Formal infectious diseases specialist consultation improves long-term outcome of methicillin-sensitive Staphylococcus aureus bacteremia

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Abstract

**Background.** Formal infectious diseases specialist (IDS) consultation has been shown to improve short-term outcome of *Staphylococcus aureus* bacteremia (SAB) but its effect on long-term outcome lacks evaluation.

**Methods.** Retrospective study of 367 methicillin-sensitive (MS) SAB patients followed for 10 years. The impact of formal IDS consultation on risk for new bacteremia and outcome during long-term follow-up were evaluated. Patients who died within 90 days were excluded to avoid interference from early deceased patients.

**Results.** 304 (83%) patients had formal IDS consultation whereas 63 (17%) received informal or no IDS consultation. Formal consultation, compared to informal or lack of consultation, associated to a reduced risk for a new bacteremia caused by any pathogen within 1-year (OR, 0.39; 95% CI, .18-.84; p=.014; 8% vs. 17%), and within 3-years (OR, 0.39; 95% CI, .19-.80; p=.010; 9% vs. 21%) whereas a trend towards a lower risk was observed within 10-years (OR, 0.56; 95% CI, .29-1.08; p=.079; 16% vs. 25%). Formal consultation, compared to informal or lack of consultation, improved outcome at 1-year (OR, 0.16; 95% CI, .06-.44; p<0.001; 3% vs. 14%), at 3-years (OR, 0.19; 95% CI, .09-.42; p<.001; 5% vs. 22%) and at 10-years (OR, 0.43; 95% CI, .24-.74; p=.002; 27% vs. 46%). Considering all prognostic parameters formal consultation improved outcome (HR, 0.42; 95% CI, .27-.65, p<.001) and lowered risk for any new bacteremia (OR, 0.45; 95% CI, .23-.88, p=.02) during 10-years follow-up.

**Conclusion.** MS-SAB management by formal IDS consultation, compared to informal or lack of IDS consultation, reduces risk for any new bacteremia episodes and improves long-term prognosis up to ten years.

**Key words** *Staphylococcus aureus bacteremia*, infectious diseases specialist consultation, long-term outcome
Introduction

*Staphylococcus aureus* causes severe bacteremia (SAB) with mortality ranging up to 30% [1]. Infectious diseases specialist consultation (IDS) improve clinical management of SAB. IDS consultation has been shown to accelerate diagnostics and eradication of infection foci [2-4] and improve choice and duration of antimicrobial therapy [5]. The superiority of formal IDS consultation, compared to informal IDS consultation, has been demonstrated [6]. Above all, IDS consultation improve SAB prognosis and IDS is advocated as a mandatory practice in SAB management by ever more clinicians [2-8].

Most studies on long-term outcome in SAB have evaluated prognostic factors of 1-year [9-14] whereas only few analyses are available on 2-5 years [15-17] or 10 years follow-up [18-20]. Parameters linked to shorter survival in these studies have been: high age [9-13,15-18], underlying conditions [12-17], severe sepsis or septic shock [12,20], unknown infection focus [10,14,18,20], pneumonia [10,20] and methicillin-resistance for *S. aureus* (MRSA) [11] whereas adequate empiric antibiotic therapy has been connected to improved survival [3,14]. However, the role of IDS consultation on long-term outcome of SAB has received surprisingly little attention. Most reports on long-term follow-up of SAB did not include or comment on the role of any IDS consultation [10-15,17,20]. Five studies provided IDS consultation or an Infectious Disease Team to 12-90% of patients concluding an improved 1-year outcome [3,18] or improved clinical management [21,22] whereas one report did not specify what clinical or prognostic impact IDS gave [20]. Two of the reports specified IDS consultation as formal or routine [3,22]. There are no reports on the effect of IDS consultation on long-term outcome beyond 1 year after SAB.

The objective here was to investigate the impact of formal IDS consultation, compared to informal or lack of IDS consultation, on risk for new bacteremia and outcome during 10 years follow-up after methicillin-sensitive (MS) SAB. Exclusion of patients that deceased within 90 days enabled evaluation of parameters affecting only long-term outcome. Inclusion of MS-SAB enabled a setting where each patient received proper non-delayed antibiotics from the first day of SAB thus avoiding the impact of differences in empirical antibiotic choice.
Materials and Methods

Study population

The present study included all adult patients with at least 1 positive blood culture for methicillin-sensitive *S. aureus* from Helsinki University Central Hospital in Finland identified during January 1999 to May 1999 and January 2000 to August 2002 and 2006–2007. Clinical patient data was retrieved from both written (1999–2002) and electronic (2006–2007) patient records. Bacteremia due to MRSA was omitted (altogether 5 cases in 1999–2002 and no cases in 2006–2007). We followed patient records meticulously for 90 days. Data documentation included: gender, age, co-morbid diseases, infection acquisition, illness severity, antibiotic therapy, radiological and laboratory findings, infection foci, IDS consultation, hospitalization and outcome. Infection foci were verified by radiological, bacteriological, or pathological investigations or by clinical suspicion. The follow-up continued from hospital records for 10 years after the initial 90 days. Data on date and causative pathogen of any new bacteremia and date of death were recorded. The death or alive status was ensured from the Population Register Centre which includes data on all people in Finland.

Definitions

The McCabe’s criteria were applied for classification of underlying conditions and comorbid diseases [23]. Patients with McCabe’s healthy and non-fatal classification were viewed as lacking severe underlying diseases. SAB was defined as nosocomial (healthcare associated) when the first positive blood culture for *S. aureus* was received i) ≥ 48 hours after admission to hospital or ii) ≤ 48 hours of hospital admission with a preceding previous hospital discharge within 7 days. Severe sepsis was categorized as sepsis in combination with hypotension, hypo-perfusion or organ failure [24]. The Modified Duke criteria were applied for definition of endocarditis [25]. The Pitt bacteremia score was used for severity of illness evaluation [26]. IDS consultation within 7 days of SAB was categorized as i) formal IDS, ii) informal IDS or iii) no IDS consultation. Formal consultation was a bedside consultation by the IDS including physical examination, review of patient records and written directives on clinical management. Informal consultation was recorded when directives given by
the IDS on management were given by telephone (or any informal communication) and the treating physician documented the directives into the records. Lack of IDS consultation was defined as no consultation [6].

Outcome
The primary outcome was mortality rate and occurrence of any new bacteremia during 1, 3 and 10 years.

Statistical analyses
Categorical variables were compared with Pearson´s X² test and non-categorical variables with Students t-test. Odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Univariate factors with p<0.1 were allowed into Cox regression model (proportional hazards regression) (Table 4) for estimation of prognostic parameters and into multivariate analysis (Table 5) for estimation of parameters predicting risk for new bacteremia. The Kaplan-Meier method was applied for survival estimates. Patients who died within 90 days were excluded from all analyses to enable statistical calculations of long-term prognostic parameters without interference from early deceased patients. Tests were two-tailed and p<0.05 was considered significant. Analyses were done with SPSS 12.0 (SPSS Inc. Chicago, IL, USA).

Results
Patient characteristics
We identified a total of 440 patients with MS-SAB, however, 73 (17%) patients died during the initial 90 days and were excluded. Formal IDS consultation was received by 304 (83%) whereas 63 (17%) were managed through informal IDS consultation or without consultation. No differences regarding age, gender or bacteremia acquisition were observed between the two groups (Table 1). Patients with formal IDS consultation, compared to patients with informal or lack of IDS consultation, had less hematological malignancy and more injection drug use (IDU) whereas no other differences were seen regarding other underlying conditions. When comparing patients with formal IDS consultation, to patients with informal or lack of IDS consultation, no differences were seen regarding McCabe´s healthy, nonfatal, ultimately-fatal or rapidly-fatal classification of diseases (Table 1). No differences on severe sepsis, intensive care unit or Pitt bacteremia scores were seen.
between patients with formal IDS consultation and those with informal or no IDS consultation (Table 1).

**Clinical management**

Altogether 260 (71%) patients had a deep infection focus. Formal IDS consultation, compared to informal or lack of IDS consultation, associated with more radiological examinations; transesophageal echocardiography, computed tomography scans and leukocyte indium-111 scintigraphy and more deep infection foci. Furthermore, deep infection focus eradication, including infected foreign body removal, was received by 27% respective 11% of patients with formal IDS consultation. Contrary to this, patients managed by informal IDS or without any IDS did not undergo any infection eradication (Table 2).

**Antibiotic therapy**

From the first day of positive blood culture each patient was treated with an intravenous antimicrobial agent effective in vitro against the *S. aureus* blood isolate. Most patients received an anti-staphylococcal penicillin 76% whereas 17% had cephalosporin and 7% vancomycin, clindamycin or a carbapenem. Adjunctive fluoroquinolone, rifampicin or aminoglycoside was received by 51%, 54% and 16% of patients, respectively. Patients with formal IDS consultation, compared to patients managed by informal IDS consultation or without IDS consultation, had more anti-staphylococcal penicillin, more adjunctive rifampicin and less cephalosporin, vancomycin, clindamycin or carbapenem therapy whereas no difference were seen with respect to adjunctive fluoroquinolone or aminoglycoside therapy (Table 2).

**Outcome**

The 1-, 3- and 10-year overall mortality rates after exclusion of patients who deceased within the first 90 days were 5%, 8% and 30%, respectively. The mortality among patients who received formal IDS consultation, as compared to patients with informal or lack of IDS consultation, was lower at 1-year, at 3-years and at 10-years (Table 3). In Cox proportional regression model analysis prognostic factors at 1, 3 and 10 years were very similar. At the two later time-points the only parameter for poor outcome was age > 65 years whereas lack of underlying diseases and formal IDS consultation were connected to better outcome at all three time-points (Table 4, Figure 1). The Cox proportional regression analyses were re-performed by excluding patients with
hematological malignancy. The results were very similar to those in Table 4 with formal IDS consultation connecting to a positive prognosis at 1-, 3- and 10-years follow-up. To further evaluate the long-term prognostic impact of formal IDS consultation we re-performed the analyses by excluding patients who died within the first 3 years (N=30). When the prognostic impact of formal IDS consultation on survival during 3 - 10 years was evaluated the following results were achieved: OR, 0.66; 95% CI, .34-1.29, p=.22.

The risk for a new bacteremia episode caused by any pathogen was 9% (34), 11% (41) and 18% (65) and the risk for a new episode of SAB was 4% (14), 4% (15) and 6% (22) at 1-, 3- and 10-years follow-up, respectively (Table 3). During the 10-years follow-up the three most common bacteremia pathogen were 1) 22 cases of Staphylococcus aureus, 2) 8 cases of various Streptococci including 3 cases of Streptococcus Viridans, 3 cases of Streptococcus Pneumoniae and 2 cases of Streptococcus Pyogenes and 3) 7 cases of Escherichia coli.

Formal IDS consultation, compared to informal or lack of IDS consultation, was connected to a lower risk for new bacteremia episodes at 1-year, at 3-years and at 10-years (Table 3). However, within 10 years follow-up, formal IDS consultation, compared to informal or no IDS consultation, presented no reduced risk for a new episode of SAB. In multivariate analysis, factors reducing the risk for any new bacteremia episode within 1 and 3 years were lack of underlying diseases and formal IDS consultation whereas IDU increased the risk. At 10 years follow-up IDU increased and formal IDS consultation decreased the risk for a any new bacteremia episode (Table 5). The multivariate analyses were re-performed by excluding patients with hematological malignancy. The results were very similar to those in Table 5: Formal IDS consultation reduced the risk for any new bacteremia episode at 1 year, 3- and at 10 years follow-up.

**Discussion**

The main observations were that formal IDS consultation, compared to informal or lack of IDS consultation, improved long-term outcome of MS-SAB. Accounting for all prognostic parameters MS-SAB patients had a 4-5 -fold lower risk for a fatal outcome during 1 and 3 years follow-up and an almost 2-fold lower risk for a fatal outcome during 10 years follow-up due to formal IDS consultation. A similar trend was seen for risk of
any new bacteremia during long-term follow-up: MS-SAB patients had a 3-fold lower risk during 1 and 3 years follow-up and an almost 2-fold reduced risk during 10 years follow up due to formal IDS consultation.

The importance of deep infection localization and eradication and the potential connection of undiagnosed infection focus to mortality has been demonstrated repeatedly in SAB [27,28,29,30]. Identification of deep infection focus has improved 1- and 5-year prognosis after SAB [10,14,18,20]. Previous reports on long-term outcome in SAB have provided echocardiography to 44-64% of patients [3,10,21,22], identified deep infection focus in 11-38% [3,9,14,10,22] with endocarditis in 4-27% [3,10,14,18,21,22] and osteomyelitis and/or septic arthritis in 10-27% of patients [3,9,22]. The present study demonstrated a strong connection of formal IDS consultation to radiological investigations resulting in deep infection focus identification in up to 78%. However, patients managed through informal IDS consultation or without IDS consultation had deep infection focus identified in 43% of cases only and no infection focus eradication was provided.

The impact of IDS consultation guided clinical management on long-term outcome in SAB has received little attention. Two prospective studies provided IDS consultation for all SAB patients: One report had all patient cases reviewed by two infectious diseases specialists [9] whereas a second report investigated bacteremia of various pathogens (42% SAB) and provided bedside infectious diseases physician evaluation to all cases [16]. A third report had 12% of patients supervised by an Infectious Diseases Team and concluded that lack of supervision was connected to poorer long-term outcome [18]. Another three reports provided IDS consultation to 27% [3], 74% [21] and 90% [22] of SAB patients and concluded that IDS consultation improved 1-year outcome [3] or increased compliance [21,22]. Contrary to the studies mentioned above, one report providing IDS consultation to 25% of SAB patients presented no benefit as a result of the consultation [20]. However, the explicit content and impact of the IDS consultation was not described [9,16,18,20,21]. Detailed content and impact of the IDS consultation has been specified in only two previous studies concluding that formal IDS consultation [3] or routine IDS consultation [22] enhanced choice and duration of antimicrobial therapy and increased diagnostics of deep infection focus and endocarditis [3,22]. However, only one of these two reports connected formal IDS consultation to improved 1-year outcome [3]. We have previously shown that informal IDS consultation cannot achieve the benefits in short-term survival that were seen with formal bedside IDS
Hence, despite solid evidence that IDS consultation improve short-term outcome of SAB, no reports are available on the detailed content and impact of IDS consultation on 1 to 10 years long-term outcome.

The present study excluded patients who died within 90 days to enable statistical analyses without interference from early deceased patients. This enabled evaluation of prognostic parameters that influence outcome after the initial 90 days. Moreover, to further evaluate the long-term prognostic impact of formal IDS consultation we re-performed the analyses by excluding patients who died within the first 3 years and investigated parameters affecting survival during 3 – 10 years. However, when excluding patients who deceased within the first 3 years no prognostic impact of formal IDS consultation on 3 - 10 years survival was observed. Hence, it appears that the major positive prognostic impact of formal IDS consultation is seen within the first 3 years and for patients who survive past the first 3 years the outcome during following years is irrespective of formal IDS consultation. To the best of our knowledge only three studies have excluded early deceased patients i.e. patients who died within 3-30 days [3,9,14]. Previous reports on SAB outcome, including studies with early deceased patients excluded, have presented mortality rates of 32-47% at 1 year, 48% at 3 years and 76% at 10 years [9,10,14,16,18,19]. The mortality rates of the present study are far lower than in these previous reports. However, comparison of mortality figures need caution as the present study excluded patients who died early.

The present study connected age and underlying conditions to poorer long-term prognosis at 1, 3 and 10 years follow-up which is in line with previous reports [9,10,11,14,15,]. Long-term prognosis in the present report was not affected by severe sepsis, pneumonia or endocarditis i.e. parameters frequently associated to poorer short-term (30-90 days) outcome [2-6]. These observations are in line with one previous report that excluded patients who deceased within 30 days and supports the observations that short-term mortality is mainly influenced by severe infection related complications such as severe sepsis or endocarditis whereas long-term outcome is dictated by background parameters such as age and comorbidity [9]. Some previous reports have presented severe sepsis, septic shock and pneumonia as drivers of long-term outcome in SAB [10,12,20]. However, these studies have not excluded early deceased patients and hence the degree to which these parameters impact long-term outcome is uncertain.
Relapse of SAB is common and previous reports present relapse rates of 5-12% during 90 days follow-up [5,31-33]. Parameters recognized as independent risk factors for relapse are deep infection focus, endocarditis, unremoved infected central venous line and vancomycin therapy for MS-SAB [32-34]. Moreover, reports have connected IDS consultation to significantly reduced risk for SAB relapse during short-term follow up of 90 days [5,31]. To the best of our knowledge only one study has reported a 6% SAB relapse during 1 year follow-up in a study setting were each patients was provided IDS consultation [9]. We observed a rate of new SAB episodes of 4% at 1 and 3 years follow-up and 6% at 10 years follow-up. In the present study, formal IDS consultation did not impact the risk for a new SAB episode during 1 to 10 years follow-up. However, a significant reduction in risk for any new bacteremia episode due to formal IDS consultation during 1, 3 and 10 years follow-up was observed. The association of proper clinical management of SAB, due to formal IDS consultation, and reduced future risk for new bacteremia, is difficult to explain. Previous studies have observed that patients who suffer from bacteremia, compared to matched control patients, are more morbid and have higher long-term mortality rates [15,35]. This excess long-term mortality is not completely understood and it has been proposed that bacteremia might be a marker of co-morbidity or an activator for a low-grade inflammatory response and infection-related inflammation resulting in the development of new diseases or accelerating earlier existing comorbidity e.g. cardiovascular or renal disease [15,36,37].

There are weaknesses in the present study that have to be accounted for when interpreting the results. First, the retrospective design includes risk for bias. Patients receiving formal IDS consultation, compared to patients with informal or lack of IDS consultation, had less hematological malignancies. However, analyses were performed twice both including and excluding hematological malignancies and the impact of formal IDS consultation on long-term outcome and risk for new bacteremia episodes were almost identical. Second, the present study demonstrated a connection between formal IDS consultation and reduced long-term mortality and risk for new bacteremia episodes which, however, does not mean a causal relationship. There is always the possibility that severely ill patients with presumed poor prognosis did not receive formal IDS consultation. However, the exclusion of patients that deceased during 90 days can correct for this potential bias. Third, the patient cohort was originally gathered during January – May 1999, January 2000 – August 2002 and year 2006 - 2007 for evaluation of the prognostic impact of fluoroquinolones, rifampicin and IDS consultation in MS-
SAB [6,38,39]. The fluoroquinolone trovafloxacin was initially included but was withdrawn from the market and later replaced by the fluoroquinolone levofloxacin. This explains why no patients were collected during June – December 1999. Considering the time-periods of year 1999-2002 and 2006-2007 it is plausible to discuss whether the data is valid for current medical practice. However, we wanted to include two separate time periods to exclude the possibility of temporary unidentified differences in treatment practices or other factors difficult to control for. Furthermore, the possible disadvantage with either information storage pattern was taken into account by including both electronic and paper records.

In conclusion, the study indicates that formal IDS consultation, compared to informal or lack of consultation, improve long-term outcome and reduce risk for new bacteremia episodes. However, the relationship and implication of properly managed SAB and reduced risk of new bacteremia need further evaluation.

Compliance with ethical standards

Conflict of interest AJ has received speakers honorary from Astellas, Biogen, Orion Pharma and Pfizer and consultation fee from CLS Behring. ER has received speakers honorary from MSD. Other authors declare that they have 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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Table 1 Demographics, underlying conditions and illness severity of 367 methicillin-sensitive *Staphylococcus aureus* bacteremia patients that survived the first 90 days. Categorization according to formal infectious specialist consultation.

| Parameters | Formal infectious diseases specialist consultation |
|------------|---------------------------------------------------|
|            | Present N=304 (83) | Absent N=63 (17) | OR (95% CI) | p-value |
| Demographics |                   |                   |             |         |
| Male gender | 205 (67)           | 38 (60)           | 1.36 (.78 - 2.38) | .28     |
| Age > 65 years | 96 (32)      | 15 (24)           | 1.48 (.79 - 2.77) | .22     |
| Age, mean (years ±SD) | 54.5 ±18     | 52.4 ±16          | ---          | .24     |
| Nosocomial bacteremia | 143 (47)     | 38 (60)           | 0.58 (.34 - 1.02) | .06     |
| Underlying conditions |                   |                   |             |         |
| McCabe’s classification ^A |                   |                   |             |         |
| i. Healthy | 30 (10)          | 5 (8)             | 1.27 (.47 - 3.41) | .64     |
| ii. Nonfatal | 210 (69)       | 37 (58)          | 1.57 (.89 - 2.74) | .11     |
| iii. Ultimately-fatal | 62 (20) | 19 (30)           | 0.59 (.32 - 1.09) | .089    |
| iv. Rapidly-fatal | 56 (18)     | 14 (22)          | 0.79 (.41 - 1.53) | .49     |
| Coronary artery disease | 45 (15)       | 8 (13)           | 1.19 (.53 - 2.68) | .67     |
| Pulmonary disease – acute or chronic | 56 (18) | 7 (11)           | 1.81 (.78 - 4.17) | .16     |
| Liver disease – acute or chronic | 36 (12)       | 10 (16)          | 0.71 (.33 - 1.52) | .38     |
| Diabetes mellitus |                   |                   |             |         |
| Chronic renal failure ^B | 2 (1)     | 2 (3)             | 0.20 (.03 - 1.46) | .080    |
| Malignancy | 56 (18)          | 14 (22)          | 0.79 (.41 - 1.53) | .49     |
| Non-hematological |                   |                   |             |         |
| Hematological | 45 (15)       | 8 (13)           | 1.19 (.53 - 2.68) | .67     |
| IDU ^C | 56 (18)          | 7 (11)          | 1.81 (.78 - 4.17) | .16     |
| HIV | 36 (12)          | 10 (16)          | 0.71 (.33 - 1.52) | .38     |
| Severity of illness |                   |                   |             |         |
| Severe sepsis ^D | 34 (11)       | 9 (14)           | 0.76 (.34 - 1.67) | .49     |
| ICU treatment, within 24 hours | 23 (8)     | 8 (13)           | 0.56 (.24 - 1.32) | .18     |
| ICU treatment, with 7 days | 6 (2)     | 16 (25)          | 0.06 (.02 - .16) | .001    |
| Pitt score ≥ 3 ^D,E | 51 (17)       | 3 (5)            | 4.03 (1.22 - 13.3) | .014    |
| Pitt score (mean ± SD) ^D,E |       |                  |             |         |
| 19 (6) | 19 (6)           | 0.63 (.24 - 1.66) | .35     |
| 55 (18) | 55 (18)       | 0.85 (.43 - 1.67) | .64     |
| 77 (25) | 77 (25)       | 0.92 (.49 - 1.69) | .78     |
| 23 (8) | 23 (8)           | 0.75 (.29 - 1.92) | .54     |
| 0.59 ± 1.4 | 0.59 ± 1.4 | ---            | ---     | .29     |
Data are No. (%) of patients. Hazards ratio (HR) and 95 % confidence intervals (CI) are presented. Abbreviations: ICU, intensive care unit; OR, odds ratio. A Underlying diseases characterized according to McCabe and Jackson [23]. B Chronically elevated serum creatinine (≥ 180 mmol/l). C Injection drug use within preceding 6 months. D At blood culture collection. E Pitt bacteremia scores [26].

Table 2: Radiology, infections and antimicrobial therapy in 367 methicillin-sensitive Staphylococcus aureus bacteremia patients that survived the first 90 days. Categorization according to formal infectious diseases specialist consultation.

| Parameters                                  | Formal infectious diseases specialist consultation | OR (95% CI) | p-value |
|---------------------------------------------|----------------------------------------------------|-------------|---------|
|                                             | Present N=304 (83) | Absent N=63 (17) |          |         |
| **Radiological investigations**             |                                                    |             |         |
| Echocardiography                            |                                                    |             |         |
| Transthoracic                               | 204 (67)                                           | 38 (60)     | 1.34 (.77 - 2.35) | .30     |
| Transesophageal                             | 44 (14)                                            | 1 (2)       | 10.5 (1.42 - 77.6) | .005    |
| Whole-body computed tomography              |                                                    |             |         |
| ≥ 1 per patient                             | 203 (67)                                           | 31 (49)     | 2.08 (1.12 - 3.59) | .008    |
| Numbers per patient, mean (± SD)            | 1.10 ± 1.0                                         | 0.49 ±0.5   | ---     | .004    |
| Magnetic resonance imaging                  |                                                    |             |         |
| ≥ 1 per patient                             | 64 (21)                                            | 0           | ---     | ---     |
| Numbers per patient, mean (± SD)            | 0.29 ±0.6                                          | 0           | ---     | ---     |
| Leukocyte indium-111 scintigraphy          | 127 (42)                                           | 7 (11)      | 5.74 (2.53 - 13.0) | < .001  |
| **Infection focus and eradication**         |                                                    |             |         |
| Pneumonia                                   | 112 (37)                                           | 11 (17)     | 2.76 (1.38 - 5.50) | .003    |
| Endocarditis                                | 40 (13)                                            | 2 (3)       | 4.62 (1.09 - 19.6) | .023    |
| Osteomyelitis and/or septic arthritis        | 120 (39)                                           | 6 (10)      | 6.23 (2.60 - 14.9) | < .001  |
| Any deep infection focus                    |                                                    |             |         |
| Eradication of deep infection focus A       | 236 (78)                                           | 24 (38)     | 5.64 (3.17 - 10.0) | < .001  |
| Eradication of infected foreign body        | 83 (27)                                            | 0           | ---     | ---     |
| **Antimicrobial therapy**                   |                                                    |             |         |
| Anti-staphyloccocal penicillin B            | 255 (84)                                           | 25 (40)     | 7.91 (4.38 - 14.3) | < .001  |
| Cephalosporine C                            | 40 (13)                                            | 23 (37)     | 0.26 (.14 - .49)  | < .001  |
| Other therapy D                             | 9 (3)                                              | 15 (24)     | 0.09 (.04 - .24)  | < .001  |
| Vancomycin                                  | 7 (2)                                              | 3 (5)       | 0.47 (.12 - 1.88) | .28     |
| Fluoroquinolone E                           |                                                    |             |         |
| Aminoglycoside E                            |                                                    |             |         |
| Rifampicin E, F                            |                                                    |             |         |
Data are No. (%) of patients. Hazards ratio (HR) and 95% confidence intervals (CI) are presented. Abbreviations: OR, odds ratio.

A Surgical or radiological eradication. B Cloxacillin. C Cefuroxime or ceftriaxone. D Vancomycin, clindamycin or a carbapenem.

E Adjunctive antimicrobial therapy. F Therapy duration ≥ 14 days.

Table 3 Risk for new bacteremia and outcome in 367 methicillin-sensitive Staphylococcus aureus bacteremia patients that survived the first 90 days. Categorization according to formal infectious diseases specialist consultation.

| Parameters                        | Formal infectious diseases specialist consultation |                  |                  |                  |                  |
|-----------------------------------|---------------------------------------------------|------------------|------------------|------------------|------------------|
|                                   | Present N=304 (83)                                | Absent N=63 (17) | OR (95% CI)      | p-value          |
| Risk for new bacteremia           |                                                   |                  |                  |                  |
| Within 1 year                     |                                                   |                  |                  |                  |
| New bacteremia due to any pathogen| 23 (8)                                            | 11 (17)          | 0.39 (.18 - .84) | .014             |
| SAB relapse                        | 9 (3)                                             | 5 (8)            | 0.77 (.18 - 3.29)| .73              |
| Within 3 years                    |                                                   |                  |                  |                  |
| New bacteremia due to any pathogen| 28 (9)                                            | 13 (21)          | 0.39 (.19 - 0.80)| .010             |
| SAB relapse                        | 10 (3)                                            | 5 (8)            | 0.89 (.23 - 3.46)| .87              |
Within 10 years

|                          | 1 year | 3 years | 10 years |
|--------------------------|--------|---------|----------|
| New bacteremia due to any pathogen | 49 (16) | 16 (25) | 0.56 (.29 - 1.08) | .079 |
| SAB relapse              | 17 (6) | 5 (8)   | 0.69 (.24 - 1.94) | .47  |

Mortality, within

|                | 1 year | 3 years | 10 years |
|----------------|--------|---------|----------|
| 1 year         | 8 (3)  | 9 (14)  | 0.16 (.06 - .44) | < .001 |
| 3 years        | 16 (5) | 14 (22) | 0.19 (.09 - .42) | < .001 |
| 10 years       | 81 (27)| 29 (46) | 0.43 (.24 - .74) | .002  |

Data is No. (%). Hazards ratio (HR) and 95% confidence intervals (CI) are presented. Abbreviations: OR, odds ratio.

**Table 4** Cox proportional regression model analysis for prognostic factors for 1-, 3- and 10-year mortality in 367 methicillin-sensitive *Staphylococcus aureus* bacteremia patients that survived the first 90 days.

| 1-year mortality | Died | Survived | OR (95% CI) | p-value | HR (95% CI) | p-value |
|------------------|------|----------|-------------|---------|-------------|---------|
| Male gender      | 13 (76) | 230 (66) | 1.69 (.54 - 5.31) | .36 | --- | --- |
| Age > 65 years   | 9 (53) | 102 (29) | 2.74 (1.03 - 7.29) | .037 | --- | --- |
| Healthy-nontatal disease | 6 (35) | 276 (79) | 0.15 (.05 - .42) | < .001 | 0.18 (.07 - .50) | .001 |
| Nosocomial bacteremia | 12 (71) | 169 (48) | 2.57 (.89 - 7.45) | .072 | --- | --- |
| Severe sepsis A  | 2 (12) | 23 (7) | 1.89 (.41 - 8.79) | .41 | --- | --- |
| Pneumonia        | 6 (35) | 117 (33) | 1.09 (.39 - 3.01) | .87 | --- | --- |
| Endocarditis     | 0 | 42 (12) | --- | --- | --- | --- |
| Bedside IDS consultation | 8 (47) | 296 (85) | 0.16 (.06 - .44) | < .001 | 0.21 (.08 - .55) | .001 |
| Telephone or no IDS consultation | 9 (53) | 54 (15) | 6.17 (2.28 - 16.7) | < .001 | --- | --- |
| Rifampicin C     | 11 (65) | 186 (53) | 1.62 (.59 - 4.47) | .35 | --- | --- |

| 3-year mortality | Died | Survived | OR (95% CI) | p-value | HR (95% CI) | p-value |
|------------------|------|----------|-------------|---------|-------------|---------|
| Male gender      | 22 (73) | 221 (66) | 1.44 (.62 - 3.34) | .39 | --- | --- |
| Age > 65 years   | 15 (50) | 96 (28) | 2.51 (1.18 - 5.34) | .014 | 2.15 (1.02 - 4.53) | .045 |
| Underlying diseases characterized according to McCabe and Jackson [23]. | At blood culture collection time-point. | Adjunctive rifampicin therapy ≥ 14 days. |
|---|---|---|
| Male gender | Age > 65 years | Health-nonfatal disease \(^A\) |
| Nosocomial bacteremia | Pneumonia | Endocarditis |
| Bedside IDS consultation | Telephone or no IDS consultation | Rifampicin \(^C\) |

Data are No. (%) of patients. Hazards ratio (HR) and 95% confidence intervals (CI) are presented. Abbreviations: IDS, infectious diseases specialist; OR, odds ratio. \(^A\) Underlying diseases characterized according to McCabe and Jackson [23]. \(^B\) At blood culture collection time-point. \(^C\) Adjunctive rifampicin therapy ≥ 14 days.

Table 5 Multivariate analysis for factors predicting the risk for new bacteremia due to any pathogen during 1-, 3- and 10-years follow-up in 367 methicillin-sensitive *Staphylococcus aureus* bacteremia patients that survived the first 90 days.

| Univariate analysis | Multivariate analysis |
|---|---|
| Bacteremia within 1 year | Present | Absent | OR (95% CI) | p-value | HR (95% CI) | p-value |
| Male gender | 23 (68) | 220 (66) | 1.07 (.51 - 2.28) | .85 | --- | --- |
| Age > 65 years | 10 (29) | 101 (30) | 0.96 (.44 - 2.08) | .91 | --- | --- |
| Healthy-nonfatal disease \(^A\) | 19 (56) | 263 (79) | 0.34 (.16 - .69) | .002 | 0.18 (.07 - .45) | <.001 |
| Nosocomial bacteremia | 19 (56) | 162 (49) | 1.34 (.66 - 2.72) | .42 | --- | --- |
| IDU \(^B\) | 11 (32) | 43 (13) | 3.23 (1.47 - 7.08) | .002 | 8.74 (3.20 - 23.8) | <.001 |
| Severe sepsis \(^C\) | 1 (3) | 24 (7) | 0.39 (.05 - 2.98) | .35 | --- | --- |
| Condition                      | Present N=41 (11) | Absent N=326 (89) | OR (95% CI) | p-value | HR (95% CI) | p-value |
|-------------------------------|-------------------|-------------------|-------------|---------|-------------|---------|
| Male gender                   | 29 (66)           | 214 (66)          | 1.27 (.62 - 2.57) | .52     | ---         | ---     |
| Age > 65 years                | 10 (24)           | 101 (31)          | 0.72 (.40 - 1.52) | .39     | ---         | ---     |
| Health-nonfatal disease A     | 24 (59)           | 258 (79)          | 0.37 (.19 - .73) | .003    | 0.17 (.07 - .41) | < .001 |
| Nosocomial bacteremia         | 22 (54)           | 159 (49)          | 1.22 (.63 - 2.33) | .56     | ---         | ---     |
| IDU B                         | 15 (37)           | 39 (12)           | 4.25 (2.07 - 8.71) | < .001 | 12.1 (4.72 - 30.8) | < .001 |
| Severe sepsis C              | 2 (5)             | 23 (7)            | 0.68 (.15 - 2.98) | .60     | ---         | ---     |
| Pneumonia                     | 14 (34)           | 109 (33)          | 1.03 (.52 - 2.05) | .93     | ---         | ---     |
| Endocarditis                  | 7 (17)            | 35 (11)           | 1.71 (.71 - 4.15) | .23     | ---         | ---     |
| Bedside IDS consultation      | 28 (68)           | 276 (85)          | 0.39 (.19 - .80) | .009    | 0.29 (.13 - .66) | .003    |
| Telephone or no IDS consultation | 13 (32)        | 50 (15)           | 2.56 (1.24 - 5.28) | .009    | ---         | ---     |
| Rifampicin D                  | 20 (49)           | 177 (54)          | 0.80 (.42 - 1.54) | .51     | ---         | ---     |

| Condition                      | Present N=65 (18) | Absent N=302 (82) | OR (95% CI) | p-value | HR (95% CI) | p-value |
|-------------------------------|-------------------|-------------------|-------------|---------|-------------|---------|
| Male gender                   | 44 (68)           | 199 (66)          | 1.08 (.61 - 1.92) | .78     | ---         | ---     |
| Age > 65 years                | 17 (26)           | 94 (31)           | 0.78 (.43 - 1.43) | .43     | ---         | ---     |
| Healthy-nonfatal disease A    | 46 (71)           | 236 (78)          | 0.68 (.37 - 1.23) | .20     | ---         | ---     |
| Nosocomial bacteremia         | 34 (52)           | 147 (49)          | 1.16 (.68 - 1.98) | .59     | ---         | ---     |
| IDU B                         | 19 (29)           | 35 (12)           | 3.15 (1.66 - 5.98) | < .001 | 3.63 (1.87 - 7.02) | < .001 |
| Severe sepsis C              | 5 (8)             | 20 (7)            | 1.18 (.42 - 3.26) | .76     | ---         | ---     |
| Pneumonia                     | 21 (32)           | 102 (34)          | 0.94 (.53 - 1.66) | .82     | ---         | ---     |
| Endocarditis                  | 7 (11)            | 35 (12)           | 0.92 (.39 - 2.18) | .85     | ---         | ---     |
| Bedside IDS consultation      | 49 (75)           | 255 (84)          | 0.56 (.30 - 1.08) | .079    | 0.45 (.23 - .88) | .02     |
| Telephone or no IDS consultation | 16 (25)        | 47 (16)           | 1.77 (.93 - 3.38) | .079    | ---         | ---     |
| Rifampicin D                  | 31 (48)           | 166 (55)          | 0.75 (.44 - 1.28) | .29     | ---         | ---     |

Data is No. (%) of patients. Hazards ratio (HR) and 95% confidence intervals (CI) are presented. Abbreviations: IDS, infectious diseases specialist consultation; OR, odds ratio. A Underlying diseases characterized according to McCabe and Jackson [23]. B Injection drug use within preceding 6 months. C At blood culture collection time-point. D Adjunctive rifampicin therapy ≥ 14 days.
Fig. 1 Kaplan-Meier analysis for probability of survival during 10 follow-up in 367 patients surviving the first 90 days after methicillin-sensitive *Staphylococcus aureus* bacteremia. Patients are categorized according to formal infectious diseases specialist consultation and informal or no consultation. The log-rank \( p < .001 \).