All-cause and infection-related mortality in *Staphylococcus aureus* bacteraemia, a multicentre prospective cohort study

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**Background:** *Staphylococcus aureus* bacteraemia (SAB) is a heterogeneous disease with changing epidemiology due to changing demographics and evolving clinical management. SAB
is associated with high mortality, but the current fraction of infection-related mortality is less well quantified.

Methods: In a multicenter prospective cohort study of consecutive patients with SAB we determined clinical features of SAB and determined 90-day mortality and risk factors of all-cause and infection-related mortality. Infection-related mortality was based on an adjudication committee evaluation.

Results: 490 patients with SAB were included, with community-acquired (n=166), health-care associated (n=163) and hospital-acquired SAB (n=161). Endocarditis (n=90, 18.3%), peripheral intravenous catheter infection (n=80, 16.3%) and septic arthritis (n=58, 11.8%) were the most frequent diagnoses, but proportions differed for community-, healthcare - and hospital acquisition. 192 patients (39%) had permanent implanted prosthetic material (e.g. prosthetic joint, heart valve, pacemaker). Day-90 all-cause mortality was 33% (n=161), with 60% adjudicated as infection-related, and 90% of infection-related deaths occurring in the first 30 days since SAB. Infection-related deaths after 30 days were rare and mainly related to endocarditis. Determinants associated with day-90 infection-related mortality were age (Odds Ratio (OR)=1.09 (95% CI 1.06 – 1.11)), Charlson comorbidity index (OR=1.13 (95% CI 1.01 – 1.26)), septic shock (OR=9.78 (95% CI 4.56 – 20.95)), endocarditis (OR=3.4 (95% CI 1.75– 6.61) and persistent SAB at 48 hours (OR = 2.36 (95% 1.27 – 4.37)).

Conclusions: Mortality due to S. aureus infection remains high and mainly occurs in the first 30 days, which could guide endpoints in future studies.

Keywords: Staphylococcus aureus, bacteraemia, sepsis, infection-related mortality, mortality

INTRODUCTION

Staphylococcus aureus is a common cause of community- and hospital-acquired bacteraemia. The estimated incidence of S. aureus bacteraemia (SAB) is between 20 to 30 per 100,000 persons per year(1-3). SAB is associated with a myriad of clinical syndromes, ranging from uncomplicated central line-associated bacteraemia to fulminant endocarditis.

The local epidemiology and management of SAB depends on demography, healthcare usage, prevalence of intravenous drug use (IVDU) and prevalence of antibiotic resistance (4). Use of diagnostic modalities such as echocardiography and PET/CT, and infectious diseases consultation may also differ between hospitals, potentially leading to differences in identification of endocarditis and other foci of infection. All of these may vary between geographic regions and over time. As such, frequent updates are needed to inform clinicians on the manifestations and complications of SAB. However, many studies on SAB are single centre and tertiary-care based, which may reduce external validity of epidemiological and prognostic findings (5-7).
Reported 90-day mortality of SAB is around 30%, although recent studies suggested that mortality is declining, possible due to improved standards of care (5, 7). Since SAB often occurs in hospitalized and frail patients, part of the all-cause mortality may result from underlying comorbidities and advanced age. A recent systematic review concluded that infection-related deaths mostly occur in the first month after SAB, but they also concluded that there is a lack of rigorously conducted large studies on this subject.(8).

In this multicentre prospective cohort study, we describe the current epidemiology and clinical features of SAB in the Netherlands and risk factors for all-cause and infection-related mortality.

METHODS

Study design and setting

The Improved Diagnostic Strategies in *Staphylococcus aureus* bacteraemia (IDISA) study was a prospective, multicentre cohort study conducted from July 1, 2017, through September 30, 2019, in seven hospitals in the Randstad metropolitan region of the Netherlands; two university and five non-university teaching hospitals. All sites had an Antimicrobial Stewardship Team providing bedside consultations for patients with SAB. The Medical Ethics Committee of the Academic Medical Centre Amsterdam approved this study (METC2017_094). This study is registered in the Netherlands Trial Register under trial code 6669.

Participants

Consecutive patients aged 18 years and older with one or more blood cultures positive for *Staphylococcus aureus* were eligible for inclusion. Patients were identified through the local hospital’s microbiology service, who notified the study team after blood culture became positive. All cases of SAB were considered clinically relevant and eligible for inclusion.

Patient consent statement

A dedicated member of the study team approached patients or their legal representatives for written informed consent. Patients who died before informed consent could be obtained were included in the study as appropriate under Dutch law. Patients could enter the study only once, and subsequent episodes of SAB within the 90 day follow-up period were recorded as relapse infection.

Study procedures

Patients were followed for up to 90 days after the first day of SAB. From the hospital electronic health records (EHR) we collected demographic data, signs and symptoms, and microbiology, laboratory and imaging data. No additional imaging or microbiology studies were required for
the study. Status at day 90 (dead or alive) was determined through telephone follow-up, GP consultation, electronic hospital record (EHR) or consultation of municipal death records.

Data extraction was performed by the study research physician (TvdV) and entered in the electronic case record file (Research Online) by trained junior researchers. The study research physician checked all data entered by the junior researchers.

**Definitions**

Comorbidity was classified using the Charlson Comorbidity Index (9). Place of acquisition (community, hospital or health-care associated) was classified based on the criteria set by Friedman (10). Infectious disease (ID) consultation was recorded only if an internal medicine or ID physician performed a bedside consultation. Patients who received only telephone consultation were judged not to have had a bedside consultation.

Presumed port of entry of *S. aureus* was the port of entry identified by the attending or consulting physician. Presumed focus of infection was the working diagnosis within two days after collection of the first positive blood culture. Definite focus of infection was the diagnosis according to the treating physician at the time of hospital discharge. A patient could have multiple presumed points of entry and infectious foci. For comparing infectious foci, we used the ranked approach of classifying focus introduced by Kaasch (4). The presence of infective endocarditis was defined using the modified Duke Criteria (11).

Sepsis and septic shock were defined according to the Sepsis-3 criteria (12). For determination of the presence of sepsis and septic shock at presentation, we used the most extreme value (highest or lowest when appropriate) for temperature, systolic blood pressure, heart rate, respiratory rate and Glasgow Coma Scale recorded within 24 hours of blood culture collection. Fever was defined as a rectal or auricular temperature >38.0 °C. Persistent fever was fever longer than 72 hours after start of effective antimicrobial therapy.

We recorded antibiotic use for all study participants. Antimicrobial agents started before culture results were known were classified as empirical therapy, and agents started thereafter as definitive therapy. Empiric therapy that was continued after culture results became known was thereafter classified as definitive therapy. For empiric therapy, all agents are reported and for definitive therapy we report the agent used for the largest part of the treatment.

Infection-related mortality at 90 days was scored using a three tier system. Mortality was considered infection-related if patients died from direct complications of infection (e.g., septic brain haemorrhage, death following infection control surgery) or in case of persistent signs of infection (ongoing fever, persistent positive blood cultures, leucocytosis, elevated CRP) at the time of death. Mortality was considered non-infection related if patients had survived to the full length of antibiotic treatment and died from a definite other cause, without signs or symptoms of
relapse. Mortality events that did not fit the definitions of infection-related or non-infection related were considered possible infection-related.

Infection-related mortality was determined by an adjudication committee of two independent infectious disease specialists (JM, AG, BL, KSt, KSi, VS). Discrepancies between two panel members were discussed with the study research physician (TvdV) until consensus was reached, if no consensus could be reached a third infectious disease specialist was consulted.

Analysis
Clinical features of SAB were reported using the appropriate descriptive statistics for normally and non-normally distributed variables, for the total cohort and for community-acquired, healthcare associated, and hospital-acquired bacteraemia separately.

For all-cause and infection-related mortality, we constructed Kaplan-Meier curves for each dominant focus of infection (4) and determined the predictive value of known risk factors for mortality (13). Relation between risk factors and all-cause and infection-related mortality was examined using univariate and multivariate logistic regression. For the multivariate models, only variables with a univariate p-value < 0.1 were entered into the model. Because of the prospective nature of the data collection, there was little missing data, and for variables with missing data (mostly laboratory values) we assumed missing values were normal. No imputation of missing data was performed.

This study is reported using the STROBE guidelines for reporting of observational studies (14). Statistical significance was tested at a two-sided p-value of 0.05, and 95% confidence intervals are reported for all inferential statistics. All statistical analysis was done in R version 4.1.2 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
Inclusion
Between August 2017 and September 2019, 636 patients with SAB were screened and 490 (77%) were included in the study. Reasons for exclusion were: patient discharged home before consent was possible (46/146), refusal to provide informed consent (29/146), and incapacitated patients without a legal representative (22/146). There were no significant differences in median age or sex of the non-included patients. Detailed follow-up data was available for 489 (99%) patients, and mortality data was available for all.
Demographics

Median patient age was 68 years (IQR 57 – 77] and 327 (66.7%) were male. Community-acquired, health-care associated and hospital-acquired bacteraemia were equally prevalent. Intravenous drug use and MRSA bacteraemia were rare (1% and 2%, respectively). Permanent implanted prosthetic material (e.g. prosthetic joint, heart valve, pacemaker) was present in 192 patients (39.2%). An overview of demographic and clinical characteristics is shown in Table 1.

Clinical characteristics

Fever was present in 426 patients (86.9%). The median duration of fever before collection of the first blood culture was 0 days (IQR: 0-1). Overall, patients with community-acquired SAB had a longer duration of symptoms before blood cultures were collected compared to hospital- and health-care associated SAB (Supplementary table S1: median 2 days versus 0 and 1 days, p <0.001). Septic shock at presentation was present in 52 patients (10.6%). A presumed port of entry was found in 344 patients (70.2%), but in only 82 of 166 patients (49.4%) with community-acquired SAB. The most common port of entry was the skin (peripheral or central venous catheter or skin or soft tissue infection (SSTI) and surgical site infection): 244 patients (49.8%). At least one presumed diagnosis (presumed focus of infection) could be identified in the first two days after the first blood culture was taken in 391 patients (79.8%) (Supplementary table S1).

At discharge, at least one diagnosis (focus of infection) was reported in 443 patients (90.4%). Table 2 provides the final diagnoses reported at discharge. Endocarditis (n=90, 18.4%,) was the most frequent definite diagnosis, followed by peripheral intravenous catheter infection (n=80, 16.3%), SSTI (n=62, 12.7%) and septic arthritis (n=58, 11.8%). In 125 patients (25.5%), two or more infectious foci were identified, while in 47 patients (9.6%), no focus of infection could be determined. In 216 patients (44.1%) S. aureus was also cultured from body sites, such as the respiratory tract (n=50, 10.2%) and urine (n=65, 13.3%). Of the 36 patients (7.3%) deemed by the treating physician to have S. aureus UTI, 31 had a urine culture positive for S. aureus, while the remaining five had an invasive procedure involving the urinary tract in the days preceding bacteraemia.

Endocarditis (53/166, 31.9%), vertebral osteomyelitis (32/166, 19.3%) and septic arthritis (24/166, 14.5%) were the most frequent diagnoses in patients with community-acquired SAB. In healthcare-associated SAB, SSTIs (30/163, 18.4%) and septic arthritis (28/163, 17.2%) were most frequent, while in hospital-acquired SAB peripheral intravenous catheter infection (72/161, 44.7%) and central venous catheter (CVC) infection (25/161, 15.5%) were most common.

In the 125 patients who acquired SAB from a peripheral IV or CVC, eight (6.4%) had endocarditis, five of whom had a predisposing heart condition for endocarditis.
Other bacteria apart from *S. aureus* were found in blood cultures in 63 patients (12.8%), the majority of which were coagulase negative staphylococci (n=23) and other skin contaminants (n=15). **Management of patients with SAB**

Bedside infectious diseases consultation was performed in 385 patients (78.6%) and withheld in 18 (3.7%) patients who died or were on palliative care before consultation could be performed. TTE and TEE were performed in 409 (83.5%) and 201 patients (41.0%), respectively, and 188 (38.3%) had both a TTE and TEE. 18-FDG-PET/CT was performed in 178 patients (36.3%). Empirical treatment, before culture results were known, consisted most frequently of a cephalosporin (n=294, 60.0%), or flucloxacillin (n=65, 13.3%), and 77 patients (15.7%) received adjunctive aminoglycosides. Definitive therapy consisted of flucloxacillin (396 patients, 80.8%), cefazolin (40 patients, 8.2%) vancomycin (19 patients, 3.9%) and other (35 patients, 7.1%).

**Mortality and risk factors for mortality**

All-cause mortality was 9.8%, 15.3%, 23.7% and 32.9% at days 7, 14, 30 and 90 days since SAB, respectively. At 90 days after SAB 162 patients had died and death was adjudicated as infection-related in 97 (59.9%), as non-infection-related in 29 (17.9%) and as possible infection-related in 36 patients (22.2%). Infection-related mortality mostly occurred early in the disease phase, while the majority of non-infection or possibly infection-related deaths happened after four weeks (Figure 1). The majority of non-infection related deaths were due to multimorbidity (24 patients) malignancy (14 patients) and other infections (11 patients). Interrater agreement for adjudicating infection-related mortality was good (Cohen’s Kappa 0.64 for identifying infection-related mortality and 0.82 for identifying non-infection related mortality). Mortality rates for infection-related, possibly infection-related and non-infection-related mortality at various time points and for different foci of infection are presented in supplementary tables S2 and S3. Infection-related mortality plateaued after 30 days for all foci except for endocarditis, and was highest for patients with endocarditis (43.3%) and lowest for patients with a CVC-related infection (7.5%) (Figure 2).

**Risk factors for mortality**

Age, comorbidity, presence of endocarditis and septic shock were all independently predictive of both 90-day all cause and infection-related mortality (Table 3). Persistent SAB at 48 hours was predictive of infection-related mortality. Despite being associated with more severe manifestations of SAB, such as endocarditis and vertebral osteomyelitis, community acquisition was not associated with higher all-cause or infection-related mortality. Pneumonia as the dominant focus of infection was associated with worse all-cause mortality, but not with increased infection-related mortality. Associations between other determinants tested, such as gender, diabetes, haemodialysis dependence and use of immunosuppressants, and 90-day mortality did not reach statistical significance.
DISCUSSION

Key findings:

In this prospective cohort study, we describe the current epidemiology and outcomes of SAB in the Netherlands. Permanent implanted prosthetic material (e.g. prosthetic joint, heart valve, pacemaker) was present in 39% of patients, and one third of cases was hospital-acquired. Metastatic infection (e.g.: endocarditis) was more common in the patients with non-hospital acquired SAB. All-cause mortality 90 days after the first day of SAB was 33%; 60% of these deaths were adjudicated as directly related to SAB and almost all these deaths occurred in the first 30 days after SAB. Age, comorbidity, presence of endocarditis and septic shock were independently predictive of 90-day all cause and infection-related mortality.

Study in context

In general, our cohort matches the epidemiological profile of other recently published cohorts of patients with SAB from high-income countries (4, 6, 15-18), though regional differences exist. For example, the proportion of patients with nosocomial acquisition of SAB was 33% in our cohort, similar to the 32% in a recent Swedish study (32%), which was lower than the reported 54% in the French VIRSTA cohort (6, 18). Moreover, proportions of patients with health-care associated SAB appear to be higher in recent studies from the USA (19, 20). Prevalence of both MRSA and IV drug use is low in the Netherlands and Nordic countries (15, 18, 21), but higher elsewhere, which influences antibiotic treatment options, and potentially patient outcome. Other demographic and clinical factors are remarkably consistent across different cohorts, such as the high median age, predominance of males, the dominance of skin lesions or intravenous catheters as source of infection and the frequent occurrence of metastatic complications such as endocarditis and vertebral osteomyelitis (6, 15, 17). Apart from regional differences, the epidemiology of SAB changes over time. In a recent single-centre study from a university hospital in the USA, prevalence of implanted prosthetic materials increased over time, as did the proportion of patients with health-care associated SAB (20). Also in our cohort, 39% of patients had permanently implanted prosthetic material, which is considerably higher than reported in studies from earlier time periods (22, 23).

The prevalence of endocarditis was 18.3%, which may result from the high proportion of patients who underwent echocardiography (>80%) and from some selection bias, as 7% of patients eligible for inclusion were discharged before informed consent could be obtained. Such patients are less likely to have endocarditis. Although one fourth of SAB episodes were associated with the presence of peripheral IV or CVC, infection-related mortality in these patients was low, being 10% and 8%, respectively. However, as these infections are potentially preventable, the presence of infection-related mortality, albeit lower than in SAB episodes originating from other sources, underscores the importance of infection control measures (24-26). A notable 7.3% of patients with SAB were also diagnosed with urinary tract infection, a prevalence comparable to
CVC infections (9.6%), peripheral osteomyelitis (6.1%) and vertebral osteomyelitis (9.2%), all of which are widely considered important foci of *S. aureus* infection. *S. aureus* UTI is associated with structural defects or prosthetic material in the urinary tract, but bacteriuria can in some cases also result from hematogenic seeding (27-29). The optimal management of *S. aureus* UTI deserves further study.

At 90 days, overall mortality was 33%, which is consistent with other recent studies on SAB mortality (4-6, 17, 30). Infection-related mortality ranged between 46% and 80% in other studies, but definitions applied also differed between studies (8, 23, 30, 31). In our cohort, 60% of deaths were considered infection-related. In some patients, the role of SAB in causing death may be ambiguous, which is a possible explanation for the varying proportions of infection-related mortality reported. We have quantified this uncertainty by adding a possibly infection-related mortality classification, which was applicable to 20% of all patients that died from SAB within 90 days. The majority of infection-related deaths occurred early in the disease: at 30 days 74% of deaths were infection-related. After 30 days, infection-related deaths were rare and occurred almost exclusively in patients with endocarditis. The majority of deaths after day 30 were unrelated to infection. Our findings, therefore, strongly support those from a systematic review on attributable mortality in SAB (8). That analysis also indicated that the majority of deaths more than one month after SAB were not infection-related and likely not preventable by an intervention that improves outcome of SAB. Treatment studies could, therefore, limit follow-up for all-cause mortality to one month, thereby reducing noise and loss of statistical power (8). Yet, an important caveat is endocarditis, in which 18% (7/39) of infection-related deaths occurred after 30 days. Therefore, for endocarditis longer follow-up is needed if the intervention continues after four weeks, as is the case in trials of treatment duration or switch to oral therapy. A 30-day follow-up period for mortality however may be considered when determining the effect of short-term interventions, such as choice of empirical therapy, short-term adjunctive (antimicrobial) treatment and other interventions in the early phase of disease.

We confirmed known risk factors such as age, comorbidity, septic shock and endocarditis on all-cause mortality and demonstrated that these risk factors were likewise risk factors for infection-related mortality, although the effects of septic shock and presence of endocarditis appeared more pronounced on infection-related mortality.

**Strengths and limitations**

The strengths of this study are the prospective multicenter design with few missing data. We recruited patients in both university and non-university hospitals, which increases the external validity of our data. The main limitation of this study is that not all patients with SAB were included, as 5% of eligible patients refused informed consent and 7% were discharged home before informed consent could be obtained. Especially the latter group may introduce some bias, as these patients were more likely to have an uncomplicated disease course. As such, it is possible that the mortality rates mortality we found are slightly overestimated, but since this was
only a small proportion of eligible patients, this is unlikely to be a large source of bias. Finally, adjudication of infection-related mortality is difficult, and we can not rule out that in some patients with infection-related death the final cause of death was not uncontrolled infection but the deterioration of the patients underlying comorbidities as a result of the infection.

**Conclusion:**

Mortality of SAB remains high, and the majority of infection-related deaths occur within the first month, with the exception of endocarditis. Future studies may consider using 28-day or 30-day mortality as endpoint for treatment interventions in patients with SAB without evidence of endocarditis.

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**TABLES AND FIGURES**

**Table 1: Characteristics of patients with SAB**

<table>
<thead>
<tr>
<th>Demographics and comorbidities#</th>
<th>All patients</th>
<th>Community-acquired</th>
<th>Healthcare-associated</th>
<th>Hospital-acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>327 (66.7)</td>
<td>108 (65.1)</td>
<td>112 (68.7)</td>
<td>107 (66.5)</td>
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<tr>
<td>Age (categorized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40</td>
<td>43 (8.8)</td>
<td>21 (12.7)</td>
<td>11 (6.7)</td>
<td>11 (6.8)</td>
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<td>41-50</td>
<td>31 (6.3)</td>
<td>12 (7.2)</td>
<td>14 (8.6)</td>
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<tr>
<td>51-60</td>
<td>89 (18.2)</td>
<td>33 (19.9)</td>
<td>26 (16.0)</td>
<td>30 (18.6)</td>
</tr>
<tr>
<td>61-70</td>
<td>122 (24.9)</td>
<td>34 (20.5)</td>
<td>48 (29.4)</td>
<td>40 (24.8)</td>
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<tr>
<td>70-80</td>
<td>114 (23.3)</td>
<td>39 (23.5)</td>
<td>42 (25.8)</td>
<td>33 (20.5)</td>
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<tr>
<td>80+</td>
<td>91 (18.6)</td>
<td>27 (16.3)</td>
<td>22 (13.5)</td>
<td>42 (26.1)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>156 (31.8)</td>
<td>50 (30.1)</td>
<td>56 (34.4)</td>
<td>50 (31.1)</td>
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<tr>
<td>Immunosuppressive medication</td>
<td>86 (17.6)</td>
<td>28 (16.9)</td>
<td>29 (17.8)</td>
<td>29 (18.0)</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>HIV – AIDS</td>
<td>3 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
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<tr>
<td>Chronic renal failure</td>
<td>135 (27.6)</td>
<td>32 (19.3)</td>
<td>51 (31.3)</td>
<td>52 (32.3)</td>
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<tr>
<td>Haemodialysis</td>
<td>28 (5.7)</td>
<td>0 (0.0)</td>
<td>21 (12.9)</td>
<td>7 (4.3)</td>
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<td>Intravenous drug use</td>
<td>5 (1.0)</td>
<td>4 (2.4)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
| Charlson Comorbidity index ≥3 | 283 (57.9)| 72 (43.4)| 102 (63.0)| 109 (67.7)|%
| Any implanted prosthetic material | 192 (39.2)| 59 (35.5)| 72 (44.2)| 61 (37.9)|%
| Prosthetic heart valve | 40 (8.2)| 7 (4.2)| 14 (8.6)| 19 (11.8)|
| Cardiac Implantable Electronic device | 54 (11.0)| 16 (9.6)| 20 (12.3)| 18 (11.2)|
| Non-vascular prosthetic materials | 94 (19.2)| 34 (20.5)| 34 (20.9)| 26 (16.1)|%
| Prosthetic joints | 64 (13.1)| 24 (14.5)| 24 (14.7)| 16 (9.9)|%
| Clinical characteristics | | | | |
| Fever | 426 (86.9)| 142 (85.5)| 140 (85.9)| 144 (89.4)|%
| Persistent fever | 54 (16.0)| 30 (25.2)| 15 (13.3)| 9 (8.5)|%
| Chills | 128 (26.1)| 43 (25.9)| 53 (32.5)| 32 (19.9)|%
| Malaise | 298 (60.8)| 122 (73.5)| 110 (67.5)| 66 (41.0)|%
| Other systemic symptoms | 170 (34.7)| 73 (44.0)| 63 (38.7)| 34 (21.1)|%
| Septic shock | 52 (10.6)| 19 (11.4)| 21 (12.9)| 12 (7.5)|%
| qSOFA score (median, IQR) | 2 [1,3]| 2 [1,2]| 2 [1,3]| 2 [1,3]|%
| MRSA | 10 (2.0)| 4 (2.4)| 2 (1.2)| 4 (2.5)|%
| Presumed port of entry of infection | | | | |
| Peripheral intravenous catheter | 76 (15.5)| 1 (0.6)| 6 (3.7)| 69 (42.9)|%
| Central venous catheter | 49 (10.0)| 0 (0.0)| 23 (14.1)| 26 (16.1)|%
| Skin or surgical site infection | 119 (24.3)| 35 (21.1)| 59 (36.2)| 25 (15.5)|%
| Urinary tract | 35 (7.1)| 18 (10.8)| 6 (3.7)| 11 (6.8)|%
| Respiratory tract | 34 (6.9)| 12 (7.2)| 20 (12.3)| 2 (1.2)|%
| Other | 81 (16.5)| 25 (15.1)| 38 (23.3)| 18 (11.2)|%
| Unknown | 146 (29.8)| 84 (50.6)| 30 (18.4)| 32 (19.9)|%

All data are n (%) unless otherwise indicated
Patients could have more than one. 

- Data missing in 2 patients,
- Data missing in 42 patients,
- Data missing in 28 patients,
- Including headache, gastrointestinal complaints, myalgia
Table 2: Definite diagnosis at discharge

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>All patients</th>
<th>Community-acquired</th>
<th>Healthcare-associated</th>
<th>Hospital-acquired</th>
</tr>
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<tr>
<td>Peripheral intravenous catheter infection</td>
<td>80 (16.3)</td>
<td>1 (0.6)</td>
<td>7 (4.3)</td>
<td>72 (44.7)</td>
</tr>
<tr>
<td>Central venous catheter infection</td>
<td>47 (9.6)</td>
<td>0 (0.0)</td>
<td>22 (13.5)</td>
<td>25 (15.5)</td>
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<tr>
<td>Skin or soft tissue infection</td>
<td>62 (12.7)</td>
<td>23 (13.9)</td>
<td>30 (18.4)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>10 (2.0)</td>
<td>0 (0.0)</td>
<td>6 (3.7)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Peripheral osteomyelitis</td>
<td>30 (6.1)</td>
<td>14 (8.4)</td>
<td>14 (8.6)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>58 (11.8)</td>
<td>24 (14.5)</td>
<td>28 (17.2)</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>36 (7.3)</td>
<td>13 (7.8)</td>
<td>22 (13.5)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>47 (9.6)</td>
<td>22 (13.3)</td>
<td>10 (6.1)</td>
<td>15 (9.3)</td>
</tr>
<tr>
<td>Vertebral osteomyelitis</td>
<td>45 (9.2)</td>
<td>32 (19.3)</td>
<td>8 (4.9)</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>18 (3.7)</td>
<td>15 (9.0)</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>90 (18.4)</td>
<td>53 (31.9)</td>
<td>23 (14.1)</td>
<td>14 (8.7)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>4 (0.8)</td>
<td>4 (2.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>62 (12.7)</td>
<td>16 (9.6)</td>
<td>27 (16.6)</td>
<td>19 (11.8)</td>
</tr>
<tr>
<td>Unknown focus</td>
<td>47 (9.6)</td>
<td>13 (7.8)</td>
<td>16 (9.8)</td>
<td>18 (11.2)</td>
</tr>
<tr>
<td>More than one focus</td>
<td>125 (25.5)</td>
<td>53 (31.9)</td>
<td>45 (27.6)</td>
<td>27 (16.8)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. Patients could have more than one diagnosis.
Table 3: Factors associated with all-cause and infection-related mortality

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate OR for 90 day all-cause mortality (95% CI)</th>
<th>Univariate OR for 90 day infection-related mortality (95% CI)</th>
<th>Multivariate OR for 90 day all-cause mortality (95% CI)</th>
<th>Multivariate OR for 90 day infection-related mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.05 (1.04 – 1.07)***</td>
<td>1.06 (1.04 – 1.08)***</td>
<td>1.05 (1.03 – 1.07)***</td>
<td>1.09 (1.06 – 1.11)***</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.96 (0.64 – 1.43)</td>
<td>0.86 (0.54 – 1.38)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.13 (0.76 – 1.70)</td>
<td>0.92 (0.57 – 1.50)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>0.67 (0.28 – 1.60)</td>
<td>0.48 (0.14 – 1.63)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Charlson score</td>
<td>1.31 (1.20 – 1.42)***</td>
<td>1.13 (1.04 – 1.23)**</td>
<td>1.3 (1.18 – 1.43)***</td>
<td>1.13 (1.01 – 1.26)***</td>
</tr>
<tr>
<td>Use of immunosuppressant drugs</td>
<td>1.20 (0.74 – 1.95)</td>
<td>0.77 (0.41 – 1.44)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Place of acquisition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital acquisition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community acquisition</td>
<td>0.58 (0.36 – 0.92) *</td>
<td>1.49 (0.85 – 2.6)</td>
<td>0.59 (0.34 – 1.19)</td>
<td>–</td>
</tr>
<tr>
<td>Health-care associated</td>
<td>0.74 (0.47 – 1.16)</td>
<td>1.28 (0.72 – 2.26)</td>
<td>0.70 (0.41 – 1.19)</td>
<td>–</td>
</tr>
<tr>
<td>Positive blood culture at 48 hours</td>
<td>1.21 (0.80 – 1.82)</td>
<td>2.14 (1.34 – 3.41)**</td>
<td>–</td>
<td>2.36 (1.27 – 4.37)**</td>
</tr>
<tr>
<td>Line infection</td>
<td>0.71 (0.44 – 1.13)</td>
<td>0.34 (0.17 – 0.68)***</td>
<td>–</td>
<td>0.55 (0.25 – 1.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.46 (1.3 – 4.66) **</td>
<td>1.75 (0.86 – 3.57)***</td>
<td>3.68 (1.68 – 8.06) **</td>
<td>–</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1.97 (1.23 – 3.14) **</td>
<td>4.68 (2.83 – 7.75) ***</td>
<td>2.81 (1.56 – 5.04) **</td>
<td>3.4 (1.75 – 6.61) ***</td>
</tr>
</tbody>
</table>

# p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001
FIGURE TITLES

Figure 1: Time to death per cause of death

![Survival time per cause of death graph](image)
Figure 2: Kaplan-Meier curves for all-cause (A) and infection-related (B) mortality, stratified by dominant focus of infection.
References:


