

# Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis

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THE RECOGNITION of methicillin-resistant *Staphylococcus aureus* (MRSA) colonisation and infection of patients in large teaching hospitals on the east coast of Australia engendered great concern in the late 1970s and early 1980s.<sup>1</sup> The organism was resistant not only to methicillin (and flucloxacillin), but also to other commonly used antistaphylococcal antibiotics. Patients required treatment with unfamiliar, often highly expensive, antimicrobials. Over the past two decades, MRSA has become endemic in many Australian hospitals. In some hospitals, as many as one in three *S. aureus* bacteraemias have been associated with MRSA.<sup>2</sup>

Because MRSA is found in patients who are severely ill, there is a continuing perception that this organism is particularly virulent. However, its virulence compared with that of methicillin-sensitive *Staphylococcus aureus* (MSSA) remains controversial. Several early studies found greater morbidity and mortality in MRSA bacteraemia than in MSSA bacteraemia.<sup>3,4</sup> However, other studies in the same period found no difference.<sup>5,6</sup> More recent studies of patients with healthcare-associated MRSA and MSSA, excluding those with community-acquired *S. aureus*, have not provided a consensus.<sup>7,8</sup>

Although healthcare-associated staphylococcal bacteraemia is considered a significant contributor to mortality, it remains rare. Its low incidence means that large samples are needed to detect an effect. All published estimates of the comparative virulence of MRSA and

**ABSTRACT**

**Objective:** To estimate the risk of death from healthcare-associated (nosocomial) bacteraemia caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and compare it with that of nosocomial bacteraemia caused by methicillin-sensitive *S. aureus* (MSSA), by meta-analysis of selected studies.

**Data sources:** Medline, EMBASE, Current Contents and Cochrane Library were searched for the period January 1978 (or earliest date of the database, if later than 1978) to December 2000.

**Study selection:** Studies which compared mortality of nosocomial MRSA and MSSA bacteraemia.

**Data synthesis:** Nine studies were analysed. All but one found an increased relative risk (RR) of death from MRSA bacteraemia, with RR ranging from 0.89 to 4.94. Meta-analysis showed that patients with MRSA bacteraemia have an RR of death, compared with patients with MSSA bacteraemia, of 2.12 (95% CI, 1.76–2.57) using the fixed-effect method, and 2.03 (95% CI, 1.55–2.65) using the random-effect method.

**Conclusion:** MRSA bacteraemia is associated with a real increase in risk of death, further justifying ongoing MRSA surveillance and control in healthcare facilities.

**MJA 2001; 175: 264-267**

MSSA have been by necessity conducted on small samples, potentially underestimating the true difference. To provide sufficient statistical power to estimate the true effect of MRSA, we undertook a meta-analysis of studies that compared mortality between healthcare-associated MRSA and MSSA bacteraemia.

**METHODS**

**Data sources and selection**

Epidemiological studies were identified through computerised searches of Medline, EMBASE, Current Contents and

the Cochrane Library for the period January 1978 (or the earliest date of the database, if later than 1978) to December 2000. Studies were reviewed independently by two of the authors (M W and M-L McL). The search was not restricted to English and used medical subject headings and free text words. Keywords used were "*Staphylococcus aureus*", "staphylococcal infections", "methicillin resistance", "bacter(a)emia" and "bloodstream infection". Citations were tracked until no new studies were found. A search of abstracts from recent relevant scientific meetings revealed no additional studies.

For inclusion in this analysis, studies had to:

- identify patients with healthcare-associated MSSA and MRSA bacteraemia; and
- provide mortality data for healthcare-associated *S. aureus* bacteraemia, separable from outcome data for community-acquired organisms.

Although all risk factors were collated, only those assessed by two or more studies were included in this analysis.

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# 1: Characteristics and findings on risk factors of studies comparing outcomes of nosocomial bacteraemia caused by methicillin-resistant and methicillin-sensitive *Staphylococcus aureus*

	Soriano <sup>17</sup>	Selvey <sup>18</sup>	Romero-Vivas <sup>8</sup>	Harbarth <sup>14</sup>	French <sup>7</sup>	Conterno <sup>13</sup>	Topeli <sup>6</sup>	Pujol <sup>19</sup>	Hershow <sup>20</sup>
<b>Study characteristics</b>									
Year of publication	2000	2000	1995	1998	1990	1998	2000	1996	1992
Country	Spain	Australia	Spain	Switzerland	Hong Kong	Brazil	Turkey	Spain	USA
Healthcare facility (beds)*	900	916	1500	1500	1360	600	1000	1000	577
<b>Study design</b>									
Mortality estimate	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Case-control
Risk factors	Case-control	Cohort	Cohort	Case-control	Cohort	Case-control	Cohort	Cohort	Case-control
<b>Number of patients (MRSA:MSSA)</b>									
Cohort	225:683	188:316	84:100	39:145	74:80	86:31	46:55	24:8	—
Case-control	163:163	—	—	38:38	—	46:90	—	—	12:13
<b>Risk factors (MRSA group:MSSA group)†</b>									
Mean age in years	62:57	NS	69:54	NS	NS	NS	NS	—	—
Male sex	67%:33%	73%:62%	NS	NS	NS	NS	NS	—	—
MRSA past history	NS	18%:5%	—	—	—	—	—	—	—
Median days of hospitalisation before bacteraemia	18:8	16:6	32:14	32:8	21:8	—	—	—	—
Prior antibiotic therapy	61%:23%	—	61%:34%	76%:29%	81%:14%	—	78%:53%	—	—
Prior surgery	27%:16%	NS	45%:31%	—	—	—	—	—	—
Immunosuppression	—	27%:15%	—	—	—	—	NS	—	—
Bacteraemia acquired in ICU (%)	26%:13%	NS	—	—	—	—	—	24%:8%	—
Tracheostomy/ventilation	8%:2%	15%:8%	NS	NS	—	—	24%:4%	—	—
Central venous catheter	—	66%:40%	NS	NS	—	—	54%:22%	—	—
Indwelling urinary catheter	—	70%:45%	58%:27%	NS	—	—	NS	—	—
Nasogastric tube	—	—	31%:13%	NS	—	—	NS	—	—
Inappropriate empiric therapy	48%:18%	NS	NS	NS	18%:0	11%:63%	NS	—	—

MRSA = methicillin-resistant *Staphylococcus aureus*. MSSA = methicillin-sensitive *Staphylococcus aureus*. — = not assessed.

NS = no significant difference ( $P > 0.05$ ). ICU = intensive care unit.

\*All facilities were public teaching hospitals. †Risk factors assessed by two or more studies are included. Values are given for prevalence if there was a significant difference between the MRSA and MSSA groups.

## Statistical analysis

Meta-analysis was performed on the combined selected studies using the fixed-effect and random-effect approaches.<sup>9</sup> The relative risk was defined as the mortality in the MRSA group ( $a/(a+b)$ , where there were  $a$  deaths in  $a+b$  patients) divided by the mortality in the MSSA group ( $c/(c+d)$ ).

Studies were combined by the Mantel-Haenszel method using the Cochrane Review manager.<sup>10</sup> In this method, relative risks are combined using weights of  $c(a+b)/N$  (where  $N$  is the total number of patients), and the variance of the logarithm of the combined estimate is that of Greenland and Robins.<sup>11</sup> This gives the fixed-effect estimate. The variance of the combined estimate is the inverse of the sum of the weights. The random-effect approach was also performed.<sup>9</sup> A test for heterogeneity of the relative risks over the studies was calculated as the  $\chi^2$  with  $k-1$

degrees of freedom, where  $k$  is the number of studies.

## RESULTS

### Data sources

We identified 273 articles published between January 1978 and December 2000 that referred to nosocomial MRSA bacteraemia. Most of these studies either did not provide data on the outcome of bacteraemia or included patients with community-acquired bacteraemia in mortality rates for MSSA bacteraemia. Eleven studies compared the outcomes of identifiable healthcare-associated MRSA and MSSA bacteraemia and fulfilled the inclusion criteria.<sup>7,8,12-20</sup>

Two of these studies were excluded from the meta-analysis.<sup>12,15</sup> One analysed a 453-patient subset of the more than 10 000 patients included in the 1992 EPIC (European Prevalence of

Infection in Intensive Care) Study. EPIC was a cross-sectional survey conducted on a single day in 1417 intensive care units in 17 Western European countries.<sup>12</sup> Analysis examined the acquisition and risk of death in 30 patients with MRSA bacteraemia and 23 with MSSA bacteraemia. The study was excluded from our meta-analysis, as not only were no risk factors provided but there were also large differences between countries in prevalence of MRSA infection (81% difference) and overall staphylococcal mortality (21% difference). A second study was excluded, as it focused on outcomes of attributable hospital stay and costs of MRSA and MSSA nosocomial bacteraemia rather than comparative mortality.<sup>15</sup>

### Study characteristics

Characteristics of the nine studies included in the meta-analysis are shown in Box 1. A total of 2209 patients were

**2: Crude estimates and relative risk of death (MRSA to MSSA bacteraemia) in a meta-analysis of nine studies**

Study	Mortality		Relative risk and 95% CI (fixed effect)	Weight	Relative risk (95% CI) (fixed effect)
	MRSA	MSSA			
Soriano et al <sup>17</sup>	49/225 (22%)	61/683 (9%)		26.3%	2.44 (1.73-3.44)
Selvey et al <sup>18*</sup>	26/188 (14%)	26/316 (8%)		16.9%	1.68 (1.01-2.81)
Romero-Vivas et al <sup>8*</sup>	35/84 (42%)	22/100 (22%)		17.5%	1.89 (1.21-2.96)
Harbarth et al <sup>14*</sup>	14/39 (36%)	40/145 (28%)		14.7%	1.30 (0.79-2.14)
French et al <sup>7*</sup>	32/74 (43%)	7/80 (9%)		5.8%	4.94 (2.32-10.51)
Conterno et al <sup>13*</sup>	43/86 (50%)	7/31 (23%)		8.9%	2.21 (1.12-4.39)
Topeli et al <sup>16*</sup>	15/46 (33%)	7/55 (13%)		5.5%	2.56 (1.14-5.74)
Pujol et al <sup>19</sup>	8/24 (33%)	3/8 (38%)		3.9%	0.89 (0.31-2.56)
Hershow et al <sup>20</sup>	1/12 (8%)	0/13 (0)		0.4%	3.23 (0.14-72.46)
<b>Total</b>	<b>223/778 (29%)</b>	<b>173/1431 (12%)</b>		<b>100.0%</b>	<b>2.12 (1.76-2.57)†</b>

MRSA = methicillin-resistant *Staphylococcus aureus*. MSSA = methicillin-sensitive *Staphylococcus aureus*.  
 Test for heterogeneity:  $\chi^2 = -13.13$ ;  $df = 8$ ;  $P = 0.11$ . Test for overall effect:  $z = 7.80$ ;  $P < 0.001$ .  
 \* Mortality rates in these studies were attributable to bacteraemia *per se*.  
 † Relative risk by random-effect model (95% CI) = 2.03 (1.55-2.65) ( $P < 0.001$ ).

assessed, comprising 778 with MRSA bacteraemia and 1431 with MSSA bacteraemia.

The study by Conterno et al assessed mortality for healthcare-associated infection, but calculated risk factors for MRSA from a nested case-control study, which included community-acquired infection.<sup>13</sup> The latter data were included in our analysis of risk factors, as community-acquired bacteraemia represented less than 14% of all episodes (19/136). The study of Topeli et al also included community-acquired bacteraemia (15/55 cases of MSSA bacteraemia and 7/46 cases of MRSA bacteraemia).<sup>16</sup> These data were also included in our assessment of mortality and risk factors, as the community-acquired cases represented less than 1% of the total of 2209 patients in the meta-analysis.

**Mortality**

All but one<sup>19</sup> of the nine studies found that the risk of death was higher in patients with MRSA bacteraemia than in those with MSSA bacteraemia, with the relative risk ranging from 0.89 to 4.94 (Box 2). Seven of the nine studies evaluated risk of death in samples of fewer than 200 patients;<sup>7,8,13,14,16,19,20</sup> the study that found a lower risk in MRSA than in MSSA bacteraemia had a relatively small sample size (32).<sup>19</sup> Five studies reported mortality rates attributed to the bacteraemia *per se*, in addition to overall mortality.<sup>7,8,13,16,18</sup>

Meta-analysis of the combined studies showed that relative risk (RR), using the fixed-effect estimate for death caused by MRSA, was significantly increased (RR, 2.12; 95% CI, 1.76-2.57;  $P < 0.001$ ). The test for heterogeneity of relative risks showed no significant difference ( $\chi^2 = 13.13$ ;  $df = 8$ ;  $P = 0.11$ ), reflecting the similarity between studies (Box 1) and supporting the use of the fixed-effect approach for combining them. Nevertheless, the random-effect approach gave a similar result, with marginally wider confidence intervals (RR, 2.03; 95% CI, 1.55-2.65;  $P < 0.001$ ).

**Risk factors**

Potential risk factors for MRSA bacteraemia assessed in two or more studies are shown in Box 1. Prevalence is shown for risk factors that were significant. Prior antibiotic therapy was found to be a significant risk factor for MRSA bacteraemia in all five studies in which it was assessed.<sup>7,8,14,16,17</sup> Similarly, inpatient stay before bacteraemia was significantly longer in patients with MRSA than in those with MSSA in the five studies in which it was assessed.<sup>7,8,14,17,18</sup> Other results were more variable: older age, male sex, past history of MRSA, prior surgery, immunosuppression, treatment in an intensive care unit and a range of invasive procedures were found to be significant risk factors in at least one study, but to be not significant in at least one other. Inappropriate empiric antibiotic

therapy was significantly associated with MRSA bacteraemia in two studies,<sup>7,17</sup> but was more common in patients with MSSA bacteraemia in the study of Conterno et al.<sup>13</sup>

**DISCUSSION**

We identified nine studies since 1990 that were designed mainly to compare the risk of mortality between healthcare-associated MRSA and MSSA bacteraemia. All but one study<sup>19</sup> found that MRSA bacteraemia has a higher risk of mortality than MSSA bacteraemia, with the relative risk varying between 0.89 and 4.94. Meta-analysis showed that patients with MRSA bacteraemia are at twice the risk of death compared with patients with healthcare-acquired MSSA bacteraemia.

As MRSA colonisation or infection has been, until recently, closely associated with patient contact with a healthcare facility, we confined our meta-analysis to studies of healthcare-associated bacteraemia. Some well constructed studies proved inappropriate for this analysis, as they included community-acquired MSSA infections in the comparison group.<sup>21,22</sup>

The reason for the higher mortality in MRSA bacteraemia remains moot, although several hypotheses have been suggested. Geographic variability in organism virulence has been postulated,<sup>8,13,23</sup> but evidence is inconsistent,<sup>7,24,25</sup> Differences in patient comorbidity may have contributed. Risk

factors for healthcare-associated MRSA versus MSSA infections included length of hospital stay and prior treatment with antibiotics,<sup>7,8,14,16-18</sup> suggesting that patients who ultimately become infected with MRSA are more seriously ill than those who become infected with MSSA. Separating the effect of the bacteraemia *per se* from the effects of patients' underlying disease and treatment is a major problem when comparing outcomes. Five of the nine studies reported mortality rates attributed to MRSA bacteraemia *per se*.<sup>7,8,13,16,18</sup> In four of these five studies, mortality exceeded 30%,<sup>7,8,13,16</sup> but, in the Australian study, was reported at only 14%.<sup>18</sup> Death attributed to MSSA bacteraemia exceeded 20% in only two studies of substantial sample size.<sup>8,13</sup>

It has also been postulated that the differences in mortality may be partly explained by differences in empiric prescribing and efficacy of the antimicrobials commonly used to treat staphylococcal bacteraemia. Roghmann was unable to confirm that hospital restrictions on empiric use of vancomycin had any deleterious effect on the outcome of patients with MRSA infections.<sup>22</sup> However, other authors have suggested that vancomycin is not as effective a therapy as commonly prescribed  $\beta$ -lactam antistaphylococcal agents in treating staphylococcal bacteraemia,<sup>26</sup> endocarditis<sup>27</sup> and pneumonia.<sup>21</sup> None of the studies included in our meta-analysis specifically addressed this point.

The association of MRSA bacteraemia with invasive procedures, including mechanical ventilation, tracheostomy and central venous and indwelling urinary catheterisation, may reflect intrinsic differences in predisposing medical conditions. Stay in an intensive care unit has been reported to increase the opportunity for skin colonisation with MRSA<sup>6,7,17,25</sup> in a setting where medical procedures frequently breach body defence barriers, further increasing the risk of bacteraemia. We were unable to adjust mortality estimates for the numerous potential confounders, as the stud-

ies included in our meta-analysis did not link risk factors with outcome in individual patients.

MRSA incidence in healthcare facilities in eastern Australia varies between States, but the organism remains endemic (Australian Group for Antimicrobial Resistance [AGAR], unpublished data). However, patient colonisation with MRSA continues to provide a reservoir for dissemination, and MRSA infection continues to lengthen hospital stay, leading to patient dissatisfaction and increased costs to the healthcare sector.<sup>15</sup> Added to these problems is the current antimicrobial resistance pattern of MRSA in Australia, with over 50% of infected patients requiring management with parenteral antimicrobial therapy in some States (AGAR, unpublished data). Regardless of the cause of the increased risk of death in MRSA bacteraemia, our findings justify ongoing surveillance and proactive management of MRSA in healthcare facilities.

**Competing Interests:** We had no financial support for the meta-analysis or the preparation of this article, and no issues creating a conflict of interest exist.

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(Received 22 Jan, accepted 7 Jun, 2001)

