Epidemiology and outcomes for *Staphylococcus aureus* bacteraemia in Australian hospitals, 2005–06:

Report from the Australian Group on Antimicrobial Resistance

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Abstract

The Australian Group on Antimicrobial Resistance studied the epidemiology and outcomes of *Staphylococcus aureus* bacteraemia in selected Australian hospitals in 2005–06. Seventeen hospital-based laboratories collected basic demographic, susceptibility and patient outcome data on all cases of *S. aureus* bacteraemia for 5 to 24 months during the study period. There were 1,511 cases of bacteraemia documented, of which 66% occurred in males and 32% originated from vascular access devices. Bacteraemia had a community onset in 60% of cases, although 31% of these were health-care associated. Overall, 57% of episodes were health-care related. Methicillin-resistant *Staphylococcus aureus* (MRSA) was the responsible pathogen in 24% of instances; of these 53% were of the typical multi-resistant hospital type, and 29% were of the community-associated type. Seven per cent of all staphylococcal bacteraemias were caused by community-associated MRSA strain types, attesting to the growing size of this problem in Australia. Outcomes were available for 51% of cases and in those the all-cause mortality at 7 days or discharge (whichever came earlier) was 11.2%. Age was strongly associated with mortality; the rate for patients aged more than 60 years was 18%. Sepsis originating from intravascular access devices had a lower mortality rate of 5%. *S. aureus* bacteraemia is a common community and hospital infection with a significant mortality. A nationally co-ordinated program documenting the incidence and outcomes of this disease would likely lead to measures designed to reduce the incidence and improve outcomes of this disease. *Commun Dis Intell* 2007;31:398–403.

Keywords: *Staphylococcus aureus,* bacteraemia, epidemiology, outcomes

Introduction

Staphylococcus aureus ranks as one of the most common and important bacterial pathogens of humans.[1] It is a commensal organism which, with the right conditions and pathogenic factors, can invade the host and cause a range of diseases from minor skin and soft tissue infections to osteomyelitis, endocarditis and life-threatening septicaemia. It is prevalent as a cause of infection both in the community and in hospital practice, and is one of the most common species found in positive blood cultures. Its versatility is further enhanced by its ability to acquire resistance and multiple resistance, exemplified by the emergence over time of penicillin resistance, methicillin resistance and multi-resistance, initially in hospitals and later in the community. There are currently no vaccines effective against this common pathogen.

Although it is recognised as an important cause of morbidity and mortality by infectious disease practitioners, there are limited data on the incidence of serious *S. aureus* sepsis in Australia, and only two regional studies on patient outcomes in patients with methicillin-resistant *S. aureus* sepsis.[2,3] The Australian Group on Antimicrobial Resistance has been monitoring resistance in *S. aureus* since 1986,[4,5] and has recently presented information on the large burden of bacteraemia in Australia.[6] The present study was designed to provide preliminary information on the outcomes of *S. aureus* bacteraemia in Australia.

Methods

Institutions

As members of the Australian Group on Antimicrobial Resistance, 17 hospital laboratories from each state and territory of Australia participated in the collection of anonymous data on cases of *S. aureus* bacteraemia from January 2005 to December 2006 over periods ranging from 5 to 24 months. The laboratories were in Queensland (3), New South Wales/Australian Capital Territory (3), Victoria/Tasmania (4), South Australia/Northern Territory (3), and Western Australia (4). With one exception, each laboratory serviced either a single hospital or submitted data from only one hospital.

Data collection methods

Cases of *S. aureus* bacteraemia were identified with the first positive blood culture from a patient with a

compatible illness. Demographic data (age and sex), disease data (date of admission, onset in community or hospital, health-care association, source of infection and mortality) were collected prospectively. Cases were in general considered to have a hospital onset of infection if the time of collection of the first positive blood culture for *S. aureus* was more than 48 hours after admission. Mortality was measured at either 7 days after the time of blood culture collection or at discharge if sooner. Participants were requested to make a judgement about the relationship between mortality and staphylococcal sepsis. No attempts were made to follow up patients after this time. The susceptibility test results were tabulated for each strain.

Data analysis

Where relevant, dichotomous outcome measures (died, survived) were compared using Chi-squared tests (for contingency tables and for trend).

Antibiograms

Strains of *S. aureus* were categorised according to their susceptibilities to a range of antibiotics as penicillin-susceptible, methicillin-susceptible or methicillin-resistant. Methicillin-resistant strains were further presumptively identified as being of the hospital-associated multi-resistant type (AUS-2/3-like) because of resistance to at least three of the following characterising agents: erythromycin, gentamicin, tetracycline, ciprofloxacin, and trimethoprim; hospital-associated United Kingdom type (EMRSA-15-like) due to resistance to ciprofloxacin ± erythromycin but none of the other three agents; or community-associated type (WA-1, South West Pacific, Queensland, and others) if susceptible to all characterising agents or resistant to erythromycin only among those agents.

Results

Data were available on 1,511 cases of *S. aureus* bacteraemia. Two thirds of cases (66.2%) were in males, and males predominated in all age groups (Figure 1).

Associated infections

Information on the type of infection with which the bacteraemia was associated was available on 709 cases (Table 1). The most common infection overall was bacteraemia from an intravascular line, either central or peripheral, or other form of vascular access (e.g. haemodialysis shunt). These accounted for 32% of all infections seen. As expected skin/skin structure infections and bone/joint infections accounted for significant proportions of the associated infections. Endocarditis was the underlying infection in nearly 8% of all cases. Between the ages of 20 and 50, a higher proportion of bacteraemias, 8%, were due to endocarditis.

Table 1. *Staphylococcus aureus* infection types associated with bacteraemia

Infections	Number	Percentage (n = 709)
Intravascular access	258	36.4
IV line infection	226	31.9
Infected AV fistula	24	3.4
Other vascular	8	1.1
Skin and skin structure	143	20.2
Cellulitis/soft tissue infection	131	18.5
Infected burns	6	0.8
Infected dermatological disease	5	0.7
Furunculosis	1	0.1
Orthopaedic	107	15.1
Septic arthritis	52	7.3
Osteomyelitis	46	6.5
Discitis	9	1.3
Cardiac	54	7.6
Endocarditis	54	7.6
Respiratory tract	53	7.4
Pneumonia	50	7.1
URTI unspecified	2	0.3
Orbital cellulitis/sinusitis	1	0.1
Surgical	51	7.2
Post-operative wound infection	38	5.4
Infected vascular prosthesis	11	1.6
Infected implanted device	2	0.3
Other	43	6.1
Urinary tract infection	18	2.5
Deep abscess	10	1.4
Cholangitis	3	0.4
Meningitis	3	0.4
Febrile neutropenia	2	0.3
Gastroenteritis	2	0.3
Peritonitis	2	0.3
Post-partum endometritis	2	0.3
Early onset neonatal sepsis	1	0.1
Unknown/not stated	802	

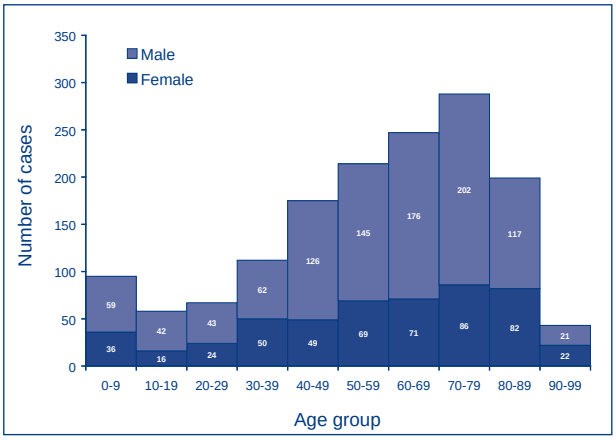
Site of onset and health-care association

Bacteraemia had its onset in the community in 59.6% (865/1,449) of cases (Table 2). Of these, 30.9% were health-care associated (216/700 instances where information on this association was provided). In 35 instances, even though the onset was in hospital, the infection was assessed as not being associated with health care. Such cases included examples such as neonatal sepsis following acquisition from the mother, or the documentation of *S. aureus* from another site at the time of admission without any medical intervention that could have provoked a bacteraemia.

Susceptibilities

Methicillin-resistant strains (MRSA) were responsible for 359 or 23.8% of infections. Of these, 191 (53%) were presumptively the typical multi-resistant hospital type (AUS-2/3-like), 44 (12%) were of the hospital type prominent in the United Kingdom (EMRSA-15-like), and 103 (29% and 6.9% overall) were of the community MRSA type (caMRSA-like). In a further 21 episodes, too few antibiotic susceptibilities were reported to be able to assign a presumptive type of MRSA. The remainder of the 1,511 strains were either penicillin susceptible (PSSA, 192 = 12.7%) or penicillin-resistant and methicillin-susceptible (MSSA, 961 = 63.6%).

Figure 1. Age and sex distribution of *Staphylococcus aureus* bacteraemia cases, (n = 1511)



Numbers on the bars represent the exact numbers of females and males in each decade of life.

Table 2. Site on onset of bacteraemia and its association with health care

Onset	Health-care associated			Total
	Yes	No	Unknown/ not stated	
Community	216	484	165	865
Hospital	452	35	97	584
Unknown/not stated	32	18	12	62
Total	700	537	274	1,511

For those strains where the information was provided, 87% (CI = 81%–93%) of AUS-2/3-like MRSA were health-care associated, compared to 74% (CI = 59%–88%) of EMRSA-15-like strains, 74% (CI = 55%–73%) of caMRSA-like strains, 50% (CI = 46%–53%) of MSSA and 54% (CI = 47%–62%) of PSSA strains (Table 3). Overall, methicillin-resistant strains were more likely to be health-care-associated than methicillin-susceptible strains (MSSA plus PSSA) (78% v. 51%, P < 0.0001), and hospital-type MRSA (AUS-2/3-like and EMRSA-15-like) were more likely to be associated with health-care than caMRSA (84% v. 64%, P = 0.0002).

Outcomes

Outcomes were available for 768 cases (51%). The all-cause mortality in this group was 11.2% (86 cases) (Table 4). The documented attributable mortality was 39/768 or 5.1%, although this is likely to be an underestimate as the cause of death was not documented in 29 of the 86 cases. Given that most of the data were collected from a laboratory base, the reliability of attribution of cause for mortality was not considered high, and thus subsequent analyses were undertaken with the all-cause mortality data.

The most significant factor associated with death was age, as highlighted in Figure 2 (and Table 5). Mortality was greater than 20% in patients aged over 80 years, with an overall trend to lower percentages the younger the patient. Survival was not influenced by sex, place of onset of sepsis, health-care versus

Table 3. Proportion of types of *Staphylococcus aureus* that were health-care associated

Type of *S. aureus*	Health-care associated		Total	Proportion health-care associated (95% Confidence interval)
	Yes	No		
AUS2/3-like	115	17	132	87.1 (81.4–92.8)
EMRSA-15-like	25	9	34	73.5 (54.6–74.3)
caMRSA*-like	57	32	89	64.0 (54.1–74.0)
MRSA-unclear type	16	2	18	88.9 (74.4–100)
MSSA	401	405	806	49.8 (46.3–53.2)
PSSA	86	72	158	54.4 (46.7–62.2)
Total	700	537	1,237	56.6 (53.8–59.4)

* Community-associated MRSA.

non-health-care association, or β-lactam resistance of any type. Mortality was significantly reduced when the source of the infection was an intravascular line.

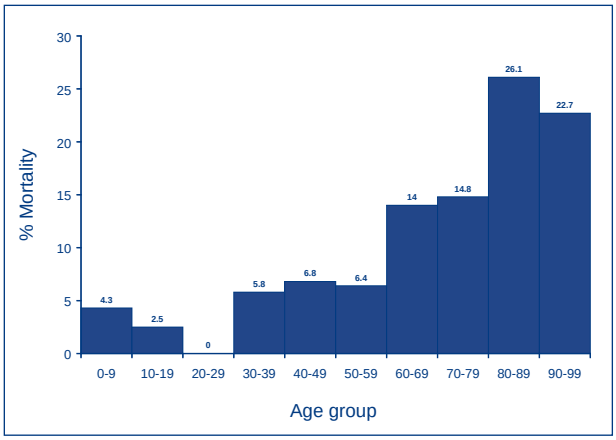
Discussion

Our data show than *S. aureus* bacteraemia remains a common problem in Australia. Unfortunately, we do not have accurate information on what proportion of the Australian population was served by the participating sites, so we could not estimate the true rates of sepsis in our population. However, our previous study showed that 0.15% of hospital admissions in Australia were for *S. aureus* bacteraemia and estimated that about 6,900 episodes occur

Table 4. Outcomes on cases

Outcome at 7d or at discharge if earlier	Number of cases
Death due to sepsis	9
Death due to sepsis and other causes	30
Death from other causes	18
Death from undocumented cause	29
Subtotal	86
Patient alive but on-going sepsis	79
Patient recovered	510
Patient recovered but with significant new morbidity	41
Patient survived at 7 days	52
Subtotal	682
Unknown/Not stated	743

Figure 2. Age stratified mortality rates *Staphylococcus aureus* bacteraemia cases, (n = 768)



Numbers on the bars represent the exact percentages in each decade of life.

Table 5. Potential risk factors for mortality

Factor	Group	Died	Survived	% Mortality	P
Age	< 60 years	20	378	5.0	< 0.0001
	≥60 years	66	304	17.8	
Sex	Female	34	245	12.2	NS*
	Male	52	437	10.6	
Health-care associated	Yes	41	345	10.6	NS
	No	41	299	12.1	
Place of onset	Community	49	413	10.6	NS
	Hospital	36	269	11.8	
Source	IV line†	9	168	5.1	0.003
	Not an IV line	77	514	13.0	
Methicillin-resistant strain	Yes	14	135	9.4	NS
	No	72	547	11.6	
β-lactam resistance	Penicillin-susceptible	13	103	11.2	NS
	Methicillin-susceptible	59	444	11.7	
	Methicillin-resistant	14	135	9.4	NS
Methicillin-resistant type	AUS-2/3-like	8	51	13.6	NS
	EMRSA-15-like	3	17	15.0	
	caMRSA-like	3	56	5.1	

* Not significant.

† Intravascular line or access.

annually in Australia.[6] Based on the average of 13.8 months of data collected from the 17 laboratories, we estimate that we captured about one fifth (approximately 1,300 per year) of all bacteraemias occurring nationally during the study period, and therefore our study provides at least an indicative sample of the problem.

The proportion of cases (24%) caused by methicillin-resistant strains is slightly higher than our previous observations (19%).[6] This may relate to the lower number of laboratories serving private hospitals captured in this study compared to the previous study or a genuine increase in the prevalence of MRSA types. More importantly, we were able to estimate what proportion was due to strains with a resistance profile resembling community-associated MRSA. The finding of 7% of all bacteraemias being due to community-associated MRSA attests to the growing size of this problem in Australia.[7] More surprising was the finding that the major proportion of caMRSA were the cause of health-care associated infections. Outbreaks of caMRSA in hospitals in Australia have been reported,[8] but are not common, and it is more likely that the health-care association is related to increasing rates of colonisation in the community. One seminal study has shown that nasal carriage, most of it present at the time of initiation of health care, accounts for about 80% of subsequent health-care associated bacteraemias.[9]

The crude mortality rate is in the range observed in recent studies from Australia and other countries in adults [10–15] and children.[16–19] Because direct follow-up after 7 days or discharge was not required as part of data collection, we believe that the mortality rate observed is lower than the true figure. We confirmed the very strong association between age and outcome. Mortality rates were significantly lower when the source of infection was an intravascular line or from other vascular access, but no other factor that we examined influenced mortality significantly. In particular, we did not show increased mortality in patients with MRSA infection, which is seen in some series and not others.[20]

Unfortunately, despite the incidence, importance and severity of staphylococcal bacteraemia, there is currently no mechanism in place nationally to monitor incidence and outcomes.[21] This infection is substantially more common and has a higher mortality rate than meningococcal sepsis,[22,23] and yet remains a 'disease in the background'. This is in part because outbreaks in the community have been difficult to detect due to the substantial incidence of sporadic cases. Their substantial impact has therefore been overlooked by the community, the media or public health authorities. However, the recent acquisition of methicillin-resistance by virulent strains has provided a prominent phenotypic marker (Panton-Valentine leukocidin) that has made the epidemic nature of these infections obvious. Their association with deaths in young otherwise healthy children and adults[24,25] has emphasised their importance as a potential target for public health and clinical intervention even more. Emergence of community-associated MRSA highlights the need for a national approach to a growing problem, and our study supports the call for mandatory central reporting of *S. aureus* bacteraemia, but one that also includes community-onset disease, as happens in the United Kingdom.[26] Only then will we be in a position to design better intervention tools.

We recognise that our methods for measuring outcomes had limitations and were subject to possible bias. Not all participating laboratories were able to provide outcome data. Those who did provide data were not audited for accuracy of data capture, and judgements about attributable mortality are acknowledged to be subjective. Nevertheless, we feel that our data provide the first national indication of the importance of serious *S. aureus* infection in the Australian community, and they should drive the future development of robust systems for measuring and improving outcomes of this common infection.

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References

1. Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med* 1998;339:520–532.
2. Maguire GP, Arthur AD, Boustead PJ, Dwyer B, Currie BJ. Clinical experience and outcomes of community-acquired and nosocomial methicillin-resistant *Staphylococcus aureus* in a northern Australian hospital. *J Hosp Infect* 1998;38:273–281.
3. Cordova SP, Heath CH, McGechie DB, Keil AD, Beers MY, Riley TV. Methicillin-resistant *Staphylococcus aureus* bacteraemia in Western Australian teaching hospitals, 1997–1999: risk factors, outcomes and implications for management. J *Hosp Infect* 2004;56:22–28.
4. Nimmo G, Bell J, Collignon P. Fifteen years of surveillance by the Australian Group for Antimicrobial Resistance (AGAR). *Commun Dis Intell* 2003;27 Suppl:S47–S54.
5. Turnidge J, Lawson P, Munro R, Benn R. A national survey of antimicrobial resistance in *Staphylococcus aureus* in Australian teaching hospitals. *Med J Aust* 1989;150:65–72.
6. Collignon P, Nimmo G, Gottlieb T, Gosbell IB, on behalf of the Australian Group on Antimicrobial Resistance. *Staphylococcus aureus* bacteraemia, Australia. *Emerg Infect Dis* 2005;11:554–561.
7. Nimmo GR, Coombs GW, Pearson JC, O'Brien FG, Christiansen KJ, Turnidge JD, et al. Methicillin-resistant *Staphylococcus aureus* in the Australian community: an evolving epidemic. *Med J Aust* 2006;184:384–388.
8. O'Brien FG, Pearman JW, Gracey M, Riley TV, Grubb WB. Community strain of methicillin-resistant *Staphylococcus aureus* involved in a hospital outbreak. *J Clin Microbiol* 1999;37:2858–2862.
9. von Eiff C, Becker K, Machka K, Stammer H, Peters G, for the Study Group. Nasal carriage as a source of *Staphylococcus aureus* bacteraemia. *N Engl J Med* 2001;344:11–16.
10. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2003;36:1418–1423.
11. Kim SH, Park WB, Lee KD, Kang CI, Kim HB, Oh MD, et al. Outcome of *Staphylococcus aureus* bacteraemia in patients with eradicable foci versis noneradicable foci. *Clin Infect Dis* 2003;37:794–799.
12. Lesens O, Methlin C, Hansmann Y, Remy V, Martinot M, Bergin C, et al. Role of comorbidity in mortality related to *Staphylococcus aureus* bacteraemia: a prospective study using the Charlson weighted index of comorbidity. *Infect Control Hosp Epidemiol* 2003;24:890–896.
13. Guilarde AO, Turchi MD, Martelli CM, Primo MG. *Staphylococcus aureus* bacteraemia: incidence, risk factors and predictors for death in a Brazilian teaching hospital. *J Hosp Infect* 2006;63:330–336.
14. Kaech C, Elzi L, Sendi P, Frei R, Laifer G, Bassetti S, Fluckiger U. Course and outcome of *Staphylococcus aureus* bacteraemia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. *Clin Microbiol Infect* 2006;12:345–352.
15. Benfield T, Espersen F, Frimodt-Møller N, Jensen AG, Larsen AR, Pallesen LV, et al. Increasing incidence but decreasing in-hospital mortality of adult *Staphylococcus aureus* bacteraemia between 1981 and 2000. *Clin Microbiol Infect* 2006;13:257–263.
16. Hill PC, Wong CGS, Voss LM, Taylor SL, Pottumarthy S, Drinkovic D, et al. Prospective study of 125 cases of *Staphylococcus aureus* bacteraemia in children in New Zealand. *Pediatr Infect Dis J* 2001;20:868–873.
17. Suryati BA, Watson M. *Staphylococcus aureus* bacteraemia in children: a 5-year retrospective review. *J Paediatr Child Health* 2002;38:290–294.
18. Denniston S, Riordan FA. *Staphylococcus aureus* bacteraemia in children and neonates: a 10 year retrospective review. *J Infect* 2006;53:387–393.
19. Frederiksen MS, Espersen F, Frimodt-Møller N, Jensen AG, Larsen AR, Pallesen LV, et al. Changing epidemiology of pediatric *Staphylococcus aureus* bacteraemia in Denmark from 1971 through 2000. *Pediatr Infect Dis J* 2007;26:398–405.
20. Lodise TP Jr, McKinnon PS. Burden of methicillin-resistant *Staphylococcus aureus*: focus on clinical and economic outcomes. *Pharmacotherapy* 2007;27:1001–1012.
21. Collignon PJ, Wilkinson IJ, Gilbert GL, Grayson ML, Whitby RM. Health care-associated *Staphylococcus aureus* bloodstream infections: a clinical quality indicator for all hospitals. *Med J Aust* 2006;184:404–406.
22. Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta–analysis. *Med J Aust* 2001;175:264–267.
23. Owen R, Roche PW, Hope K, Yohannes K, Roberts A, Liu C, et al. Australia's notifiable diseases status, 2005: annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2007;31:1–70.
24. Peleg AY, Munckhof WJ, Kleinschmidt SL, Stephens AJ, Huygens F. Life-threatening community-acquired methicillin-resistant *Staphylococcus aureus* infection in Australia. *Eur J Clin Microbiol Infect Dis* 2005;24:384–387.
25. Risson DC, O'Connor ED, Guard RW, Schooneveldt JM, Nimmo GR. A fatal case of necrotising pneumonia due to community-associated methicillin-resistant *Staphylococcus aureus*. *Med J Aust* 2007;186:479–480.
26. Johnson AP, Pearson A, Duckworth G, Surveillance and epidemiology of MRSA bacteraemia in the UK. *J Antimicrob Chemother* 2005;56:455–462.