

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

Table 1. Descriptive characteristics of patients with SAB

Characteristic	Number	Percentage
Total	439	100.0
Age		
<15 years	71	16.2
15 to <65 years	186	42.4
≥65 years	182	41.5
Sex		
Male	298	67.9
Female	141	32.1
Organism		
MSSA	363	82.7
MRSA	76	17.3
Admitting team		
Infectious Diseases	55	12.5
Non-Infectious Diseases	384	87.5
Admitting team type		
Surgical	112	25.5
Non-surgical	327	74.5
SAB focus		
Known	385	87.7
Unknown	54	12.3
Eradicable	132	30.1
Non-eradicable	307	69.9
SAB related to intravascular device		
Yes	103	23.5
No	336	76.5
Endocarditis		
Yes	27	6.2
No	412	93.8
Acquisition location		
Community	183	41.7
Inpatient healthcare-associated	169	38.5
Non-inpatient healthcare associated	79	18.0
Maternal	6	1.4
Unknown	2	0.5
Early outcome measure		
Full recovery in up to 3 weeks	271	61.7
Ongoing sepsis or new morbidity	123	28.0
Number of episodes		
Single	406	92.5
Multiple	33	7.5

significantly older than the mean age of 39.9 (range 0 to 92.7) years for the 251 (57%) surviving patients ($P < 0.0001$). The mortality rates were 9.6%, 17%, 24%, 29% and 32% at 7, 30, 90, 180 and 365 days respectively (Figs 2 and 3).

Of the 188 deaths, 42 (22%), 75 (40%), 104 (55%), 125 (67%) and 140 (75%) occurred within the first 7, 30, 90, 180 and 365 days respectively.

Different age groups differed markedly in long-term survival (Fig. 4). The percentage of patients dead at the end of the study was 9.9%, 31% and 68% for those aged <15 years, aged 15 to <65 years and aged ≥65 years, respectively. The median survival was 398 days for those aged ≥65 years. Long-term survival was significantly better for those aged <15 years compared with those aged 15 to <65 years (log-rank $P = 0.0006$; HR 0.38, 95% CI 0.22 to 0.66) and to those aged ≥65 years (log-rank $P < 0.0001$; HR 0.22, 95% CI 0.15 to 0.32). Long-term survival was also significantly better

for those aged 15 to <65 years compared with those aged ≥65 years (log-rank $P < 0.0001$; HR 0.30, 95% CI 0.22 to 0.40). For the subset of patients with MSSA bacteraemia, similar significant differences in survival trends were also observed across the three age groups. There was no statistically significant difference in survival curves for males and females.

Sixty-three percent of patients with MRSA bacteraemia were dead by the end of the study, compared with 39% of those with MSSA bacteraemia. Those with MRSA bacteraemia had a median survival of 398 days and were more likely to die than those with MSSA bacteraemia (log-rank $P < 0.0001$; HR 2.87, 95% CI 1.87 to 4.39) (Fig. 5). However, there were major differences in age. Of the 76 patients with MRSA bacteraemia, the median age was 69.5 (range 8.6 to 98.6) years, which was significantly older than the median age of 53.7 (range 0 to 97.3) years for the 363 patients with MSSA bacteraemia ($P < 0.0001$).

With regard to admitting team, 26% of patients with SAB admitted under Infectious Diseases had died by the end of the study, compared with 45% for those admitted under other teams (log-rank $P = 0.02$; HR 0.60, 95% CI 0.39 to 0.93). There was no significant difference in survival following SAB whether a patient was admitted under a surgical or non-surgical team (median 3025 and 3495 days, respectively).

For patients with SAB who had a known focus of infection, 40% had died by the end of the study, compared with 63% for those who had an unknown focus of infection. The median survival times were 3495 and 440 days for those with known and unknown infection foci, respectively (log-rank $P = 0.001$; HR 0.44, 95% CI 0.27 to 0.73).

There was no significant difference in survival between those with eradicable and non-eradicable foci of infection (median 3037 and 3169 days, respectively). There was also no significant difference in survival between those with SAB related to an intravascular device and those with SAB not related to such a device (median 3037 and 3169 days, respectively). Patients with endocarditis as a primary focus did not have a difference in survival compared with those without endocarditis (median 3113 and 3169 days, respectively).

With regard to acquisition location, the percentage of patients dead at the end of the study were 34%, 51% and 48% for those with community-associated, inpatient healthcare-associated and non-inpatient healthcare-associated SAB, respectively. The median survival was 3495, 1987 and 2712 days, respectively. Long-term survival was significantly better for those with community-associated SAB compared with those with inpatient healthcare-associated SAB (log-rank $P = 0.004$; HR 0.61, 95% CI 0.44 to 0.85) but not statistically significantly different compared with those with non-inpatient healthcare-associated SAB. For the subset with MSSA bacteraemia, the survival curves for all three groups of patients with different acquisition location were not significantly different.

Poorer early clinical outcome was associated with lower long-term survival. A total of 394 patients who were not

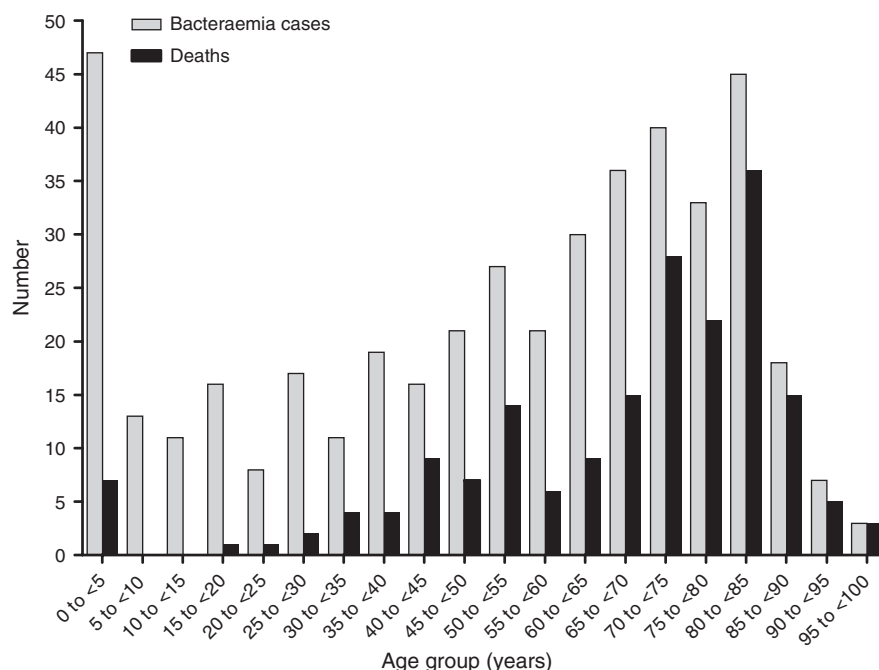


Fig. 1. SAB patients and deaths – age distribution.

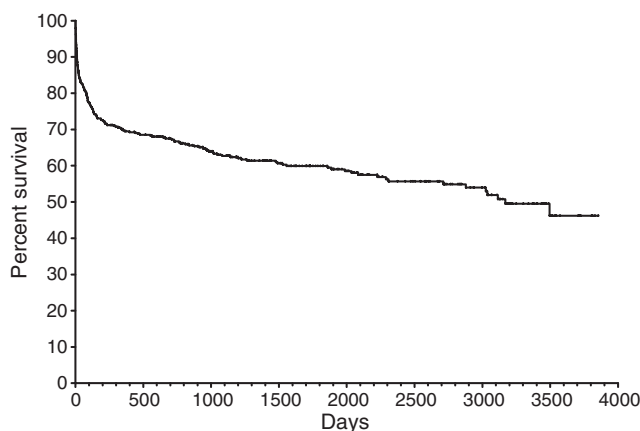


Fig. 2. Survival curve for SAB patients.

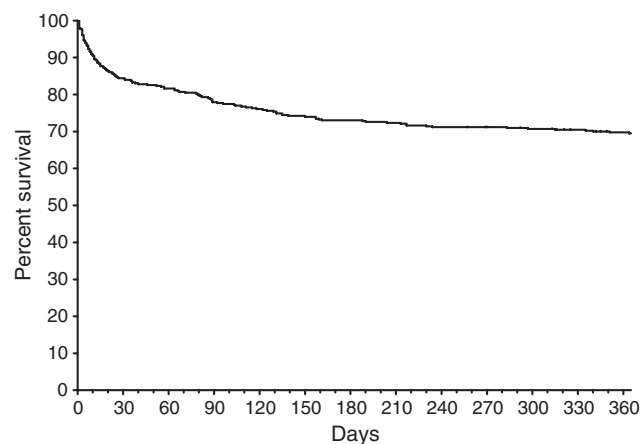


Fig. 3. Survival curve for SAB patients to 365 days.

already dead at 7 days were analysed. Of those designated ‘full recovery in up to 3 weeks’, 34% were dead by the end of the study observation period, compared with 43% for those designated ‘ongoing sepsis or new morbidity’ (log-rank $P=0.03$; HR 0.66, 95% CI 0.46 to 0.95).

A multiple Cox regression model incorporated age (as a continuous variable), MRSA vs MSSA, Infectious Diseases vs non-Infectious Diseases admitting team, known vs unknown infection focus, community-associated vs inpatient healthcare-associated, community vs non-inpatient healthcare associated, sex, eradicability of focus, involvement of IV device, surgical vs non-surgical admitting team and presence or absence of endocarditis as covariates. Only older age, admission under a non-Infectious Diseases team and unknown

infection focus were identified as independent risk factors for poorer long-term survival, as shown in Table 2.

Discussion

To our knowledge, this is the largest group of patients with SAB for which survival data is available over such a long observation time following bacteraemia. Our 30-day mortality of 17% is similar to the 19%, 19.7% and 23.2% reported by Hill and colleagues,¹³ Fätkenheuer and colleagues⁷ and Mylotte and colleagues,² respectively. Our 24% mortality at 90 days is the same as reported by Ringberg and colleagues at 12 weeks.¹⁴ We have shown, however, that ongoing deaths continue beyond the periods of those studies and high rates are

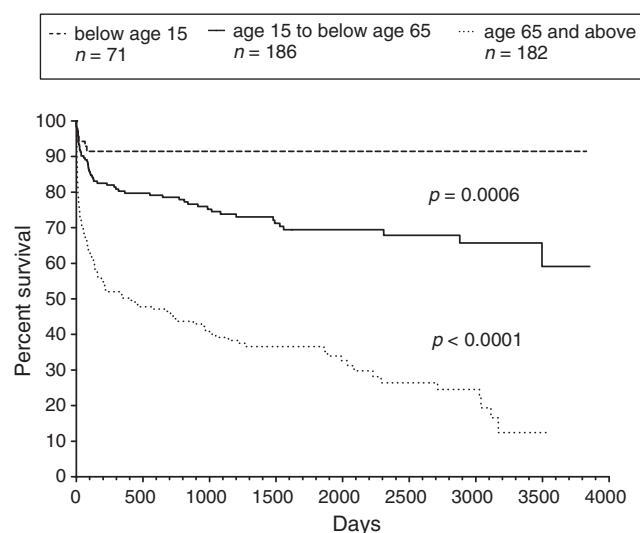


Fig. 4. Survival curve for SAB patients by age groups.

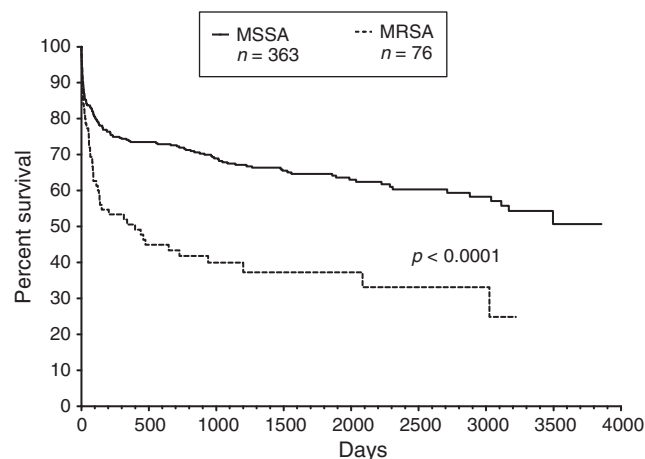


Fig. 5. Survival curve for SAB patients by organism (MRSA compared with MSSA).

still present 6 to 12 months after the episode of sepsis. In their 1-year follow-up study, Hanses and colleagues have also demonstrated considerable additional mortality beyond 90 days following SAB, reporting crude-mortality at 30 days, 90 days and 1 year of 28.8%, 37.5% and 47.5%, respectively.¹⁵ Not all of these deaths are necessarily attributable to SAB, and the differences between all-cause and attributable mortality from SAB varies between studies. For example, Hill and colleagues¹³ reported an all-cause mortality of 22.4% and an attributable mortality of 18.9% whereas the corresponding figures reported by Sharma and colleagues¹⁶ were 22.8% and 14.1%. However, deaths after SAB are not due to underlying disease in patients and thus their hospitalisation. Berger and colleagues¹⁷ (at 30 days following SAB), de Kraker and colleagues¹⁸ (at 30 days following SAB), Wolkewitz and colleagues¹⁹ (at 90 days following admission) and Primo and colleagues,²⁰ all showed that survival was

Table 2. Multivariate analysis of risk factors for long-term survival (Cox regression analysis)

HR = hazard ratio; CI = confidence interval

Risk factor	HR	95% CI of HR	P-value ^A
Age ^B	1.03	1.03–1.04	<0.0001
Admitted under non-Infectious Diseases team	1.99	1.11–3.56	0.02
Unknown infection focus	2.20	1.44–3.37	0.0003
MRSA	1.37	0.95–1.97	0.10
Inpatient healthcare-associated	1.07	0.71–1.60	0.75
Non-inpatient healthcare associated	1.04	0.66–1.62	0.88
Male	1.32	0.95–1.83	0.10
Eradicable focus	1.35	0.77–2.37	0.30
IV device related	1.03	0.56–1.87	0.93
Surgical admitting team	0.76	0.54–1.09	0.14
Endocarditis	1.51	0.77–2.98	0.23

^A $P < 0.05$ was considered significant. Significant values are in bold.

^B Age was analysed as a continuous variable. The HR represents the increase in hazard for each year increase in age.

significantly worse in patients hospitalised with SAB compared with hospitalised controls without SAB.

Our data showed long-term survival was poorer with older age. Others have also shown this at 30 days,^{2,13} 3 months²¹ and 1 year.⁷ This is likely related to co-morbidities. MRSA was more common in elderly patients but this was not likely the major factor causing an increased mortality. We found that increased age was associated with poorer long-term survival even in the subset with MSSA bacteraemia. Chia and colleagues²² found that an age over 65 years was an independent predictor of mortality in a study of MSSA bacteraemia. Others have shown that, in the short-term, SAB mortality is lower in children than adults.²³ Although we know of no published long-term studies in children, our data suggests that mortality risk stabilises after an initial 3-month period (Fig. 4). This is probably because multiple other co-morbidities are relatively rare, compared with adults. We saw 5 (6.8%) deaths in 74 children with SAB within the first 30 days, which is similar to the 4 (3.2%) deaths in 125 children reported by Hill and colleagues.²⁴

In our study, 50.9% of patients with MRSA bacteraemia had died within one year, which is comparable to the 46.2% overall all-cause mortality following MRSA bacteremia noted in a recent Australian study, which was a 10-year retrospective review of all cases at a single institution.²⁵ Patients with MRSA bacteraemia had poorer survival than those with MSSA bacteraemia. This was reported in other studies at 30 days^{5,8} even with adjustments for disease severity.⁶ In a multicentre, prospective, matched-cohort study carried out in 13 European countries, de Kraker and colleagues clearly demonstrated that 30-day mortality was higher following MRSA than MSSA bacteraemia.¹⁸ MRSA bacteraemia is also associated with higher mortality at 6 and 12 months.⁸ A large meta-analysis of 31 cohort studies has clearly demonstrated that mortality rates from MRSA were higher than those from MSSA.²⁶ The reason for this is not entirely clear. While this difference has been attributed to a delay in initiation of

appropriate antibiotic therapy for MRSA,²⁷ there have also been findings to the contrary.^{28,29} One recent study did not support the hypothesis that earlier empirical glycopeptide use reduces mortality in hospital-acquired MRSA bacteraemia.⁹ Whether MRSA directly increases the likelihood of death or merely serves as a marker for a population with greater comorbidity who are at risk of death from other causes needs to be further addressed by other studies. It should be noted, however, that in our study, after multivariate analysis, MRSA was not identified as an independent risk factor for poorer outcome. It is interesting to note that the Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis (ANZCOSS) data for 1865 SAB patients followed up to 30 days also had age and MRSA as predictors of increased mortality on their univariate analysis but, on multivariate analysis, MRSA infection was not an independent predictor of mortality although age still was.³⁰ The ANZCOSS investigators concluded that this could be explained, at least in part, by the inferior efficacy of treatment (i.e. vancomycin), since treatment with a glycopeptide was identified as an independent predictor of mortality. Unfortunately, our study did not include treatment information to enable similar analysis.

Patients admitted under our hospital's Infectious Diseases team had better long-term survival. Jenkins and colleagues³¹ reported that routine consultation with an Infectious Diseases Service for all cases of SAB resulted in more investigations (e.g. echocardiography) and adherence to all 4 standards of care in SAB management – removal of intravascular foci of infection, obtaining follow-up blood cultures, use of parenteral β -lactams for MSSA where possible and administration of at least 28 days of therapy for complicated infections. Fowler and colleagues³² demonstrated that where Infectious Diseases specialist recommendations were followed by the attending physician of a SAB patient, cure was more likely and relapse less likely over a 12 week follow-up period. Robinson and colleagues have reported that Infectious Diseases consultation was associated with decreased mortality at 7 days, 30 days and 1 year, because patients were more likely to have received effective initial antibiotics.³³

Our study shows that long-term survival is poorer if the focus of infection is unknown. This may be due to an undiscovered metastatic focus or deep infection which increases the risk of inadequate antibiotic treatment dose or duration and/or, failure to eradicate infective foci. Another explanation is that the patients die too early for the focus to be located and therefore represent a subset whose 'unknown' focus is a marker of the severity of illness rather than the direct cause of mortality. The association between unknown infection focus and increased mortality has been observed in some studies – at 30 days^{2,13} and 1 year⁷ follow-up – but not in others²¹ (at 3 month follow-up).

Our study indicates that an early clinical assessment of outcome (at Day 7) can provide some longer-term prognostic information. Patients assessed as 'full recovery in up to 3 weeks' had better survival than those with 'ongoing sepsis or

new morbidity'. However, this prospective assessment was subjective, based on the judgement of the clinician collecting the data at the time, with reference to the patient's clinical and laboratory data.

Although long-term survival appeared to be better in the group with community-associated SAB compared with the group with inpatient healthcare-associated SAB on direct comparison, this difference was not significant in the multivariate model. Furthermore, when only MSSA cases were considered, there was no significant difference. In the study by Chia and colleagues²² of community-onset MSSA bacteraemia (as in our study) there was no significant difference in 12 week mortality between community-acquired and healthcare-associated MSSA SAB. Jensen and colleagues²¹ showed that community or hospital acquisition had no significant impact on 3 month mortality following SAB.

One limitation of our study is that there was no control group comprising hospitalised patients who did not have SAB. While other studies have clearly demonstrated that early deaths following SAB can be largely attributed to SAB, this may not necessarily be the case in deaths occurring in the longer term. We looked at all-cause mortality, not attributable mortality, in this study and, therefore, it is unclear when exactly (if ever) during the long follow-up period did the effect on mortality of having had a SAB become relatively negligible compared with the effects of advanced age or co-morbidity or the fact of hospitalisation itself. Another limitation of our study is the retrospective nature of data collection, which did not allow specific variables of interest to be prospectively defined and data collected such as co-morbidity. Co-morbidity contributes to death in patients with SAB, as shown in a prospective study with at least 3 months follow-up.³⁴ However, some of the limitations of a retrospective design will have been offset because all of the Blood Stream Infection Surveillance Database information had been prospectively collected. Another issue is whether any deaths were missed in ACT residents because they died at a later stage outside of our hospital and out of the ACT (although we have no reason to suppose that such cases constitute large numbers). Of the 188 deaths in the study, we obtained dates of death for 180 patients from the Blood Stream Infection Surveillance Database and the hospital medical records system. The search of the ACT Register of Deaths yielded only 8 additional deaths. Our method does, however, mean that the estimates of rates of death events are conservative and therefore the actual mortality rates may be higher than what we have indicated.

In summary, high rates of death appear to 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. On this basis, we support the call of others for longer-term data (beyond 90 days) to be taken into account in outcome studies.¹⁵ If accurate data on SAB-associated mortality is needed, then follow-up of these patients will need to be for at least 90 days, ideally

performed prospectively with a matched control group consisting of hospitalised patients without SAB.

Conflicts of interest

The authors have no conflicts of interest to declare.

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