Infectious disease consultation for Staphylococcus aureus bacteremia – A systematic review and meta-analysis

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Infectious disease consultation for Staphylococcus aureus bacteremia – A systematic review and meta-analysis

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Summary  Objective: Mortality and morbidity of Staphylococcus aureus bacteremia (SAB) still remains considerably high. We aimed to evaluate the impact of infectious disease consultation (IDC) on the management and outcomes of patients with SAB.
Methods: We systematically searched 3 publication databases from inception to 31st May 2015 and reference lists of identified primary studies.
Results: Our search returned 2874 reports, of which 18 fulfilled the inclusion criteria, accounting for 5337 patients. Overall 30-day mortality was 19.95% [95% CI 14.37–27.02] with a significant difference in favour of the IDC group (12.39% vs 26.07%) with a relative risk (RR) of 0.53 [95% CI 0.43–0.65]. 90-day mortality and relapse risk for SAB were also reduced significantly with RRs of 0.77 [95% CI 0.64–0.92] and 0.62 [95% CI 0.39–0.99], respectively. Both, the appropriateness of antistaphylococcal agent and treatment duration was improved by IDC (RR 1.14 [95% CI 1.08–1.20] and 1.85 [95% CI 1.39–2.46], respectively). Follow-up blood cultures and echocardiography were performed more frequently following IDC (RR 1.35 [95% CI 1.25–1.46] and 1.98 [95% CI 1.66–2.37], respectively).

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Introduction

*Staphylococcus aureus* is a common pathogen causing hospital- and community-acquired bacteremia with an overall population-based incidence rate of 15–40 cases per 100,000 population and year and the second leading pathogen causing sepsis in industrialized countries.1–3 *Staphylococcus aureus* bacteremia (SAB) is associated with case fatality rates of approximately 15–25%, significant morbidity, frequent complications and imposes a significant burden on the healthcare system.3–5 Typical complications of SAB are relapse of bacteremia and metastatic infection including infective endocarditis, central nervous system embolism and septic arthritis. Moreover, occurrence of resistance (MRSA) is rife and even aggravates antimicrobial treatment.5

Results from a recent analysis of hospital discharge data suggest that when an infectious diseases (ID) specialist is involved in a patient’s care and the physician in charge follows ID recommendations, patients are more often correctly diagnosed, have shorter lengths of stay, receive more appropriate therapies, have fewer complications, may need fewer antibiotics overall and have higher hospital survival rates.7 So far, the positive impact of IDC has been most conclusively shown for SAB. Tong and Fowler state in a recent narrative review on *S. aureus* infections that an ID consultation (IDC) should be regarded as the standard of care for patients with SAB in institutions where this subspecialty service is available.8 However, most existing studies regarding the impact of ID specialty care are constrained by moderate to small sample sizes and methodological pitfalls, including retrospective observational designs and selection bias, which limit both the external and internal validity of the findings.7 Data suggest that evidence-based clinical management may improve the prognosis of SAB by adherence to quality care indicators (QCIs) as appropriate choice and duration of antibiotic therapy including de-escalation, an adequate diagnostic evaluation using follow-up blood cultures, early source control, echocardiography and other imaging if necessary.10–14

For those reasons, we aimed to conduct a systematic review and meta-analysis to evaluate the impact of IDC on the management and outcomes of patients with SAB including considerations of heterogeneity and potential covariates at both the level of studies and patients.

Material and methods

Applied principle

Our systematic review and meta-analysis conforms to the PRISMA statement (see Supplementary Appendix) as far as possible for non-randomized and quasi-experimental studies. All studies discovered through systematic search were evaluated for eligibility with reference to the PICO principle including characterization of the study populations, interventions, comparisons and outcome measures.15

Inclusion criteria

The target population of our systematic search and meta-analysis were patients with SAB, diagnosed by the detection of *S. aureus* in a blood culture. The intervention group of interest received at least one formal consultation by an ID specialist and was compared with a control group that did not. The primary outcome was mortality until day 30 and 90, secondary endpoints were relapse of bacteremia until day 90, and the following QCIs that have been carved out in former studies: obtention of follow-up blood cultures, performance of transthoracic or transesophageal echocardiography, and appropriate antimicrobial therapy including agent and treatment duration.4,16

Search strategy

Literature was systematically reviewed for studies that investigated the impact of IDC on the outcome and management of patients with SAB. The search was done by three authors independently and discrepancies were resolved by consensus. Databases of Medline via PubMed, the Cochrane Library and Web of Knowledge were included until May 31, 2015. Search of the reference lists of the identified articles led to identification of further relevant articles. As a consequence, the search terms were adapted. In detail, we combined several search keywords and MeSH terms for identification and limitation of the study population AND the intervention AND the outcome measurements. Keywords with similar meanings were combined with the operator OR. We used *S. aureus, S. aureus* and MRSA for the causative pathogen in combination with *bacteremia, bacteraemia, blood stream infection, positive blood culture, CLABSI, infective endocarditis* and *sepsis* for characterization of the study population. The intervention was identified with consult*, specialist, recommendation, intervention, stewardship and quality of care*. We also conducted searches to find studies with interesting outcome measurements with the terms mortality, death, complication, management, relapse, recurrence, follow-up blood cultures and appropriate antibiotic therapy (see Table A1, Supplementary Appendix).

For inclusion, studies had to fulfil the PICO criteria. Three authors independently assessed all titles and abstracts to identify matching criteria. Discrepancies were resolved by consensus. Additional filters were not used. We did not make any restriction on age or language since all eligible studies were written in English.
Data extraction

Each investigator recorded the number of patients and events in the IDC and control group. Corresponding authors were contacted in case of missing information. Moreover, we extracted summary information on patient characteristics, potential heterogeneity of the study populations including age, sex, source and site of infection, prevalence of methicillin-resistant S. aureus (MRSA), underlying conditions, and information about the study design including duration and setting as well as methodological information. Selected studies were assessed for the quality evidence according to the guidelines of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (using the Cochrane GRADEpro 3.6 version software)17,18 and summary of finding tables were generated by two authors.

Statistical analysis

We analysed the eligible studies with focus on common QCIs with R (The R Project for Statistical Computing, Version 3.0.2. in RStudio; Version 0.98.501). We calculated and plotted risk ratios for the binary outcomes and 95% confidence intervals applying a random effects model using the method by DerSimonian and Laird19 as implemented R package META20 (functions "metabin" and "forest.meta"). Based on this model, we also calculated a 95% prediction interval for 30-day case fatality21 to predict potential outcomes of future studies. Funnel plots were used to investigate our results for potential evidence of publication bias (function "metabias"; method "linreg"). Finally, we performed a "leave-one-out" sensitivity analysis to assess the influence of the individual studies (function "metainf"). Throughout, we applied an explorative significance level of 5% (two-sided) and did not correct for the multiple outcomes or subgroups analysed.

Results

Systematic search

We retrieved 2874 articles of which 2381 were excluded after screening titles and abstracts (Fig. 1). For outcome analyses further 452 had to be excluded after full text review, leaving 18 studies16,22–37 published between 2008 and 2015 comprising a total of 5337 patients including 2778 patients consulted by infectious disease specialists and 2559 controls (Fig. A1, Supplementary Appendix). Mortality rates until day 30 and/or 90 were documented in 14 studies16,22,25,27–30,32–38 with 2433 and 2328 patients with and without intervention, respectively (Fig. A2,

Figure 1  PRISMA flow diagram. Study identification and selection process for outcome analysis according to the PICO (Population, Intervention, Control, and Outcome) principle, modified from Moher and colleagues.15

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Age</th>
<th>Male gender</th>
<th>Diabetes</th>
<th>Dialysis</th>
<th>Type of infection</th>
<th>Source of infection</th>
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<tr>
<td>Bai et al. 2015</td>
<td>847 (506/341)</td>
<td>65 (63/68)</td>
<td>545 (332/213)</td>
<td>280 (181/99)</td>
<td>107 (63/44)</td>
<td>145 (82/63)</td>
<td>306 (173/133)</td>
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<tr>
<td>Borde et al. 2014</td>
<td>59 (20/39)</td>
<td>77 (78/77)</td>
<td>29 (7/22)</td>
<td>—</td>
<td>—</td>
<td>2 (1/1)</td>
<td>—</td>
</tr>
<tr>
<td>Choi et al. 2015</td>
<td>100 (42/58)</td>
<td>74 (74.5/72.5)</td>
<td>76 (35/41)</td>
<td>23 (19/4)</td>
<td>8 (5/3)</td>
<td>81 (35/46)</td>
<td>76 (32/44)</td>
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<td>Forsblom et al. 2013</td>
<td>270 (244/26)</td>
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<td>181 (160/21)</td>
<td>38 (30/8)</td>
<td>35 (31/4)</td>
<td>163/280 (141/22)</td>
<td>0 (0/0)</td>
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<td>Fries et al. 2013</td>
<td>177 (142/35)</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>90 (78/12)</td>
<td>49 (36/13)</td>
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<td>Honda et al. 2010</td>
<td>341 (111/230)</td>
<td>56 (56/56)</td>
<td>189 (56/133)</td>
<td>111 (32/79)</td>
<td>71 (13/58)</td>
<td>3045</td>
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<td>Isobe et al. 2012</td>
<td>115 (46/69)</td>
<td>64.4/60.5</td>
<td>75 (27/48)</td>
<td>35 (15/20)</td>
<td>16 (9/7)</td>
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<td>115 (46/69)</td>
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<td>Jenkins et al. 2008</td>
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<td>(47/50)</td>
<td>148 (87/61)</td>
<td>65 (39/26)</td>
<td>33 (22/11)</td>
<td>160 (72/88)</td>
<td>78 (44/34)</td>
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<td>Jegenfors et al. 2013</td>
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<td>—</td>
<td>97 (62/35)</td>
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<td>Lahey et al. 2009</td>
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<td>57.9/51.7</td>
<td>139 (72/67)</td>
<td>74 (41/33)</td>
<td>50 (22/28)</td>
<td>131 (77/54)</td>
<td>96 (52/44)</td>
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<td>Lopez-Cortes et al. 2013</td>
<td>508 (221/287)</td>
<td>(67/66)</td>
<td>338 (140/198)</td>
<td>148 (65/83)</td>
<td>46 (25/21)</td>
<td>424 (186/228)</td>
<td>102 (57/45)</td>
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<td>Nagao et al. 2010</td>
<td>346 (152/194)</td>
<td>(63.2/62.1)</td>
<td>210 (89/121)</td>
<td>66 (24/42)</td>
<td>21 (9/12)</td>
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<td>175 (109/66)</td>
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<td>Pragman et al. 2013</td>
<td>185 (149/36)</td>
<td>(66/68)</td>
<td>230 (178/52)</td>
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<td>212 (161/51)</td>
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<td>Rieg et al. 2009</td>
<td>431 (300/131)</td>
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<td>Robinson et al. 2012</td>
<td>599 (162/437)</td>
<td>(56-5/65)</td>
<td>383 (105/278)</td>
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<td>63 (7/56)</td>
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<td>Saundersen et al. 2014</td>
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<td>40 (20/20)</td>
<td>1 (1/0)</td>
<td>—</td>
<td>45 (26/19)</td>
<td>5 (3/2)</td>
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</tbody>
</table>

(continued on next page)
Supplementary Appendix). Six studies reported both,\textsuperscript{16,25,27,34,36,38} further four studies reported solely 30-day mortality\textsuperscript{28,32,35,37} and the remaining four studies solely reported mortality until day 90.\textsuperscript{22,29,30,33} For the analysis of QCIs, another four studies comprising 576 patients without reported 30- or 90-day mortality rates were also included.\textsuperscript{23,24,26,31}

### Study characteristics

The quality of the selected studies was limited in different ways regarding appropriateness of eligibility criteria, methods for measuring both exposure and outcome, and adequate control of confounding (Tables A2 and A3, Supplementary Appendix). Most studies were retrospective cohort studies\textsuperscript{23,26,28,30} or prospective case–control studies\textsuperscript{16,27,29,36} with pre–post comparisons\textsuperscript{16,23,26,28–39} or subsequent comparisons of patients with or without ID consultations.\textsuperscript{24–28,31,33–35,37} Only two studies were multicentric.\textsuperscript{16,22} Most studies were not limited to one department, but were conducted throughout the hospital including intensive care units and general wards of primary, secondary, and tertiary care hospitals in North America,\textsuperscript{22,26,27,29,31,33} Europe,\textsuperscript{16,23,25,28,30,34,36–38} Asia\textsuperscript{4,28,32} and Australia.\textsuperscript{35} The number of enrolled patients ranged from 59 to 847 and the study period from 12 to 120 months. Further study and patient characteristics are shown in Tables 1 and A4.

### Mortality

The overall mortality was 19.95% [95% CI 14.37–27.02] until day 30 in the entire study population with documented 30-day mortality.\textsuperscript{16,25,27,28,32,34–38} Some of these studies excluded all patients who died within up to four days after SAB onset from the final analysis, assuming that they had no opportunity to take advantage of the ID consultation.\textsuperscript{16,25,27,36,38} In the remaining group of 3337 patients, 1578 in the intervention and 1759 in the control group, the overall 30-day mortality was still as similarly high as in the entire population (18.56% [95% CI 12.38–26.87]). There was a significant difference in favour of the IDC group with a 30-day mortality of 12.39% [95% CI 8.74–17.27] and 26.07% [95% CI 19.42–34.03] in the intervention and control group, respectively. The relative risk (RR) was 0.53 [95% CI 0.43–0.65] as shown in the forest plot (Fig. 2). The mortality among the studies providing information about overall 90-day mortality including early deaths was 21.31% [95% CI 15.02–31.80] in the entire study population.\textsuperscript{16,22,25,27,29,30,33,34,36,38} Excluding early deaths, as some of these studies did,\textsuperscript{16,22,25,27,29,31} the mortality was 20.34% [95% CI 13.38–29.68] with 18.62% [95% CI 12.17–27.41] and 26.10% [95% CI 18.04–36.16] in the intervention and control group, respectively. The RR was 0.77 [95% CI 0.64–0.92] as shown in the forest plot (Fig. 2).

### Relapse of bacteremia

Relapse of bacteremia occurred less often in the IDC group with 3.81% and 4.26% in the intervention and control group,
Figure 2  **Forest plots – outcome.** The forest plots represent the relative risks for 30-day and 90-day mortality, as well as for a bacteremia relapse until day 90 together with their 95% confidence intervals comparing patients receiving IDC and the control groups.
respectively. The RR was 0.62 [95% CI 0.39–0.99] as shown in the forest plot (Fig. 2).

Quality of care indicators (QCIs)

Adherence to QCIs was significantly improved in the IDC group (Fig. 3). Appropriate antibiotic therapy was observed more frequently, for both appropriate antistaphylococcal agent (80.35% vs 70.45%; RR 1.14 [95% CI 1.08–1.20]) and for appropriate antimicrobial treatment duration (79.59% vs 45.81%; RR 1.85 [95% CI 1.39–2.46]), respectively. Definitions of appropriate agent and duration of antimicrobial therapy are listed in Table A5 of Supplementary Appendix. Follow-up blood cultures were obtained (69.84% vs 52.80%; RR 1.35 [95% CI 1.25–1.46]) and echocardiography was performed more frequently (71.40% vs 37.32%; RR 1.98 [95% CI 1.66–2.37]).

Heterogeneity

The between-study heterogeneity varied considerably for the different outcome analyses as shown in the forest plots (Figs. 2 and 3). We calculated low heterogeneity for 90-day relapse and 30-day mortality with I² estimates of 0% and 26%, respectively, while heterogeneity was high for QCIs with I² estimates ranging from 56% to 91%.

Discussion

Our meta-analysis demonstrates that patient-specific management advised by infectious diseases (ID) consultants significantly reduces 30- and 90-day mortality of patients with S. aureus bacteremia by over 50% and nearly 30%, respectively.

Patients for whom ID recommendations were followed were more likely to be prevented of a relapse of bacteremia and to be diagnosed of infective endocarditis because more frequent follow-up blood cultures and echocardiography studies were performed. Furthermore, IDC-guided antimicrobial therapy is more often targeted and appropriate. In summary, all these improvements may contribute to a better management and outcome of patients with SAB. However, this holds only true for improvements in long-term mortality, since early IDC is often not possible in patients, who die early. There are several limitations to this meta-analysis.

First, the study design of most of the included studies does not comply with the PRISMA requirements and the...
number of patients excluded by the authors was substantial. The studies were not randomized, predominantly retrospective and had moderate to small sample sizes.\textsuperscript{24–26,29–33,35} Furthermore, differences between the control and intervention groups cannot be totally excluded.

Second, publication bias cannot be totally excluded. However, for 30-day mortality we found no evidence of publication bias ($t = -0.09, p = 0.93$). There is a wide range of statistical heterogeneity between studies, with large heterogeneity values for QCI indicators. However, with respect to the 95% prediction interval for relative risk of 30-day mortality [0.34–0.83] we found that the intervention should work in almost all settings.

Third, we did not consider studies which included patients with blood stream infections caused by other pathogens, because the number of patients and events in the respective subgroups with SAB were low or additional data was not available. Furthermore, some studies excluded patients, who died within the first few days after onset of SAB based on the argument that these patients had no chance to receive a consultation.\textsuperscript{16,24,25,27,29,33,37} However, the overall observed case fatality rate irrespective of including or excluding these patients is consistent with data from population-based studies.\textsuperscript{3}

Fourth, the qualification and education of the ID specialists and the compliance of the treating physician with the requested QCI may have influenced the results. We only included studies with formal consultation, because it is better documented and more common in published studies. Other interventions may have less pronounced effects on outcome. For instance, Forsblom et al. found that telephone consultation is not as effective as bedside IDC in the management of SAB.\textsuperscript{25} However, the absence of a precise definition of a telephone consultation makes it difficult to understand the results of this study.\textsuperscript{40}

Furthermore, the studies provided poor information about the level of IDC education whereas specialist training programs differ in the involved countries.\textsuperscript{39,41} In addition, it is difficult to prove that the beneficial effect of consultation is based solely on the QCI and not on other beneficial effects exerted during the consultation, for instance the identification of other foci of infection. Moreover, the compliance rates with IDC pieces of advice were not reported.

Fifth, selection bias may present a serious problem in most of the studies since SAB cases were retrospectively collected and patients receiving IDC may have been more severely ill. Furthermore since before-and-after studies are not entirely retrospective enhanced identification of patients may result in capture of patients who were previously deemed to be lower risk. A prior meta-analysis of studies of specialist versus generalist care for individual conditions also highlighted several of such potential methodological pitfalls, including selection bias.\textsuperscript{9}

Sixth, the definition of outcomes differed among some of the studies. The QCI with the largest heterogeneity was the definition of appropriate antibiotic treatment. Most investigators defined appropriate antibiotic therapy as intravenously administered beta-lactam antibiotics for patients with methicillin susceptible \textit{S. aureus} (MSSA) bacteremia.\textsuperscript{16,24,27,29,31,35} However, \textit{in vitro} susceptibility of antibiotics does not always translate into clinical success. This holds true particularly for SAB. Several studies have shown that patients with MSSA treated with vancomycin for which almost all \textit{S. aureus} isolates show \textit{in vivo} susceptibility have a significantly poorer outcome compared to patients treated with nafcillin or cefazoline.\textsuperscript{32,43} But even within the beta-lactams, there are major differences. Two recent studies found a higher rate of treatment failure when patients were treated with cefuroxime instead of dicloxacillin, whereas cefazoline seems to be equally effective as antistaphylococcal penicillins.\textsuperscript{44–46} Recommended agents for patients with methicillin-resistant \textit{S. aureus} (MRSA) bacteremia or patients with beta-lactam allergy differed between the included studies. Two studies defined appropriate antibiotic therapy as the use of any antibiotic with tested \textit{in vitro} susceptibility for empirical treatment, which is an issue of debate as outlined above.\textsuperscript{16,35} A length for antibiotic intervention of at least 14 days was considered appropriate by all investigators.\textsuperscript{16,24,25,32,34} However, according to a recent IDSA recommendation for complicated MRSA bacteremia\textsuperscript{47} two weeks are only appropriate for uncomplicated bacteremia which comprises not only absence of endocarditis but also absence of implanted prostheses.

**Conclusion**

We conclude, that IDC may promote implementation of several standards of evidence-based clinical management and thus seems to be an important element to improve outcomes of patients with SAB. However, the quality of selected studies is low and further research is likely to have an important impact on our confidence in the estimate of effect. Therefore, large, well conducted cluster-randomized controlled multicenter trials are urgently needed to confirm these findings. Moreover, further work is needed to validate and refine the bundle elements and their individual contributions to the overall effect.

**Conflict of interest**

The authors declare that they have no conflict of interest related to the research question published here.

**Acknowledgements**

**Funding**

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**Appendix A. Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2015.09.037.
Infectious disease consultation for *S. aureus* bacteremia

References


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