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Long-term survival outcome following *Staphylococcus aureus* bacteraemia

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Abstract. ***Aims*:** To describe long-term survival (beyond 200 days) following *Staphylococcus aureus* bacteraemia (SAB) and to determine if certain patient subgroups had poorer long-term survival outcomes.

***Methods*:** A single-centre, retrospective, cohort study of all SAB cases at The Canberra Hospital, a tertiary referral centre, from January 1998 to December 2007 was performed. Clinical and demographic data were obtained from a pre-existing prospectively collected database. Patients were followed-up for a minimum of 9 months. Subsets within the cohort were analysed for differences in long-term survival. The main outcome measure was death from any cause.

***Results*:** During the 3889-day study observation period, 439 patients had SAB and were followed for a total of 546 360 person-days. The overall median survival was 3169 days. The mortality rates were 9.6%, 17%, 24%, 29% and 32% at 7, 30, 90, 180 and 365 days respectively. A total of 188 (43%) patients died. Of the 188 deaths, 22%, 40%, 55%, 67% and 75% occurred within the first 7, 30, 90, 180 and 365 days respectively after their SAB episode. Initial analysis showed poorer long-term survival in those patients with older age, MRSA, with an unknown focus of infection, and who were not admitted under the Infectious Diseases team. However, on multivariate analysis, the only independent risk factors for poorer survival were older age, unknown focus of infection and not being admitted under the Infectious Diseases team. MRSA, sex, surgical vs non-surgical admitting team and an association with an intravascular device were not associated with poorer long-term survival.

***Conclusions*:** High rates of death continue for many months after patients have an episode of SAB. Short-term follow-up studies (30 days or less) may miss large numbers of SAB-associated deaths. If accurate data on SAB-associated mortality is needed, then follow-up of these patients will be needed for at least 90 days, ideally performed prospectively with a matched control group consisting of hospitalised patients without SAB.

Additional keywords: bacteraemia, *Staphylococcus aureus*, survival.

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Introduction

Staphylococcus aureus bacteraemia (SAB) is common and associated with high morbidity and mortality.[1–8] Prognostic factors have been identified but studies are usually of short-term survival and/or in-hospital mortality.[1–6] Serious complications from SAB (e.g. endocarditis) are common and may lead to death, weeks or months later. These deaths will be missed if there is inadequate follow-up. Few groups have studied long-term outcome[7–9] and even 90 day follow up is unusual. The present study was conducted to provide data on short-, medium- and long-term survival (200 days and beyond). It also determined if certain subgroups had poorer long-term survival outcomes and examined independent risk factors for mortality.

Methods

Study design

A retrospective cohort study at The Canberra Hospital – a 500-bed, tertiary-care academic hospital in Canberra, Australian Capital Territory (ACT), Australia – was performed. All patients known to be resident within ACT who were admitted with SAB during the period 1 January 1998 to 31 December 2007 were included in this study. Follow up was until either

Implications

- High rates of death continue for many months after patients have an episode of SAB.
- Short-term follow-up studies (30 days or less) will miss large numbers of SAB-associated deaths.
- More medium- to long-term follow-up studies, ideally performed prospectively with a suitable control group, are required to fully understand the impact of SAB on mortality.

death or the end of the study period (25 August 2008, i.e. a minimum of 238 days). Patients resident within other states were excluded.

Data were obtained from prospectively-collected information in the Blood Stream Infection Surveillance Database (part of a quality improvement project involving all hospitalised patients with bacteraemia), as described elsewhere.[10] Briefly, trained infection control practitioners visited the microbiology laboratory daily to directly obtain information on all new positive blood cultures. All cases were then reviewed while they were inpatients, with standardised definitions applied.[11] Classification consensus was obtained at a weekly team meeting with a specialist infectious diseases physician, who reviewed all cases before data entry. All patients were followed-up for 7 days or to discharge, if earlier. Early clinical outcome was assessed at 7 days (or discharge, if earlier). For this study, early outcome was categorised into one of three groups: Patients with expected 'full recovery in up to 3 weeks', those with evidence of 'ongoing sepsis or new morbidity' and those who had died at or before 7 days.

The only study outcome was death from any cause. All deaths occurring during this period were included. For patients who did not have a date of death obtainable from the database, the date was obtained from the hospital medical records system. The ACT government Register of Deaths was also searched to ascertain if any other death had been missed.

Ethics approval was obtained from the ACT Health Human Research Ethics Committee.

Definitions

SAB was defined as a patient having at least one blood culture positive with *Staphylococcus aureus* – either Methicillin-sensitive *Staphylococcus aureus* (MSSA) or Methicillin-resistant *Staphylococcus aureus* (MRSA). Further positive blood cultures obtained within the first 14 days of the initial positive culture were regarded as the same episode of bacteraemia.

Residency within ACT was defined as a patient having a home address and postal code within the ACT.

Acquisition location was categorised as 'community-associated' if the positive blood culture was obtained within the first 48 h of admission and there was no recent healthcare contact, 'inpatient healthcare-associated' if the positive blood culture was obtained after the patient had been in a hospital for at least 48 h, and 'non-inpatient healthcare-associated' if the positive blood culture had been obtained within the first 48 h of admission but SAB was a complication of a pre-existing indwelling medical device, a surgical site infection (within 30 days of surgery), an invasive procedure or associated with neutropenia from cytotoxic therapy.

Foci of infection were classified based on the primary body system involved (e.g. cardiovascular, genitourinary, gastrointestinal or as unknown). Foci were also categorised as 'eradicable' and 'non-eradicable' similarly to Kim and colleagues.[12] Eradicable foci included surgically-removable infections or drainable abscesses and indwelling foreign bodies, such as peripheral and central venous catheters. Non-eradicable foci included unknown primary site, pneumonia, endocarditis, osteomyelitis and arthritis.

Data analysis

Survival was defined as the number of days from the index positive blood culture until the date of death. Survival was censored at the end of the study observation period (25 August 2008). All patients not known to be dead at the end of the study observation period were assumed to be alive. Patients who had more than one new episode of SAB during the study period were included only once, based on their first episode of SAB. The Mann-Whitney U test was used to compare continuous variables and Fisher's exact test for categorical variables. A time-to-event method was used to estimate the effect of SAB on survival for both the entire cohort and on defined subsets of the cohort. Kaplan-Meier analysis was used to evaluate the unadjusted relationship between SAB and death. The log-rank test was applied for survival curve comparisons. Unadjusted hazard ratios (HR) and corresponding confidence intervals (CI) were calculated using the Mantel-Haenszel method. All tests were two-tailed and $P \leq 0.05$ was considered significant, except in the case of comparing three survival curves by three paired comparisons, where the Bonferroni-corrected threshold of $P < 0.02$ was considered significant. Statistical analyses were performed using GraphPad Prism 5 for Windows version 5.01 (GraphPad Software, Inc., San Diego, California, USA). In order to identify independent risk factors for mortality, multiple Cox regression analysis was performed, using MedCalc for Windows, version 12.4.0.0 (MedCalc Software, Mariakerke, Belgium).

Results

During the 10 year study period, there were 188 deaths in 439 SAB patients (43%). Descriptive characteristics of the patients are shown in Table 1. The observation period was 3889 days and they were followed for 546 360 person-days. Their mean age was 51.3 years (range 0 to 98.6). Median survival was 3169 days.

Most SAB episodes occurred in older patients, but with another peak in those <5 years (Fig. 1). Of the 188 patients who died, the mean age was 66.4 (range 0 to 98.6) years, which is