Comparison of Mortality Associated with Methicillin-Resistant and Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Meta-analysis

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A meta-analysis was performed to summarize the impact of methicillin-resistance on mortality in *Staphylococcus aureus* bacteremia. A search of the MEDLINE database for studies published during the period of 1 January 1980 through 31 December 2000 and a bibliographic review identified English-language studies of *S. aureus* bacteremia. Studies were included if they contained the numbers of and mortality rates for patients with methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteremia. Data were extracted on demographic characteristics of the patients, adjustment for severity and comorbid illness, source of bacteremia, and crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality. When the results were pooled with a random-effects model, a significant increase in mortality associated with MRSA bacteremia was evident (OR, 1.93; 95% CI, 1.54–2.42; $P < .001$); significant heterogeneity was present. We explored the reasons for heterogeneity by means of subgroup analyses. MRSA bacteremia is associated with significantly higher mortality rate than is MSSA bacteremia.

Infections with antibiotic-resistant organisms are thought to result in higher morbidity and mortality rates than are similar infections with antibiotic-susceptible strains [1]. However, the extent of this finding may vary according to the causative organism, the infection site, and the patient's characteristics.

Rates of *Staphylococcus aureus* infection have increased during the past 2 decades [2]. Bacteremia due to *S. aureus* has been reported to be associated with mortality rates of 15%–60% [3, 4]. Resistance to methicillin among *S. aureus* isolates is a growing problem: 52.3% of nosocomial infections in patients in the intensive care unit (ICU) are due to methicillin-resistant *S. aureus* (MRSA), representing a 37% increase in the incidence of MRSA infections from 1994 to 1998 [2]. Community-acquired MRSA infections are an emerging problem [5].

To assess the impact of methicillin-resistance in *S. aureus*, several studies have investigated the differences in the mortality rates for patients who have methicillin-susceptible *S. aureus* (MSSA) bacteremia compared with patients who have MRSA bacteremia, and the results have been conflicting. As a consequence, both clinicians and policy makers have varying opinions about the impact of MRSA on patient outcomes. This study aims to determine the effect of methicillin resistance on mortality for patients with *S. aureus* bac-

teremia by conducting a systematic review of studies that report mortality rates associated with both MSSA and MRSA bacteremia.

MATERIALS AND METHODS

Identification of relevant literature. A literature search to identify all studies of *S. aureus* bacteremia that were published from January 1980 through December 2000 was performed by use of the MEDLINE database and by a review of the bibliographies of relevant articles. The study included only studies that reported cases that occurred after 1975 because, before 1975, few cases of MRSA were reported and therapy for MRSA had not yet been standardized. A full-text search of the MEDLINE database that used the search terms "'*aureus*' AND 'bacteremia,'" "'*aureus*' AND 'endocarditis,'" "'*aureus*' AND 'outcome,'" or "'*aureus*' AND 'mortality'" revealed 3688 references. Thirteen additional references were obtained from the bibliographies of retrieved articles. Abstracts of all identified references were reviewed, and any study that may have been relevant, as determined on the basis of the abstract, was reviewed in full. We identified 225 articles for review on the basis of the criteria stated below. Any studies that did not clearly meet these criteria were reviewed by 2 investigators who reached a consensus regarding inclusion or exclusion of the article.

Inclusion and exclusion criteria. Inclusion and exclusion criteria were established by the investigators before reviewing abstracts and articles. Studies were included if they were written in English, involved human subjects, and had data on the numbers of and mortality rates for patients with MSSA and MRSA bacteremia. Studies that evaluated *S. aureus* endocarditis were included because the cases were, by definition, also cases of bacteremia. Studies were excluded for the following reasons: (1) the OR for mortality due to MRSA bacteremia compared with MSSA bacteremia could not be determined, (2) there were ≤2 cases of MRSA bacteremia reported, (3) subjects were all children, or (4) the study described results that used previously published data with >1 year of overlap or 75% time overlap between studies (in these cases, one representative study was chosen).

Hypotheses and data extraction. The main objective of this study was to summarize the relative risk of mortality associated with MRSA bacteremia compared with MSSA bacteremia. We hypothesized that the measure of effect may be influenced by confounding factors. Therefore, 2 investigators independently extracted the following information from each study: country of study origin; study period; number of patients and mortality rates in the MRSA and MSSA bacteremia groups; percentage of cases that were nosocomial; length of hospital stay before the onset of infection; mean patient age; primary comorbidity; bacteremia source; presence of an outbreak of

MRSA infection; method of adjustment for age, sex, severity of illness, and ICU stay; adequacy of therapy; and crude and adjusted ORs and 95% CIs for all-cause and *S. aureus* bacteremia–related mortality for MRSA versus MSSA bacteremia. The investigators compared their evaluations and reviewed studies together as necessary.

All of the studies that we examined were retrospective analyses. We did not attempt to assign a quality score to the studies that we included, because studies did not differ in design or in the methods used for recruiting patients. We did a subgroup analysis of studies that adjusted for confounding variables.

Data and statistical analysis. References to all identified publications were entered into reference-managing software (EndNote, version 4.0; Niles Software). Statistical analyses were performed by use of Stata software, version 6.0 (Stata). We elected to use ORs as the measure of effect in our analysis to allow comparison of the pooled risk measures in studies that adjusted for confounding variables and those that did not; studies that adjusted for confounding variables via logistic regression reported adjusted relative risks as ORs. We also determined a pooled risk ratio (RR) for 30 of the 31 studies; 1 study reported only ORs and could not be included in this analysis [6]. Crude ORs and 95% CIs were calculated on the basis of the primary data reported in the study. One case was added to empty cells to allow calculation of the OR. Although this may bias our results to the null, we did not use the more traditional method of adding 0.5 cases to each cell because we felt that this would exaggerate the true OR in studies with empty cells. We used the DerSimonian and Laird random-effects model to obtain pooled estimates of the ORs and 95% CIs for groups of studies [7]. We tested for heterogeneity in the results of different studies by use of the Q statistic, and we considered heterogeneity to be significant if the P value was <.10.

Publication bias was evaluated by plotting the point estimate against the percentage weight of the study (1 divided by variance, a measure of the power of the study) and constructing a funnel diagram originating from the pooled OR of the studies (Excel 97; Microsoft). The Egger regression asymmetry test and the Begg and Mazumdar adjusted rank correlation test were also used to test for publication bias [8, 9].

RESULTS

Thirty-one cohort studies that contained data regarding the mortality associated with both MSSA and MRSA bacteremia were identified in 31 published articles that met inclusion criteria [6, 10–39]. One study described 2 separate analyses for patients with endocarditis and patients with bacteremia; we grouped the studies together and reported a combined OR [26]. For one study, we obtained an adjusted OR and 95% CI by

Table 1. Summary of studies included in a meta-analysis of *Staphylococcus aureus* bacteremia (SAB).

Reference	Study period, month/year	Total no. of cases	MRSA, % of cases	≥70% Of cases were nosocomial	CR cases, %	IE, % of cases	SAB-related mortality rate, %		OR (95% CI)	
							MRSA	MSSA	Crude	Adjusted
[10]	1/1991–9/1992	136	66.2	Yes	25.7	NS	48.9 (48.9)	19.6 (19.6)	3.93 (1.7–9.09)	4.22 (1.6–11.2)
[11]	1/1979–1/1982	58	50.0	Yes	NS	NS	48.3	51.7	0.87 (0.31–2.44)	—
[12]	12/1991–5/1993	110	16.4	Yes	40.9	NS	22.2	9.8	2.63 (1.71–9.73)	—
[13]	9/1994–1/1998	59	35.6	No	50.8	100.0	23.8	21.1	1.17 (0.33–4.18)	—
[14]	5/1984–6/1988	141	43.3	NS	NS	NS	31.1	8.8	4.72 (1.83–12.15)	1.4 (0.38–5.19)
[15]	6/1992–12/1998	60	86.7	Yes	NS	NS	25.0	25.0	1.0 (0.18–5.58)	—
[16]	1/1989–12/1993	56	19.6	NS	NS	100.0	54.5	24.4	3.71 (0.94–14.56)	—
[17]	4/1991–8/1991	13	69.2	NS	100.0	NS	11.1	25.0	0.37 (0.02–8.1)	—
[18]	7/1975–12/1977	102	16.7	No	NS	NS	52.9	41.2	1.6 (0.56–4.57)	—
[19]	1/1994–12/1995	76	50.0	No	32.9	10.5	34.2 (18.4)	34.2 (23.7)	1.0 (0.39–2.58)	1.0 (0.4–2.5)
[20]	8/1978–12/1986	80	15.0	No	0.0	100.0	16.7	10.3	1.74 (0.32–9.62)	—
[21]	1/1989–12/1989	25	48.0	Yes	NS	NS	8.3	7.7	1.09 (0.06–19.63)	—
[22]	7/1997–7/1999	94	48.9	NS	NS	NS	37.0	25.0	1.76 (0.72–4.27)	—
[23]	1/1985–12/1991	11	54.5	Yes	NS	NS	83.3	40.0	0.5 (0.46–122.7)	—
[24]	1976–1979; 1986–1989	184	3.3	No	NS	15.2	83.3	27.0	13.54 (1.54–118.9)	—
[25]	1/1982–1/1983	45	40.0	No	NS	91.1	0.0	7.4	0.69 (0.06–8.26)	—
[26]	1/1979–1/1981	56	50.0	No	0.0	46.4	3.6	3.6	1.0 (0.06–16.82)	1.0 (0.06–16.82)
[27]	1/1982–12/1988	28	50.0	Yes	42.9	NS	42.9	28.6	1.88 (0.39–9.01)	1.88 (0.39–9.01)
[6]	9/1994–2/1998	NS	NS	NS	NS	NS	NS	NS	1.66 (0.66–4.21)	1.6 (0.62–4.11)
[28]	1/1982–12/1991	85	64.7	NS	NS	NS	74.5	20.0	11.71 (3.97–34.53)	—
[29]	4/1983–10/1985	111	25.2	Yes	34.2	1.8	42.9 (42.9)	28.9 (28.9)	1.48 (0.66–3.35)	—
[30]	1/1992–8/1993	89	34.8	No	NS	NS	45.2	34.5	1.56 (0.64–3.81)	—
[31]	1/1995–2/1999	293	30.4	No	21.8	6.1	23.6	23.0	1.03 (0.57–1.86)	1.0 (0.48–2.01)
[32]	2/1990–12/1991	181	37.0	Yes	62.4	3.3	25.4	21.9	1.21 (0.6–2.45)	—
[33]	10/1995–1/1998	128	29.7	No	30.5	NS	31.6	25.6	1.34 (0.59–3.09)	—
[34]	1/1990–9/1993	184	45.7	Yes	22.8	3.3	58.3 (41.7)	32.0 (22.0)	2.98 (1.63–5.44)	3.0 (1.44–6.25)
[35]	1/1992–12/1997	504	37.3	Yes	50.8	NS	18.6	13.0	1.53 (0.94–2.51)	—
[36]	1/1991–12/1998	908	24.8	No	NS	NS	21.8	8.9	2.84 (1.88–4.28)	2.48 (1.56–3.95)
[37]	1/1979–1/1981	20	50.0	Yes	NS	NS	20.0 (20.0)	30.0 (30.0)	0.58 (0.07–4.56)	0.58 (0.07–4.56)
[38]	1/1992–12/1994	25	44.0	NS	100.0	NS	45.5	21.4	3.1 (0.53–17.46)	—
[39]	5/1990–10/1994	101	45.5	Yes	30.7	NS	58.7 (32.6)	30.9 (12.7)	3.18 (1.4–7.2)	5.6 (1.18–26.47)

NOTE. CR, catheter-related; IE, infective endocarditis; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus;* NS, not stated; —, not applicable.

personal communication with an author of that study [31], and we obtained an adjusted OR and 95% CI from a published letter that described a reanalysis of data presented in an article included in this review [36, 40]. Characteristics of the studies are outlined in table 1.

The 31 studies described on a total of 3963 patients with *S. aureus* bacteremia; 2603 patients (65.7%) had MSSA bacteremia, and 1360 patients (34.3%) had MRSA bacteremia. Twenty-four studies (77.4%) found no significant difference in the mortality rates for MRSA and MSSA bacteremia, 7 studies (22.6%) found significantly higher mortality rates associated with MRSA bacteremia, and no studies found significantly lower mortality rates associated with MRSA bacteremia (figure 1).

When the results of all studies are combined, a significant increase in mortality associated with MRSA bacteremia com-

pared with MSSA bacteremia is evident, with a pooled OR of 1.93 (95% CI, 1.54–2.42; $P < .001$). These results are statistically significant, although there is significant heterogeneity among the studies' results ($P = .03$). This suggests that the included studies are not estimating a single common effect of the impact of methicillin resistance on mortality associated with *S. aureus* bacteremia. The pooled RR for the 30 studies for which RRs could be determined is 1.42 (95% CI, 1.25–1.63; $P < .001$).

The causes of heterogeneity in the results were explored according to our a priori hypotheses by subgroup analysis (figure 2). We analyzed the 11 studies that were adjusted for potential confounding factors under the assumption that such adjustment gives a more accurate reflection of the true relationship between methicillin resistance and mortality in patients with *S. aureus* bacteremia [6, 10, 14, 19, 26, 27, 31, 34, 36, 37, 39].
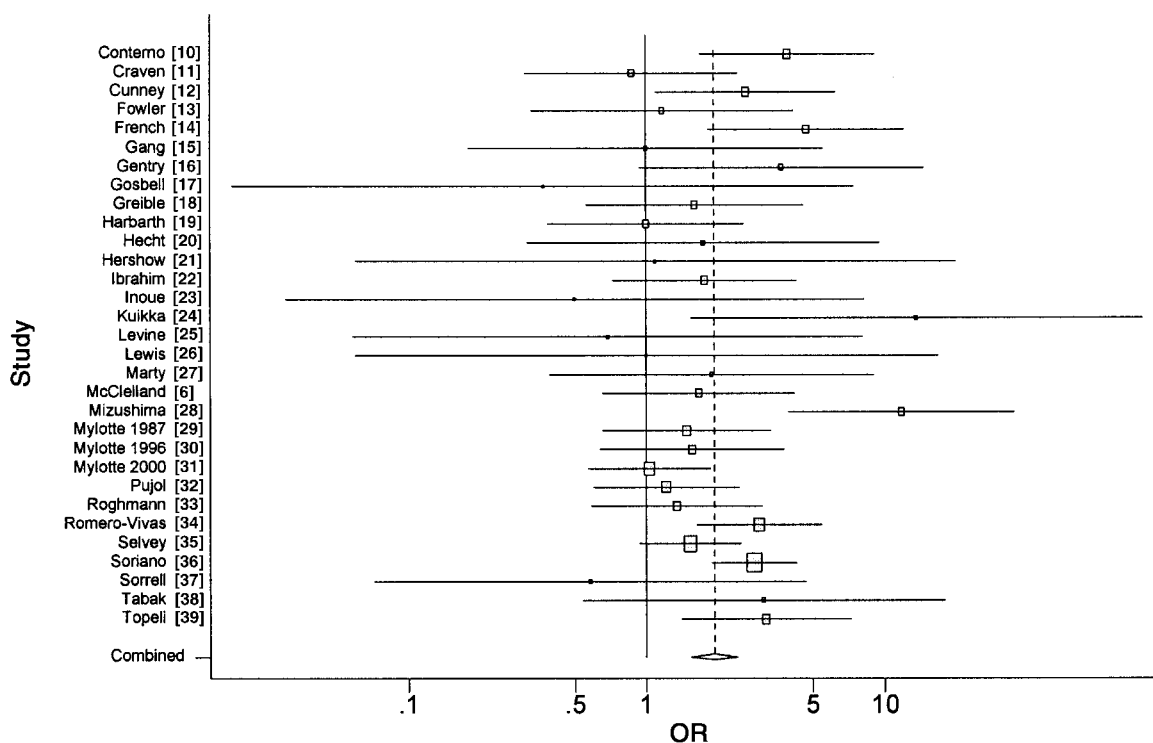
Figure 1. Forest plot summary of the unadjusted results of the 31 studies included in the meta-analysis. The OR and 95% CI are shown for each study. The pooled OR is 1.93 (95% CI, 1.54–2.42). There was significant heterogeneity among the studies' results ($P = .03$).

In 4 of these studies, confounding was adjusted for by matching, and multivariable regression models were used in 8 studies (both methods were used in 1 study). The method of adjustment for severity of illness varied. The McCabe score was used in 6 studies and the APACHE score was used in 5 [41–43]. One study restricted the analysis to a uniform population of young injection drug users, and one used the number of microbiology samples before the first positive blood culture. Nine studies adjusted for age and sex, and 5 studies adjusted for length of hospitalization before infection.

The pooled OR for the 11 studies that adjusted for potential confounding is 1.88 (95% CI, 1.33–2.69; $P < .001$). There is no significant heterogeneity among the studies' results ($P = .16$), which suggests that these studies estimate a single common effect of the impact of methicillin resistance in *S. aureus* bacteremia. The pooled OR for the 20 remaining unadjusted studies is 1.7 (95% CI, 1.32–2.18; $P < .001$). There is no significant heterogeneity among the studies' results ($P = .36$).

Our next a priori hypothesis was that there may be worse outcomes in studies that primarily involve nosocomial *S. aureus* infections than there are in studies that involve a significant proportion of community-acquired infections. Twenty-four studies reported the number of nosocomial cases of *S. aureus* bacteremia. In the 13 studies in which ≥70% of the cases of bacteremia were nosocomially acquired [10–12, 15, 21, 23,

27, 29, 32, 34, 35, 37, 39], the pooled OR is 2.03 (95% CI, 1.48–2.76; $P < .001$), whereas, in the 11 studies in which <70% of the cases of bacteremia were nosocomially acquired [13, 18–20, 24–26, 30, 31, 33, 36], the pooled OR is 1.56 (95% CI, 1.06–2.29; $P = .03$).

Our third a priori hypothesis was that the presence of an outbreak may influence the mortality associated with MRSA. The pooled OR for the 4 studies that took place during outbreaks of infection is 1.61 (95% CI, 0.92–2.84; $P = .1$) [11, 18, 32, 34]. The pooled OR for the studies that did not take place during an outbreak of infection is 2.0 (95% CI, 1.57–2.55; $P < .001$). To assess our a priori hypothesis that the source of infection was related to mortality in patients with *S. aureus* bacteremia, we examined the studies that reported data on patients who had central venous line infections and who had endocarditis. Sixteen studies contained data about the percentages of patients with catheter-related *S. aureus* bacteremia. The pooled OR for the studies in which <40% of the infections involved a central venous catheter [10, 19, 20, 26, 29, 31, 33, 39] is 1.87 (95% CI, 1.42–2.46; $P < .001$). The pooled OR for the studies in which ≥40% of the infections were associated with a central venous catheter [12, 13, 17, 27, 32, 34, 35, 38] is 1.57 (95% CI, 1.12–2.2; $P = .008$). Five studies primarily examined patients with endocarditis [13, 16, 20, 25, 26]. The pooled OR of these studies is 1.79 (95% CI, 0.84–3.81; $P =$
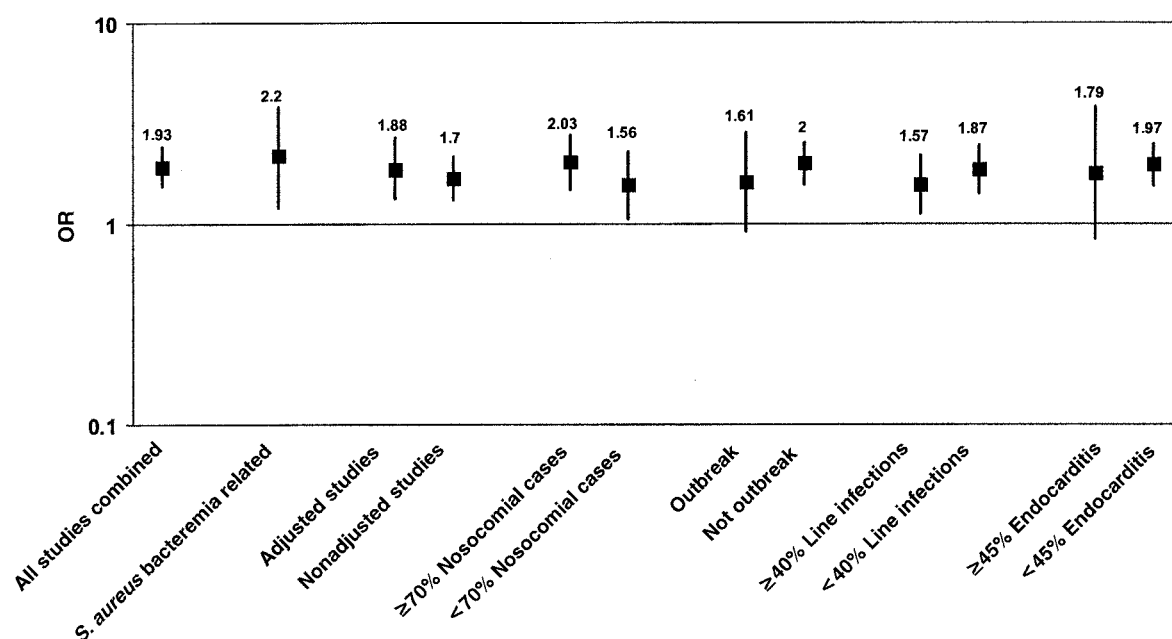
Figure 2. Summary of the subgroup analyses performed to explain the heterogeneity found in the pooled OR for all studies. The OR and 95% CI are shown for each subgroup. These analyses showed consistently increased rates of mortality associated with methicillin resistance, and there was minimal or no significant heterogeneity in each group.

.13). The pooled OR of studies that had small numbers of patients with endocarditis (<16%) or did not state the number of cases of endocarditis is 1.97 (95% CI, 1.55–2.5; $P < .001$).

We next examined mortality specifically related to *S. aureus* bacteremia rather than all-cause mortality; we hypothesized that this would provide a more accurate estimate of the true effect of MRSA bacteremia compared with MSSA bacteremia. The pooled OR of the 6 studies that examined this outcome is 2.2 (95% CI, 1.2–3.8; $P = .007$). The results of the additional subgroup analyses showed minimal or no heterogeneity. No evidence of publication bias was noted in the funnel plot, the regression asymmetry test ($P = .61$), or the adjusted rank correlation test ($P = .44$).

DISCUSSION

This synthesis of published studies on mortality for patients with *S. aureus* bacteremia indicates that patients who have MRSA bacteremia have an increased risk of mortality compared with patients who have MSSA bacteremia (OR, 1.93). Because ORs could overestimate the effect size in our study, in which the mean mortality rate for MSSA bacteremia was 23.4%, we also calculated a pooled RR of 1.42. This value may better reflect the magnitude of the effect of methicillin resistance on mortality.

The increased mortality rate was apparent in subgroup analyses of studies in which confounding variables were ad-

justed for, the majority of cases of bacteremia (both MRSA and MSSA bacteremia) were nosocomial, an outbreak of infection was underway, and large numbers of cases were associated with central venous catheters or endocarditis. In all of these subgroup analyses, the OR consistently remained at 1.56–2.03. Moreover, when mortality specifically related to bacteremia was analyzed, the OR for mortality associated with methicillin resistance was even higher (OR, 2.2). The number of individual studies ($n = 7$) showing a significant increase in mortality associated with MRSA bacteremia compared with MSSA bacteremia is low probably because most individual studies were small and lacked the power to detect an association between methicillin resistance and mortality. That 77.4% of published studies failed to show an effect of MRSA on mortality accounts for the belief that MRSA is not associated with increased mortality. However, when the studies are combined, the relationship between methicillin resistance and mortality in patients with *S. aureus* bacteremia becomes apparent.

The heterogeneity among study results found in our primary analysis was explained by the fact that some studies were adjusted for confounding variables but others were not. When those studies that were adjusted for confounding variables were analyzed separately from studies that were not adjusted, the results for each group were not heterogeneous.

A priori, we hypothesized that adjustment for severity of illness and examination of mortality attributable to *S. aureus* bacteremia would decrease the association of mortality due to

MRSA compared with mortality due to MSSA. These hypotheses were related to the belief that patients with MRSA bacteremia are sicker and therefore more likely to die because of other factors, such as admission to the ICU or immunosuppression. Surprisingly, we found that the association between MRSA bacteremia and mortality persists even when adjustments are made for comorbidities or severity of illness and when mortality due to *S. aureus* bacteremia is examined. The likely explanation is that MRSA and MSSA affect patients with similar severities of illness and that the effect of the *S. aureus* bacteremia dominates underlying disease as a determinant of mortality. Another explanation is that studies did not completely adjust for important confounding variables.

We found that studies in which ≥40% of patients had central venous line–associated *S. aureus* bacteremia had a lower pooled OR (OR, 1.57) than did studies in which <40% of patients had central venous line infections (OR, 1.87). This finding suggests that the magnitude of effect of MRSA on mortality was lower in cohorts of patients with central venous line infections, perhaps because these patients have a removable focus of infection and are more easily treated.

Studies that specifically examined patients with endocarditis did not differ in measure of effect from the other studies examined; however, the pooled OR was not statistically significant, which is probably because only 5 studies reported large numbers of patients with endocarditis. Removal of these studies from the analysis did not change the magnitude of the effect of methicillin resistance on mortality associated with *S. aureus* bacteremia (pooled OR, 1.97), perhaps because 5%–64% of patients with *S. aureus* bacteremia also have endocarditis that may not be clinically detected [44]. Potential reasons why MRSA may cause worse outcomes include (1) enhanced virulence of the antibiotic-resistant organism, (2) decreased effectiveness of vancomycin, which was invariably used to treat MRSA, and (3) delay in microbiologically appropriate antibiotic selection.

There has been no evidence to suggest that MRSA strains are more virulent than MSSA strains, although there is evidence that suggests that vancomycin may be an inferior antistaphylococcal antibiotic compared with semisynthetic penicillins, especially for the treatment of deep-seated *S. aureus* infections, such as endocarditis [45–47]. Administration of inadequate antimicrobial therapy once culture data is available was associated with increased mortality at one institution, where 32.6% of MRSA bloodstream infections were inappropriately treated [22]. In addition, patients with MRSA bacteremia may not receive empiric vancomycin therapy, particularly in settings in which the proportion of MRSA isolates is underappreciated by clinicians, leading to a delay in appropriate antibiotic coverage. Indeed, we found that the measure of association between MRSA bacteremia and mortality was lower in outbreak situations than in nonoutbreak situations (OR, 1.61 vs. 2.0), which may be related to a greater suspicion of MRSA infection and consequent empiric coverage for this organism.

The relative effects of a delay in appropriate treatment and decreased efficacy of vancomycin in the outcomes of patients with MRSA bacteremia are unclear. Further investigation will help clarify whether efforts should be directed at early MRSA detection that uses newer rapid tests to expedite use of appropriate therapy or at modification of antibiotic therapy with new agents, drug combinations, or different doses [48–50].

Our analysis is limited in that the studies that we review contain data about different patient populations; however, pooling the available data suggests that the trend toward increased mortality in patients with MRSA bacteremia seen in smaller studies is real. We were unable to obtain detailed information about the source of the bacteremia and the adequacy of antimicrobial therapy for many studies; consequently, we were unable to fully assess whether these factors were potential confounders in the true relationship between methicillin resistance and mortality. In addition, although we found that studies in which there was adjustment for severity of illness did not have a different measure of effect of methicillin resistance on mortality than studies in which there was no adjustment, the lack of a validated method of adjustment for severity of illness in patients with infections limits our conclusions. Future studies that involve many health care centers and that adjust for potential confounding variables should be undertaken to address these issues.

We conclude that bacteremia due to methicillin-resistant *S. aureus* is associated with increased mortality compared with MSSA bacteremia. This finding remains significant after examining the effects of adjustment for confounding variables. This analysis will help in the assessment of the implications of the emerging problem of MRSA and emphasize the important roles of infection control and appropriate antibiotic use.

Acknowledgment

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