiotics, as it is known to weaken prognosis of MS-SAB (2, 39, 40). Furthermore, the infectious disease specialist guidance has been shown to enhance clinical management and improve outcome (2, 4, 5). The present study provided formal infectious disease specialist bedside consultation for each patient and included solely MS-SAB cases. In consequence, all patients were provided with proper antibiotic therapy from the first day of MS-SAB diagnosis avoiding potential effect of suboptimal medication. There were no cases of septic shock, less than one-third of patients required ICU treatment and deceased patients were excluded. Hence, it is plausible to assume that among surviving MS-SAB patients proper clinical management may result in a rapid decline in the *S. aureus* bacterial load resulting in a reduced inflammation activity and lowered systemic coagulation activation.

Most previous studies have reported hemostasis parameters at a single time-point only. In addition, the patient cohorts have been heterogeneous and included critically ill patients irrespective of etiology or patients with severe sepsis, bacteremia or endocarditis regardless of the causative pathogen (17–22, 25, 26). Our study provides a homogenous patient cohort with respect to the primary condition (MS-SAB) and follow-up until 3 months. Unlike previous studies, we used SAB patients as a control group which further strengthens the homogeneity of the patient cohort. The patient cohort here was initially gathered for evaluation of the prognostic impact of fluoroquinolone therapy on outcome in SAB (34). Data for hemostasis parameter changes in SAB were collected simultaneously.

The present study includes limitations that have to be taken into account when interpreting the results.

First, the size of the study population was small, however, large enough to observe changes in the acute phase of certain hemostasis parameters when comparing subjects with gender-age adjusted controls. The main results were achieved also when patients were categorized according to ICU treatment or level of D-dimer which indicate that the results are robust. Furthermore, modified power analyses were made to estimate the reliability of the patient cohort. Regarding the endocarditis group, the mean observed power coefficient may be interpreted as satisfactory and together with the narrow 95% CIs it may be assumed that similar results would be achieved with higher patient n-numbers as well. However, the mean observed power coefficient and the wide 95% CIs in the thromboembolic events group suggests that the results have to be interpreted with caution and larger studies are needed to further assess the connection of hemostasis parameters to thromboembolic events. Second, the study excluded patients who deceased. The overall mortality in SAB ranges from 15% to 30% and complications such as endocarditis may further increase mortality (1–3). This study is not able to give answers on changes in hemostasis parameters in more severely ill patients with a fatal outcome. Third, day 4 hemostasis parameters were not influenced by anticoagulants (as anticoagulant was not yet commenced at this timepoint) whereas days 10 and 90 hemostasis parameters were influenced by anticoagulation. Fourth, the patient cohort was gathered during years 1999–2002. Although the clinical practice of SAB treatment continuously develops, the essential management of SAB has not changed. The authors view that infectious consultation in the present study has guaranteed recording of relevant data and enabled proper management of SAB.

In conclusion, nonfatal MS-SAB patients with endocarditis or thromboembolic events, as compared to gender-age adjusted MS-SAB controls, presented only few hemostasis parameter changes. However, the observed early alterations in antithrombin III, activated partial thromboplastin time and thrombin–antithrombin complex, may have some predictive value for endocarditis or thromboembolic events. These results suggest that proper clinical management in surviving MS-SAB patients may result in decline of bacterial load, reduced inflammation activity and lower systemic coagulation activation.

REFERENCES

1. Kobayashi D, Yokota K, Takahashi O, Arioka H, Fukui T. A predictive rule for mortality of inpatients with Staphylococcus aureus bacteraemia: a classification and regression tree analysis. Eur J Intern Med 2014;25:914–8.
2. Rieg S, Peyerl-Hoffmann G, de With K, Theilacker C, Wagner D, Hübner J, et al. Mortality of S. aureus bacteremia and infectious diseases specialist consultation - a study of 521 patients in Germany. J Infect 2009;59:232–9.
3. Malani PN, Rana M, Banerjee M, Bradley S. Staphylococcus aureus bloodstream infections: the association between age and mortality and functional status. J Am Geriatr Soc 2008;56:1485–9.
4. Saunderson R, Gouliouris T, Nickerson E, Cartwright E, Kidney A, Aliyu S, et al. Impact of routine bedside infectious disease consultation on clinical management and outcome of Staphylococcus aureus bacteraemia in adults. Clin Microbiol Infect 2015;21:779–85.
5. Forsblom E, Ruotsalainen E, Ollgren J, Järvinen A. Telephone consultation cannot replace bedside infectious disease consultation in the management of Staphylococcus aureus bacteremia. Clin Infect Dis 2013;56:527–35.
6. Lodise T, McKinnon P, Swiderski L, Rybak M. Outcomes analysis of delayed antibiotic treatment for hospital acquired Staphylococcus aureus bacteremia. Clin Infect Dis 2003;36:1418–23.
7. Nadji G, Rémadi J, Coviaux F, Mirode A, Brahim A, Enriquez-Sarano M, et al. Comparison of clinical and morphological characteristics of Staphylococcus aureus endocarditis with endocarditis caused by other pathogens. Heart 2005;91:932–7.
8. Miro J, Anguera I, Cabell C, Chen AY, Stafford J, Corey G, et al. Staphylococcus aureus native valve infective endocarditis: report of 566 episodes from the International Collaboration on Endocarditis Merged Database. Clin Infect Dis 2005;41:507–414.
9. Weinstein L, Schlesinger JJ. Pathoanatomic, pathophysiologic and clinical correlations in endocarditis. N Engl J Med 1974;291:832–7 and 1122-1126.
10. McAdow M, Missiakas DM, Schneewind O. Staphylococcus aureus secretes coagulase and von Willebrand factor binding protein to modify the coagulation cascade and establish host infections. J Innate Immun 2012;4:141–8.
11. Valtonen V, Kuikka A, Syrjanen J. Thromboembolic complications in bacteremic infections. Eur Heart J 1993;14:20–3.
12. Syrjanen J. Infection as a risk factor for cerebral infarction. Eur Heart J 1993;14:17–9.
13. Mejer N, Westh H, Schønheyder H, Jensen A, Larsen A, Skov R, et al. Increased risk of venous thromboembolism within the first year after Staphylococcus aureus bacteraemia: a nationwide observational matched cohort study. J Intern Med 2014;275:387–97.
14. Mejer N, Gotland N, Uhre ML, Westh H, Schønheyder H, Petersen A, et al. Increased risk of arterial thromboembolic events after Staphylococcus aureus bacteremia: a matched cohort study. J Infect 2015;71:167–78.
15. Dalager-Pedersen M, Søgaard M, Schønheyder H, Thomsen R, Baron J, Nielsen H. Venous thromboembolism after community-acquired bacteraemia: a 20-year Danish cohort study. PLoS ONE 2014;23: e86094.

16. Corrales-Medina V, Fatemi O, Serpa J, Valayam J, Bozkurt B, Madjid M, et al. The association between Staphylococcus aureus bacteremia and acute myocardial infarction. Scand J Infect Dis 2009;41:511–4.
17. Collins P, Macchiavello L, Lewis S, Macartney N, Saayman A, Luddington R, et al. Global tests of haemostasis in critically ill patients with severe sepsis syndrome compared to controls. Br J Haematol 2006;135:220–7.
18. Schwameis M, Steiner M, Schoergenhofer C, Lagler H, Buchtele N, Jilma-Stohlawetz P, et al. D-dimer and histamine in early stage bacteremia: a prospective controlled cohort study. Eur J Intern Med 2015;26:782–6.
19. Reitsma P, Branger J, Van Den Blink B, Weijer S, Van Der Poll T, Meijers JC. Procoagulant protein levels are differentially increased during human endotoxemia. J Thromb Haemost 2003;1:1019–23.
20. Buyukasýk N, Ileri M, Alper A, Senen K, Atak R, Hisar I, et al. Increased blood coagulation and platelet activation in patients with infective endocarditis and embolic events. Clin Cardiol 2004;27:154–8.
21. Ileri M, Alper A, Senen K, Durmaz T, Atak R, Hisar I, et al. Effect of infective endocarditis on blood coagulation and platelet activation and comparison of patients with to those without embolic events. Am J Cardiol 2003;15:689–92.
22. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis-associated disseminated intravascular coagulation and thromboembolic disease. Mediterr J Hematol Infect Dis 2010;2:e2010024.
23. Levi M, Schultz M, van der Poll T. Disseminated intravascular coagulation in infectious disease. Semin Thromb Hemost 2010;36:367–77.
24. Levi M, van der Poll T, Schultz M. Infection and inflammation as risk factors for thrombosis and atherosclerosis. Semin Thromb Hemost 2012;38:506–14.
25. Turak O, Canpolat U, Ozcan F, Yayla C, Mendi MA, Oksuz F, et al. D-dimer level predicts in-hospital mortality in patients with infective endocarditis: a prospective single-centre study. Thromb Res 2014;134:587–92.
26. Allingstrup M, Wetterslev J, Ravn FB, Møller AM, Afshari A. Anti-thrombin III for critically ill patients. Cochrane Database Syst Rev 2016;8:CD005370.
27. Spika JS, Peterson P, Wilkinson B, Hammerschmidt D, Verbrugh H, Verhoef J, et al. Role of peptidoglycan from Staphylococcus aureus in leukopenia, thrombocytopenia, and complement activation associated with bacteremia. J Infect Dis 1982;146:227–34.
28. Fitzgerald J, Foster T, Cox D. The interaction of bacterial pathogens with platelets. Nat Rev Microbiol 2006;4:445–57.
29. de Haas C, Weeterings C, Vughs M, de Groot P, Van Strijp J, Lisman T. Staphylococcal superantigen-like 5 activates platelets and supports platelet adhesion under flow conditions, which involves glycoprotein Ibalpha and alpha IIb beta 3. J Thromb Haemost 2009;7:1867–74.
30. McCabe WR, Jackson GG. Gram negative bacteraemia. Etiology and ecology. Arch Intern Med 1962;110:847–55.
31. Li J, Sexton D, Mick N, Nettles R, Fowler V Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–8.
32. Levy MM, Fink MP, Marshall JC, et al. SCCM/ESICM/ACCP/ATS/SIS: 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6.
33. Pelkonen K, Wartiovaara-Kautto U, Nieminen M, Ahonen K, Sinisalo J. Low normal level of protein C or of anti-thrombin increases risk for recurrent cardiovascular events. Blood Coagul Fibrinolysis 2005;16:275–80.
34. Ruotsalainen E, Järvinen A, Koivula I, Kauma H, Rintala E, Lumio J, et al. Levofloxacin does not decrease mortality in Staphylococcus aureus bacteraemia when added to the standard treatment: a prospective and randomized clinical trial of 381 patients. J Intern Med 2006;259:179–90.
35. Forsblom E, Ruotsalainen E, Järvinen A. Improved outcome with early rifampicin combination treatment in methicillin-sensitive Staphylococcus aureus bacteraemia with a deep infection focus - a retrospective cohort study. PLoS ONE 2015;10:e0122824.
36. Rublee D, Opal S, Schramm W, Keinecke H, Knaub S. Quality of life effects of antithrombin III in sepsis survivors: results from the KyberSept trial. Crit Care 2002;6:349–56.
37. Franco Moreno A, García Navarro M, Ortiz Sánchez J, Martín Díaz R, Madroñal Cerezo E, de Ancos Aracil CL, et al. A risk score for prediction of recurrence in patients with unprovoked venous thromboembolism (DAMOVES). Eur J Intern Med 2016;29:59–64.
38. Thota R, Ganti A, Subbiah S. Apparent heparin resistance in a patient with infective endocarditis secondary to elevated factor VIII levels. J Thromb Thrombolysis 2012;34:132–4.
39. Cosgrove S, Sakoulas G, Perencevich E, Schwaber M, Karchmer A, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis 2003;36:53–9.
40. Kim S, Kim K, Kim H, Kim N, Kim E, Oh M, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible Staphylococcus aureus bacteremia. Antimicrob Agents Chemother 2008;52:192–7.