Original Investigation

Association Between Vancomycin Minimum Inhibitory Concentration and Mortality Among Patients With *Staphylococcus aureus* Bloodstream Infections

A Systematic Review and Meta-analysis

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IMPORTANCE *Staphylococcus aureus* bacteremia (SAB) is a worldwide problem. It is unclear whether higher-vancomycin minimum inhibitory concentration (MIC) is associated with mortality. This potential association has direct consequences for patients and public health.

DATA SOURCES PubMed, Embase, the Cochrane Library, Evidence-based Medicine BMJ, and the American College of Physicians Journal Club were searched from inception through April 2014.

STUDY SELECTION Studies reporting mortality and vancomycin MIC in patients with SAB were included.

DATA EXTRACTION AND SYNTHESIS Two authors performed the literature search and the study selection separately. Random-effects modeling was used for all analyses.

MAIN OUTCOMES AND MEASURES All-cause mortality.

FINDINGS Among 38 included studies that involved 8291 episodes of SAB, overall mortality was 26.1%. The estimated mortality was 26.8% among SAB episodes (n = 2740) in patients with high-vancomycin MIC (≥1.5 mg/L) compared with 25.8% mortality among SAB episodes (n = 5551) in patients with low-vancomycin MIC (<1.5 mg/L) (adjusted risk difference [RD], 1.6% [95% CI, −2.3% to 5.6%]; *P* = .43). For the highest-quality studies, the estimated mortality was 26.2% among SAB episodes (n = 2318) in patients with high-vancomycin MIC compared with 27.8% mortality among SAB episodes (n = 4168) in patients with low-vancomycin MIC (RD, 0.9% [95% CI, −2.9% to 4.6%]; *P* = .65). In studies that included only methicillin-resistant *S aureus* infections (n = 7232), the mortality among SAB episodes (n = 2384) in patients with high-vancomycin MIC was 27.6% compared with mortality of 27.4% among SAB episodes (n = 4848) in patients with low-vancomycin MIC (adjusted RD, 1.6% [95% CI, −2.3% to 5.5%]; *P* = .41). No significant differences in risk of death were observed in subgroups with high-vancomycin MIC vs low-vancomycin MIC values across different study designs, microbiological susceptibility assays, MIC cutoffs, clinical outcomes, duration of bacteremia, previous vancomycin exposure, and treatment with vancomycin.

CONCLUSIONS AND RELEVANCE In this meta-analysis of SAB episodes, there were no statistically significant differences in the risk of death when comparing patients with *S aureus* exhibiting high-vancomycin MIC (≥1.5 mg/L) to those with low-vancomycin MIC (<1.5 mg/L), although the findings cannot definitely exclude an increased mortality risk. These findings should be considered when interpreting vancomycin susceptibility and in determining whether alternative antistaphylococcal agents are necessary for patients with SAB with elevated but susceptible vancomycin MIC values.

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Staphylococcus aureus is among the most common causes of health care–associated infection throughout the world.[1,2] It causes a wide range of infections, with bloodstream infections (*S aureus* bacteremia [SAB]) among the most common and lethal.[3] In addition, SAB is associated with prolonged hospital stay, need for intensive care, requirement for surgical intervention, and increased costs for patients and the health care system.[4]

For more than 50 years, the primary therapy for *S aureus* infections has been either semisynthetic penicillins or vancomycin. More recent reports have documented an increase in the minimum inhibitory concentration (MIC) for vancomycin, referred to as vancomycin "MIC creep."[5] Although this phenomenon may be influenced by the type of microbiological susceptibility assay used, type of *S aureus* strain examined, or type of patient population evaluated, what is more concerning are reports suggesting that elevations in vancomycin MIC values may be associated with increased treatment failure and mortality.

Three previous meta-analyses[6-8] have attempted to address the potential association between MIC values and clinical outcomes and suggested that elevated vancomycin MIC levels may be associated with worse outcomes. However, all 3 studies included highly heterogeneous patient populations, combined different sites of infection, primarily analyzed non-SAB infections, evaluated mostly treatment failure (a soft outcome susceptible to measurement bias and highly dependent on local management practices), and lacked recently published literature. Several important questions concerning the potential clinical ramifications of vancomycin MIC remain unanswered. Are elevated (but still susceptible) vancomycin MIC levels associated with higher mortality? If higher-vancomycin MIC values are associated with worsened outcome, which method of MIC testing is the most predictive? Should vancomycin be avoided when MIC levels are elevated?

This study focused on addressing these questions by systematically evaluating the available evidence regarding the association of vancomycin MIC elevation with mortality in patients with SAB.

Methods

Literature Search

PubMed, Embase, the Cochrane Library, Evidence-based Medicine BMJ, and the American College of Physicians Journal Club were searched from inception through April 2014. Also, abstracts from the following societies' annual meetings were searched from 2006-2013: the Infectious Diseases Society of America, the Interscience Conference on Antimicrobial Agents and Chemotherapy, and the Society for Healthcare Epidemiology of America. The literature search strategy is presented in eAppendix 1 (in the Supplement). No language restrictions were applied. Two authors (A.K. and T.V.) performed the literature search and the study selection separately. Authors of included studies were contacted if any clarification was needed for the original report. Any disagreement was resolved by a final consensus.

Inclusion and Exclusion Criteria

All human studies that evaluated patients with SAB, reported vancomycin MICs, and provided mortality outcomes were included.

Studies were excluded if all-cause mortality outcome was not provided; mortality was not stratified by MIC values; mortality from bloodstream infections was not reported or it could not be separated from other sites of infection; or if MICs were measured only by automated susceptibility assays.

Data Extraction

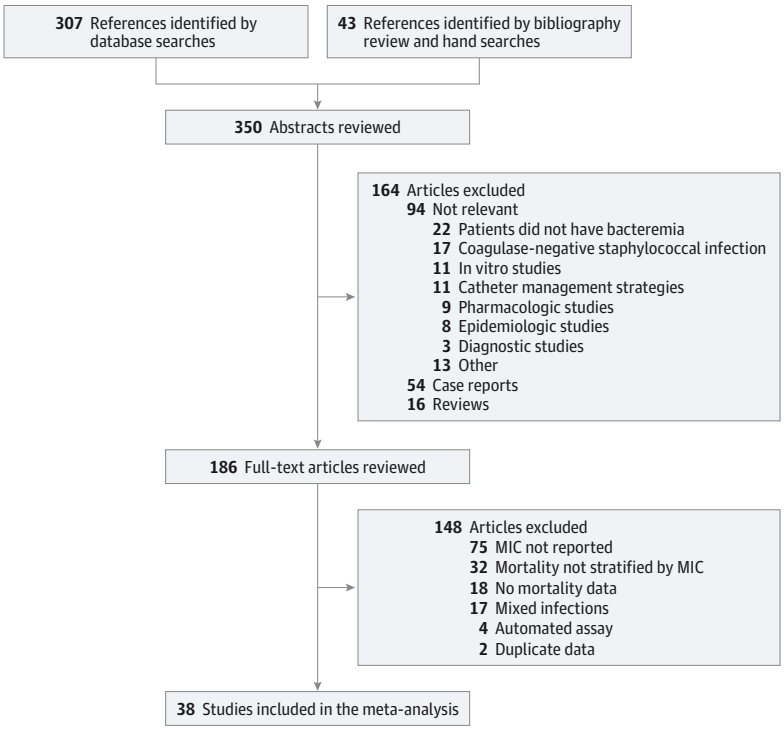
The following variables were collected from all studies: authors, publication year, study design, sample size, patient age, MIC cutoff, microbiological susceptibility assay, test for heteroresistance, methicillin-resistance status, duration of bacteremia, intensive care unit (ICU) exposure, APACHE II score, Charlson score, previous vancomycin exposure, presence of endocarditis, antistaphylococcal drugs used for treatment, vancomycin trough levels, and all-cause mortality.

Definitions

The a priori definition for the high-vancomycin MIC group for this study required an MIC of greater than or equal to 1.5 mg/L with no upper-limit values. This cutoff was chosen in order to use a conservative level and minimize the risk of not detecting a clinically meaningful outcome difference. Additionally, in contrast to broth microdilution susceptibility testing, which typically detects MIC values in 2-fold dilutions (eg, 0.5, 1.0, 2.0 mg/L), Etest methodology (Epsilometer test in which the MIC is determined through use of a rectangular antibiotic-impregnated strip) was also used because it can detect other values (eg, 1.5 mg/L). Thus, the use of greater than or equal to 1.5 mg/L as the vancomycin interpretive cutoff value includes those studies using both broth microdilution (MIC values <1.0 mg/L are the low-vancomycin group; MIC values ≥2.0 mg/L are the high-vancomycin group) and Etest (MIC values <1.5 mg/L are the low-vancomycin group; MIC values ≥1.5 mg/L are the high-vancomcyin group). The definition of high-vancomycin MIC was extracted according to the original report from each study.

Subgroup analyses were also planned a priori to evaluate different MIC cutoffs, different microbiological susceptibility assays, methicillin-resistance status, and the presence of heteroresistance (phenotype in which a small subpopulation of bacterial cells have decreased susceptibility or are resistant to vancomycin), as defined by individual studies. The prospective defined primary outcome was all-cause mortality. Subgroup analyses were prospectively planned to evaluate different follow-up times, ie, combined 28- and 30-day mortality, hospital mortality, and overall mortality by severity of illness, previous vancomycin exposure, ICU admission, duration of bacteremia, vancomycin trough levels, presence of endocarditis, and vancomycin treatment. The Newcastle-Ottawa scale[9] was used to evaluate the quality of the studies, with the best-quality score being 9 (maximum), and the highest-quality studies defined by a score of at least 8.

Figure 1. Study Selection for for Vancomycin MIC and Mortality in Patients With *Staphylococcus aureus* Bacteremia



MIC indicates minimum inhibitory concentration.

Statistical Analysis

The risk difference (RD) was calculated for all analyses. All data were pooled by the use of random-effects modeling according to DerSimonian and Laird methodology.[10] Random-effects modeling accounted for both within-study and between-study variances and then used both to assign the study weights. Because random-effects modeling does not assume a common effect size for all studies, its results are more generalizable to different populations. Positive RDs indicate higher mortality with high-vancomycin MIC compared with low-vancomycin MIC values. The T^2 method was used to assess the magnitude of between-study variance (heterogeneity). The T^2 method is measured in the same units of study outcome and does not increase with number or size of studies; heterogeneity degree was defined as low (<0.01), moderate (0.01-0.1), and high (>0.1).[11]

A mixed-effects meta-regression was performed by the method of moments[12] to evaluate statistically the effect of continuous variables on the risk of mortality with high-vancomycin MIC. The variables evaluated by meta-regression were age, APACHE II score, Charlson score, MIC cutoff, previous vancomycin exposure, vancomycin trough level, duration of bacteremia, proportion of patients with endocarditis, patient hospitalization in the ICU, and vancomycin treatment. The MOOSE guidelines[13] for meta-analysis of observational studies were followed (eTable 1 in the Supplement), and PRISMA criteria[14] were performed for the search methodology (**Figure 1**). Egger regression and the Begg and Mazumdar methods were used to evaluate publication bias.[15-17]

Results with 2-sided *P* values less than .05 were considered statistically significant. All meta-analyses were performed with Comprehensive Meta-analysis software version 3.0 (Biostat).

Results

Figure 1 describes the literature search. A total of 38 studies (N = 8291 episodes of SAB) were included in this meta-analysis (**Table 1** and **Table 2**).[18-55] Overall mortality was 26.1%.

Vancomycin MIC and Mortality Outcome

The adjusted absolute risk of mortality among patients with SAB with high-vancomycin MIC (≥1.5 mg/L; n = 2740 patients; mortality, 26.8%) was not statistically different from patients with SAB with low-vancomycin MIC (<1.5 mg/L; n = 5551 patients; mortality, 25.8%) with an RD of 1.6% (95% CI, −2.3% to 5.6%), *P* = .43, and T^2 = 0.007 (**Figure 2**). When the outcome was analyzed by 30-day mortality or by hospital mortality separately, the results for 30-day mortality (high-vancomycin MIC: n = 1827 patients; mortality, 22.2%; vs low-vancomycin MIC: n = 3498 patients; mortality, 22.4%) showed an RD of 1.0% (95% CI, −4.7% to 6.8%), *P* = .73, and T^2 = 0.011; and for hospital mortality (high-vancomycin MIC: n = 913 patients; mortality, 36%; vs low-vancomycin MIC: n = 2053 patients; mortality, 31.6%), the RD was 2.5% (95% CI, −1.9% to 6.8%), *P* = .27, and T^2 = 0.001 (**Figure 3**).

Table 1. Vancomycin MIC and Mortality in Patients With *S aureus* Bacteremia Studies, 2003-2010[a]

Source (Location)	Design	Diagnosis	High-/Low-Vancomycin MIC		No. of Patients/ Deaths	High-Vancomycin Group MIC Cutoff, µg/mL	Assay Method	Mortality Outcome	Newcastle-Ottawa Score	Patients Received Vancomycin Treatment, No. (%)
			Mean Age, y	Men, %						
Retrospective Studies										
Schwaber et al,[18] 2003 (US)	Two-center, cohort	MRSA bacteremia	61/64	61/60	148/39	≥4.0	BMD	Hospital	7	NA
Charles et al,[19] 2004 (Australia)	Single-center, cohort	MRSA bacteremia	63.6/65.9	NA	53/18	≥8.0	Etest	30-d	7	53 (100)
Howden et al,[20] 2004 (Australia)	Single-center, case series	Sterile site infections due to *S aureus*	66.6/65	57/40	17/10	≥4.0	BMD	Hospital	5	17 (100)
Maor et al,[21] 2007 (Israel)	Single-center, cohort	hVISA bacteremia	53.8/72.3	50/67	16/12	≥4.0	Etest	Hospital	7	16 (100)
Neoh et al,[22] 2007 (Japan)	Single-center, case series	MRSA bacteremia	52.2/55	50/63	18/10	≥2.0	BMD	30-d	5	18 (100)
Lodise et al,[24] 2008 (US)	Single-center, cohort	MRSA bacteremia	59.3/60.9	73/65	92/15	≥1.5	Etest	30-d	7	92 (100)
Bae et al,[26] 2009 (US, Europe, Oceania, Middle East)	Multicenter, cohort	MRSA infective endocarditis	67.5/65.6	64/46	65/24	≥1.5	Etest	Hospital	7	61 (94)
Fong et al,[27] 2009 (Singapore)	Single-center, cohort	Persistent MRSA infection	58/59	40/53	40/24	≥8.0	Etest	30-d	6	39 (98)
Jang et al,[28] 2009 (Korea)	Single-center, case series	Persistent *S aureus* bacteremia	NA	NA	35/14	≥2.0	BMD	30-d	6	35 (100)
Maor et al,[29] 2009 (Israel)	Single-center, case-control	hVISA and MRSA bacteremia	67/64	70/65	250/117	≥8.0	Etest	Hospital	8	250 (100)
Musta et al,[30] 2009 (US)	Single-center, cohort	MRSA bacteremia	NA	NA	285/81	≥1.5	Etest	Hospital	8	253 (89)
Lalueza et al,[32] 2010 (Spain)	Single-center, cohort	MRSA bacteremia	NA	NA	63/16	≥1.5	Etest	Hospital	7	63 (100)
Lewis et al,[33] 2010 (UK)	Single-center, cohort	MRSA bacteremia	NA	NA	142/34	≥1.5	Etest	30-d	8	132 (93)
Lin et al,[34] 2010 (Taiwan)	Single-center, cohort	Persistent MRSA bacteremia	71/71	58/59	227/102	≥2.0	BMD	30-d	8	204 (90)[b]
Moore et al,[35] 2010 (US)	Single-center, case series	MRSA bacteremia	NA	NA	16/10	≥1.5	Etest	30-d	7	12 (75)
Neuner et al,[36] 2010 (US)	Single-center, cohort	MRSA bacteremia	NA	NA	196/40	≥2.0	Etest	Hospital	7	196 (100)
Takesue et al,[37] 2010 (Japan)	Single-center, cohort	MRSA bacteremia	NA	NA	759/95	≥2.0	Etest	30-d	7	599 (79)[b]
Prospective Studies										
Liao et al,[23] 2008 (Taiwan)	Single-center, cohort	MRSA bacteremia	65.8/71.7	59/59	177/59	≥2.0	BMD	Hospital	8	177 (100)
Soriano et al,[25] 2008 (Spain)	Single-center, cohort	MRSA bacteremia	66.2/63.5	67/65	414/116	≥2.0	Etest	30-d	8	182 (44)
Price et al,[31] 2009 (UK)	Single-center, cohort	*S aureus* bacteremia	NA	NA	45/12	≥1.5	Etest	30-d	7	45 (100)
Wang et al,[38] 2010 (Taiwan)	Single-center, cohort	MRSA bacteremia	63.6/70.3	54/70	123/40	≥2.0	BMD	30-d	8	90 (73)

Abbreviations: BMD, broth microdilution; hVISA, heteroresistant vancomycin-intermediate *S aureus*; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-sensitive *S aureus*; NA, not available; *S aureus*, *Staphylococcus aureas*.

[a] Tables 1 and 2 are divided by years due to space limitations; data in both tables are derived from the same literature search and study selection process.

[b] Included vancomycin or teicoplanin.

Vancomycin MIC Cutoff and Mortality Outcome

Various definitions of high-vancomycin MIC were used and the results obtained when specific MIC cutoffs were analyzed (**Figure 4**) showed no evidence that the specific MIC cutoff was associated with mortality. For MIC of greater than or equal to 1.5 mg/L (high-vancomycin MIC: n = 1880 patients; mortality, 25.2%; and low-vancomycin MIC: n = 2537 patients; mortality, 25.2%), RD was 1.0% (95% CI, −4.6% to 6.6%), P = .72, and T^2 = 0.007. For MIC of greater than or equal to 2.0 mg/L (high-vancomycin MIC: n = 753 patients; mortality, 29.6%; and low-vancomycin MIC: n = 2614 patients; mortality, 23.6%), RD was 3.3% (95% CI, −3.4% to 9.9%), P = .34, and T^2 = 0.011. For MIC of greater than or equal to 4.0 mg/L (high-vancomycin MIC: n = 65 patients; mortality, 27.7%; and low-vancomycin MIC:

Table 2. Vancomycin MIC and Mortality in Patients With *S aureus* Bacteremia Studies, 2011-2014[a]

Source (Location)	Design	Diagnosis	High-/Low-Vancomycin MIC		No. of Patients/ Deaths	High-Vancomycin Group MIC Cutoff, µg/mL	Assay Method	Mortality Outcome	Newcastle-Ottawa Score	Patients Received Vancomycin Treatment, No. (%)
			Mean Age, y	Men, %						
Retrospective Studies										
Aguado et al,[39] 2011 (Spain)	Single-center, cohort	MSSA catheter-related bacteremia	62.9/63.6	57/69	99/14	≥1.5	Etest	30-d	7	64 (65)
Clemens et al,[40] 2011 (US)	Single-center, cohort	MRSA bacteremia	60.3/51.1	71/79	118/12	≥2.0	Etest	30-d	8	112 (95)
de Sanctis et al,[41] 2011 (US)	Single-center, cohort	MRSA bacteremia	NA	NA	97/26	≥2.0	Etest	30-d	8	88 (91)
Khatib et al,[44] 2011 (US)	Single-center, cohort	MRSA bacteremia	54.8/59.8	NA	281/68	≥2.0	BMD	Hospital	8	244 (87)
Schweizer et al,[45] 2011 (US)	Single-center, cohort	*S aureus* bacteremia	NA	NA	814/109	≥1.5	Etest	30-d	8	700 (86)
van Hal et al,[46] 2011 (Australia)	Single-center, cohort	MRSA bacteremia	NA	NA	268/74	≥2.0	BMD	30-d	8	225 (84)
Walraven et al,[47] 2011 (US)	Single-center, cohort	MRSA bacteremia	47.7/52.2	70/71	139/42	≥2.0	Etest	Hospital	8	139 (100)
Chen et al,[48] 2012 (Taiwan)	Single-center, cohort	Health care-associated MRSA bacteremia	68.7/69.5	64/46	291/82	≥2.0	BMD	30-d	7	262 (90)
Han et al,[49] 2012 (US)	Two-center, cohort	*S aureus* bacteremia	58/57	59/63	392/60	≥1.5	Etest	30-d	8	392 (100)
Miller et al,[50] 2012 (UK)	Single-center, cohort	MRSA bacteremia	58.7/64.1	65/67	694/206	≥1.5	Etest	Hospital	8	694 (100)[b]
Rojas et al,[51] 2012 (Spain)	Single-center, cohort	MRSA bacteremia	NA	NA	361/161	≥1.5	Etest	Hospital	8	361 (100)
Yeh et al,[52] 2012 (Taiwan)	Single-center, cohort	MRSA bacteremia	70.2/68.4	65/64	140/57	≥1.5	Etest	Hospital	8	54 (39)
Kan et al,[54] 2014 (Taiwan)	Single-center, cohort	MRSA bacteremia in patients on hemodialysis	75.2/68.9	99/59	44/16	≥2.0	Etest	30-d	8	44 (100)
Prospective Studies										
Holmes et al,[42] 2011 (Australia, New Zealand)	Multicenter, cohort	*S aureus* bacteremia	59.2/63.5	69/68	523/90	≥1.5	Etest	30-d	8	261 (50)
Honda et al,[43] 2011 (US)	Single-center, cohort	MRSA bacteremia	59/54	46/55	163/35	≥2.0	BMD	30-d	8	163 (100)
Gasch et al,[53] 2013 (Spain)	Multicenter, cohort	MRSA bacteremia	NA	NA	552/179	≥1.5	Etest	30-d	8	303 (55)
Yoon et al,[55] 2014 (Korea)	Multicenter, cohort	Health care-associated MRSA bacteremia	NA	NA	134/45	≥1.5	Etest	Hospital	8	134 (100)

Abbreviations: BMD, broth microdilution; hVISA, heteroresistant vancomycin-intermediate *S aureus*; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-sensitive *S aureus*; NA, not available; *S aureus*, *Staphylococcus aureas*.

[a] Tables 1 and 2 are divided by years due to space limitations; data in both tables are derived from the same literature search and study selection process.

[b] Included vancomycin or teicoplanin.

n = 99 patients; mortality, 33.3%), RD was −6.4% (95% CI, −32% to 19%), P = .62, and T^2 = 0.015. For MIC of greater than or equal to 8.0 mg/L (high-vancomycin MIC: n = 42 patients; mortality, 47.6%; and low-vancomycin MIC: n = 301 patients; mortality, 46.2%), RD was −1.8% (95% CI, −18% to 14%), P = .82, and T^2 = 0.

Vancomycin MIC Assay Type and Mortality Outcome

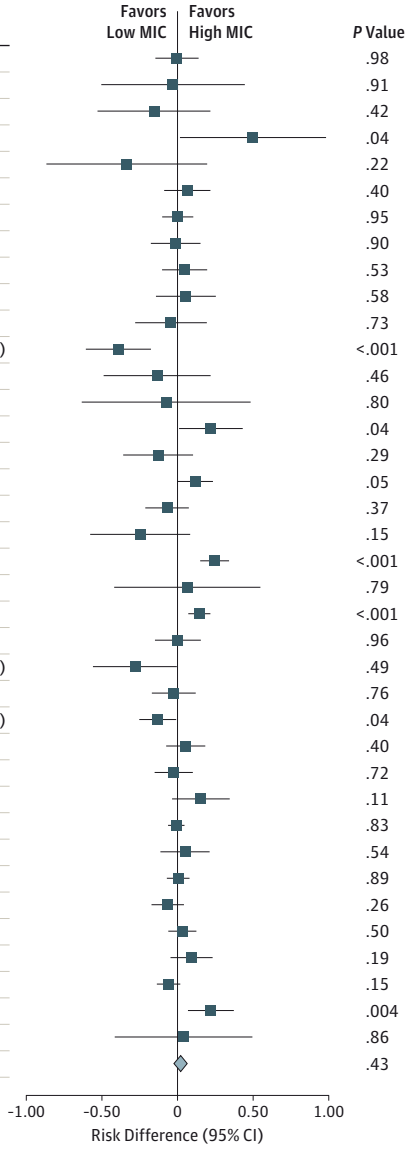
Various methods were used to assess vancomycin MIC values but the majority of studies used broth microdilution (BMD) or the Etest. For BMD (high-vancomycin MIC: n = 447 patients; mortality, 30%; and low-vancomycin MIC: n = 1301 patients; mortality, 30.7%), the RD was 1.3% (95% CI, −5.5% to 8.1%), P = .71, and T^2 = 0.004. For the Etest (high-vancomycin MIC: n = 2293 patients; mortality, 26.2%; and low-vancomycin MIC: n = 4250 patients; mortality, 24.3%), RD was 1.5% (95% CI, −3.3% to 6.2%), P = .55, and T^2 = 0.008 (**Figure 5**). There was no evidence that the method of vancomycin MIC determination was associated with mortality.

Staphylococcal Heteroresistance and Mortality Outcome

Not all studies evaluated for the presence of heteroresistant vancomycin-intermediate-*S aureus* (hVISA); however, 7 stud-

Figure 2. Risk Difference for Overall Mortality for High-Vancomycin MIC vs Low-Vancomycin MIC

Source	High MIC, No. Deaths	High MIC, No. Total	Low MIC, No. Deaths	Low MIC, No. Total	Risk Difference (95% CI)	*P* Value
Schwaber et al,[18] 2003	16	61	23	87	-0.002 (-0.146 to 0.142)	.98
Howden et al,[20] 2004	4	7	6	10	-0.029 (-0.505 to 0.447)	.91
Charles et al,[19] 2004	1	5	17	48	-0.154 (-0.530 to 0.222)	.42
Neoh et al,[22] 2007	2	2	8	16	0.500 (0.016 to 0.984)	.04
Maor et al,[21] 2007	2	4	10	12	-0.333 (-0.867 to 0.200)	.22
Lodise et al,[24] 2008	12	66	3	26	0.066 (-0.088 to 0.221)	.40
Soriano et al,[25] 2008	26	92	90	322	0.003 (-0.101 to 0.107)	.95
Liao et al,[23] 2008	13	40	46	137	-0.011 (-0.176 to 0.155)	.90
Musta et al,[30] 2009	14	43	67	242	0.049 (-0.102 to 0.200)	.53
Maor et al,[29] 2009	14	27	103	223	0.057 (-0.143 to 0.256)	.58
Bae et al,[26] 2009	13	37	11	28	-0.042 (-0.279 to 0.196)	.73
Price et al,[31] 2009	1	20	11	25	-0.390 (-0.607 to -0.173)	<.001
Fong et al,[27] 2009	5	10	19	30	-0.133 (-0.488 to 0.221)	.46
Jang et al,[28] 2009	1	3	13	32	-0.073 (-0.633 to 0.487)	.80
Wang et al,[38] 2010	13	26	27	97	0.222 (0.010 to 0.434)	.04
Lalueza et al,[32] 2010	2	13	14	50	-0.126 (-0.358 to 0.106)	.29
Neuner et al,[36] 2010	21	76	19	120	0.118 (-0.002 to 0.238)	.05
Lin et al,[34] 2010	24	60	78	167	-0.067 (-0.212 to 0.078)	.37
Lewis et al,[33] 2010	0	3	34	139	-0.245 (-0.576 to 0.087)	.15
Takesue et al,[37] 2010	33	97	62	662	0.247 (0.150 to 0.343)	<.001
Moore et al,[35] 2010	4	6	6	10	0.067 (-0.418 to 0.551)	.79
Holmes et al,[42] 2011	48	179	42	344	0.146 (0.073 to 0.220)	<.001
Walraven et al,[47] 2011	21	69	21	70	0.004 (-0.148 to 0.157)	.96
deSanctis et al,[41] 2011	0	4	26	93	-0.280 (-0.558 to -0.001)	.49
Khatib et al,[44] 2011	8	36	60	245	-0.023 (-0.169 to 0.123)	.76
van Hal et al,[46] 2011	8	47	66	221	-0.128 (-0.252 to -0.005)	.04
Honda et al,[43] 2011	26	112	9	51	0.056 (-0.075 to 0.186)	.40
Clemens et al,[40] 2011	2	24	10	94	-0.023 (-0.150 to 0.104)	.72
Aguado et al,[39] 2011	6	23	8	76	0.156 (-0.037 to 0.348)	.11
Schweizer et al,[45] 2011	82	619	27	195	-0.006 (-0.061 to 0.049)	.83
Yeh et al,[52] 2012	27	62	30	78	0.051 (-0.113 to 0.215)	.54
Han et al,[49] 2012	21	134	39	258	0.006 (-0.070 to 0.081)	.89
Rojas et al,[51] 2012	102	240	59	121	-0.063 (-0.171 to 0.046)	.26
Miller et al,[50] 2012	36	111	170	583	0.033 (-0.062 to 0.127)	.50
Chen et al,[48] 2012	19	53	63	238	0.094 (-0.047 to 0.235)	.19
Gasch et al,[53] 2013	69	237	110	315	-0.058 (-0.136 to 0.020)	.15
Yoon et al,[55] 2014	36	87	9	47	0.222 (0.069 to 0.375)	.004
Kan et al,[54] 2014	2	5	14	39	0.041 (-0.414 to 0.496)	.86
Overall (*z* score = 0.797; *P* = .43; T^2 = 0.007)	734	2740	1430	5551	0.016 (-0.023 to 0.056)	.43



High-vancomycin minimum inhibitory concentration (MIC) was defined as greater than or equal to 1.5 ug/mL. The size of each data marker indicates the relative weight of each study.

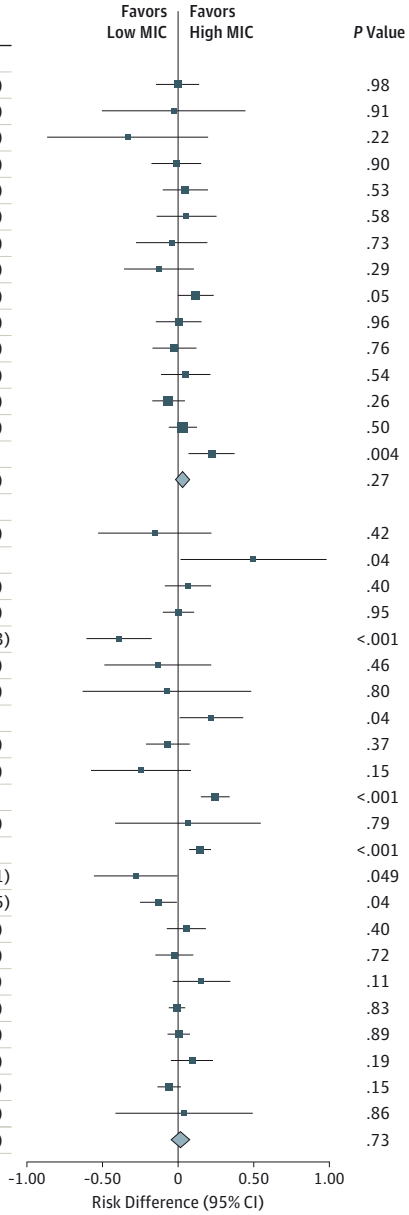
ies did and showed the following results. The presence of heteroresistance for high-vancomycin MIC (n = 166 patients; mortality, 30.7%) vs low-vancomycin MIC (n = 807 patients; mortality, 35.4%) showed an RD of −7.0% (95% CI, −14.6% to 0.6%), *P* = .07, and T^2 = 0. The absence of heteroresistance reporting for high-vancomycin MIC (n = 885; mortality, 27.9%) vs low-vancomycin MIC (n = 2263; mortality, 20.6%) showed an RD of 1.2% (95% CI, −6.7% to 9.0%), *P* = .77, and T^2 = 0.001. The unavailable heteroresistance information for high-vancomycin MIC (n = 1689; mortality, 25.8%) vs low-vancomycin MIC (n = 2481; mortality, 27.4%) showed an RD of 1.9% (95% CI, −2.0% to 5.9%), *P* = .33, and T^2 = 0.002. Heteroresistance was further analyzed by the type of measurement, ie, for population-based for high-vancomycin MIC (n = 122; mortality, 25.4%) vs low-vancomycin MIC (n = 510; mortality, 28.4%), the RD was −2.5% (95% CI, −17.2% to 12.1%), *P* = .74, and T^2 = 0.011; and not population-based for high-vancomycin MIC (n = 135; mortality, 34.1%) vs low-vancomycin MIC (n = 564; mortality, 35.9%), the RD was 1.9% (95% CI, −7.2% to 11%), *P* = .68, and T^2 = 0.

Methicillin Susceptibility Status and Mortality Outcome

Vancomycin MIC values were not associated with mortality when evaluated by methicillin resistance status for high-vancomycin MIC (≥1.5 mg/L; n = 2384; mortality, 27.6%) vs low-vancomycin MIC (n = 4848; mortality, 27.4%), which showed an RD of 1.6% (95% CI, −2.3% to 5.5%), *P* = .41, and T^2 = 0.005. In studies with outcomes for both methicillin-

Figure 3. Risk Difference for Hospital, 30-Day, and Overall Mortality for High-Vancomycin MIC vs Low-Vancomycin MIC

Source	High MIC, No. Deaths	High MIC, No. Total	Low MIC, No. Deaths	Low MIC, No. Total	Risk Difference (95% CI)	*P* Value
Hospital Mortality						
Schwaber et al,[18] 2003	16	61	23	87	-0.002 (-0.146 to 0.142)	.98
Howden et al,[20] 2004	4	7	6	10	-0.029 (-0.505 to 0.447)	.91
Maor et al,[21] 2007	2	4	10	12	-0.333 (-0.867 to 0.200)	.22
Liao et al,[23] 2008	13	40	46	137	-0.011 (-0.176 to 0.155)	.90
Musta et al,[30] 2009	14	43	67	242	0.049 (-0.102 to 0.200)	.53
Maor et al,[29] 2009	14	27	103	223	0.057 (-0.143 to 0.256)	.58
Bae et al,[26] 2009	13	37	11	28	-0.042 (-0.279 to 0.196)	.73
Lalueza et al,[32] 2010	2	13	14	50	-0.126 (-0.358 to 0.106)	.29
Neuner et al,[36] 2010	21	76	19	120	0.118 (-0.002 to 0.238)	.05
Walraven et al,[47] 2011	21	69	21	70	0.004 (-0.148 to 0.157)	.96
Khatib et al,[44] 2011	8	36	60	245	-0.023 (-0.169 to 0.123)	.76
Yeh et al,[52] 2012	27	62	30	78	0.051 (-0.113 to 0.215)	.54
Rojas et al,[51] 2012	102	240	59	121	-0.063 (-0.171 to 0.046)	.26
Miller et al,[50] 2012	36	111	170	583	0.033 (-0.062 to 0.127)	.50
Yoon et al,[55] 2014	36	87	9	47	0.222 (0.069 to 0.375)	.004
Overall (z score = 1.102; P = .27; T^2 = 0.001)	329	913	648	2053	0.025 (-0.019 to 0.068)	.27
30-d Mortality						
Charles et al,[19] 2004	1	5	17	48	-0.154 (-0.530 to 0.222)	.42
Neoh et al,[22] 2007	2	2	8	16	0.500 (0.016 to 0.984)	.04
Lodise et al,[24] 2008	12	66	3	26	0.066 (-0.088 to 0.221)	.40
Soriano et al,[25] 2008	26	92	90	322	0.003 (-0.101 to 0.107)	.95
Price et al,[31] 2009	1	20	11	25	-0.390 (-0.607 to -0.173)	<.001
Fong et al,[27] 2009	5	10	19	30	-0.133 (-0.488 to 0.221)	.46
Jang et al,[28] 2009	1	3	13	32	-0.073 (-0.633 to 0.487)	.80
Wang et al,[38] 2010	13	26	27	97	0.222 (0.010 to 0.434)	.04
Lin et al,[34] 2010	24	60	78	167	-0.067 (-0.212 to 0.078)	.37
Lewis et al,[33] 2010	0	3	34	139	-0.245 (-0.576 to 0.087)	.15
Takesue et al,[37] 2010	33	97	62	662	0.247 (0.150 to 0.343)	<.001
Moore et al,[35] 2010	4	6	6	10	0.067 (-0.418 to 0.551)	.79
Holmes et al,[42] 2011	48	179	42	344	0.146 (0.073 to 0.220)	<.001
deSanctis et al,[41] 2011	0	4	26	93	-0.280 (-0.558 to -0.001)	.049
van Hal et al,[46] 2011	8	47	66	221	-0.128 (-0.252 to -0.005)	.04
Honda et al,[43] 2011	26	112	9	51	0.056 (-0.075 to 0.186)	.40
Clemens et al,[40] 2011	2	24	10	94	-0.023 (-0.150 to 0.104)	.72
Aguado et al,[39] 2011	6	23	8	76	0.156 (-0.037 to 0.348)	.11
Schweizer et al,[45] 2011	82	619	27	195	-0.006 (-0.061 to 0.049)	.83
Han et al,[49] 2012	21	134	39	258	0.006 (-0.070 to 0.081)	.89
Chen et al,[48] 2012	19	53	63	238	0.094 (-0.047 to 0.235)	.19
Gasch et al,[53] 2013	69	237	110	315	-0.058 (-0.136 to 0.020)	.15
Kan et al,[54] 2014	2	5	14	39	0.041 (-0.414 to 0.496)	.86
Overall (z score = 0.349; P = .73; T^2 = 0.011)	405	1827	782	3498	0.010 (-0.047 to 0.068)	.73



High-vancomycin minimum inhibitory concentration (MIC) was defined as greater than or equal to 1.5 ug/mL. The size of each data marker indicates the relative weight of each study.

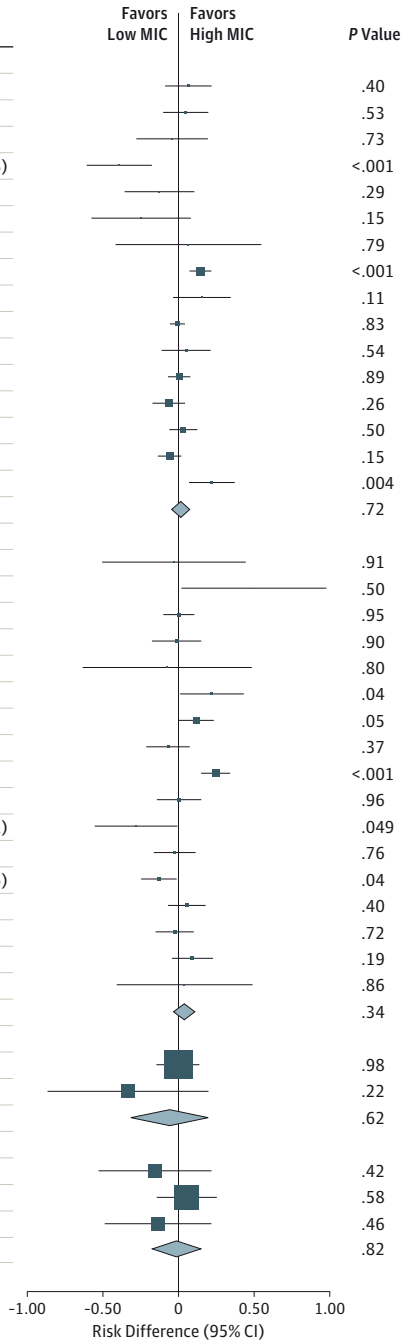
resistant *S aureus* (MRSA) and methicillin-sensitive *S aureus* (MSSA), high-vancomycin MIC (≥1.5 mg/L; n = 356; mortality, 21.3%) vs low-vancomycin MIC (n = 703; mortality, 21.1%) showed an RD of 0.1% (95% CI, −16.6% to 16.4%), P = .99, and T^2 = 0.023. No MSSA-only analysis could be performed since no study reported the mortality outcome separated for MSSA only.

Vancomycin Treatment and Mortality Outcome

Many of the studies reported use of multiple antistaphylococcal drugs according to clinician preference, so outcome analysis related to each specific drug treatment when more than 1 drug was used could not be performed. However, this meta-analysis could stratify the studies by the proportion of patients who received vancomycin treatment. For vancomycin administered to 100% of patients (high-vancomycin MIC: n = 1021; mortality, 31.0% vs low-vancomycin MIC: n = 1868; mortality, 30.6%), RD was 1.1% (95% CI −4.9% to 7.1%), P = .72, and T^2 = 0.007. For vancomycin administered to 50% to 99% of patients (high-vancomycin MIC: n = 1504; mortality, 23.1% vs low-vancomycin MIC: n = 3196; mortality, 22.4%), RD was 1.8% (95% CI, −4.6% to 8.2%), P = .58, and T^2 = 0.011. For vancomycin administered to less than 50% of patients (high-vancomycin MIC: n = 154; mortality, 34.4% vs low-

Figure 4. Mortality by Different MIC Cutoffs and Overall for High-Vancomycin MIC vs Low-Vancomycin MIC

Source	High MIC, No. Deaths	High MIC, No. Total	Low MIC, No. Deaths	Low MIC, No. Total	Risk Difference (95% CI)	P Value
1.50 MIC Cutoff						
Lodise et al,[24] 2008	12	66	3	26	0.066 (-0.088 to 0.221)	.40
Musta et al,[30] 2009	14	43	67	242	0.049 (-0.102 to 0.200)	.53
Bae et al,[26] 2009	13	37	11	28	-0.042 (-0.279 to 0.196)	.73
Price et al,[31] 2009	1	20	11	25	-0.390 (-0.607 to -0.173)	<.001
Lalueza et al,[32] 2010	2	13	14	50	-0 126 (-0.358 to 0.106)	.29
Lewis et al,[33] 2010	0	3	34	139	-0.245 (-0.576 to 0.087)	.15
Moore et al,[35] 2010	4	6	6	10	0.067 (-0.418 to 0.551)	.79
Holmes et al,[42] 2011	48	179	42	344	0.146 (0.073 to 0.220)	<.001
Aguado et al,[39] 2011	6	23	8	76	0.156 (-0.037 to 0.348)	.11
Schweizer et al,[45] 2011	82	619	27	195	-0.006 (-0.061 to 0.049)	.83
Yeh et al,[52] 2012	27	62	30	78	0.051 (-0.113 to 0.215)	.54
Han et al,[49] 2012	21	134	39	258	0.006 (-0.070 to 0.081)	.89
Rojas et al,[51] 2012	102	240	59	121	-0.063 (-0.171 to 0.046)	.26
Miller et al,[50] 2012	36	111	170	583	0.033 (-0.062 to 0.127)	.50
Gasch et al,[53] 2013	69	237	110	315	-0.058 (-0.136 to 0.020)	.15
Yoon et al,[55] 2014	36	87	9	47	0.222 (0.069 to 0.375)	.004
Overall (*z* score = 0.356; *P* value = .72; T^2 = 0.007)	473	1880	640	2537	0.010 (-0.046 to 0.066)	.72
2.00 MIC Cutoff						
Howden et al,[20] 2004	4	7	6	10	-0.029 (-0.505 to 0.447)	.91
Neoh et al,[22] 2007	2	2	8	16	0.500 (0.016-0.984)	.50
Soriano et al,[25] 2008	26	92	90	322	0.003 (-0.101-0.107)	.95
Liao et al,[23] 2008	13	40	46	137	-0.011 (-0.176-0.155)	.90
Jang et al,[28] 2009	1	3	13	32	-0.073 (-0.633 to 0.487)	.80
Wang et al,[38] 2010	13	26	27	97	0.222 (0.010 to 0.434)	.04
Neuner et al,[36] 2010	21	76	19	120	0.118 (-0.002 to 0.238)	.05
Lin et al,[34] 2010	24	60	78	167	-0.067 (-0.212 to 0.078)	.37
Takesue et al,[37] 2010	33	97	62	662	0.247 (0.150 to 0.343)	<.001
Walraven et al,[47] 2011	21	69	21	70	0.004 (-0.148 to 0.157)	.96
deSanctis et al,[41] 2011	0	4	26	93	-0.280 (-0.558 to -0.001)	.049
Khatib et al,[44] 2011	8	36	60	245	-0.023 (-0.169 to 0.123)	.76
van Hal et al,[46] 2011	8	47	66	221	-0.128 (-0.252 to -0.005)	.04
Honda et al,[43] 2011	26	112	9	51	0.056 (-0.075 to 0.186)	.40
Clemens et al,[40] 2011	2	24	10	94	-0.023 (-0.150 to 0.104)	.72
Chen et al,[48] 2012	19	53	63	238	0.094 (-0.047 to 0.235)	.19
Kan et al,[54] 2014	2	5	14	39	0.041 (-0.414 to 0.496)	.86
Overall (*z* score = 0.953; *P* value = .34; T^2 = 0.011)	223	753	618	2614	0.033 (-0.034 to 0.099)	.34
4.00 MIC Cutoff						
Schwaber et al,[18] 2003	16	61	23	87	-0.002 (-0.146 to 0.142)	.98
Maor et al,[21] 2007	2	4	10	12	-0.333 (-0.867 to 0.200)	.22
Overall (*z* score = -0.496; *P* value = .62; T^2 = 0.015)	18	65	33	99	-0.064 (-0.317 to 0.189)	.62
8.00 MIC Cutoff						
Charles et al,[19] 2004	1	5	17	48	-0.154 (-0.530 to 0.222)	.42
Maor et al,[29] 2009	14	27	103	223	0.057 (-0.143 to 0.256)	.58
Fong et al,[27] 2009	5	10	19	30	-0.133 (-0.488 to 0.221)	.46
Overall (*z* score = -0.225; *P* value = .82; T^2 = 0)	20	42	139	301	-0.018 (-0.176 to 0.140)	.82



High-vancomycin minimum inhibitory concentration (MIC) was defined as greater than or equal to 1.5 ug/mL. The size of each data marker indicates the relative weight of each study.

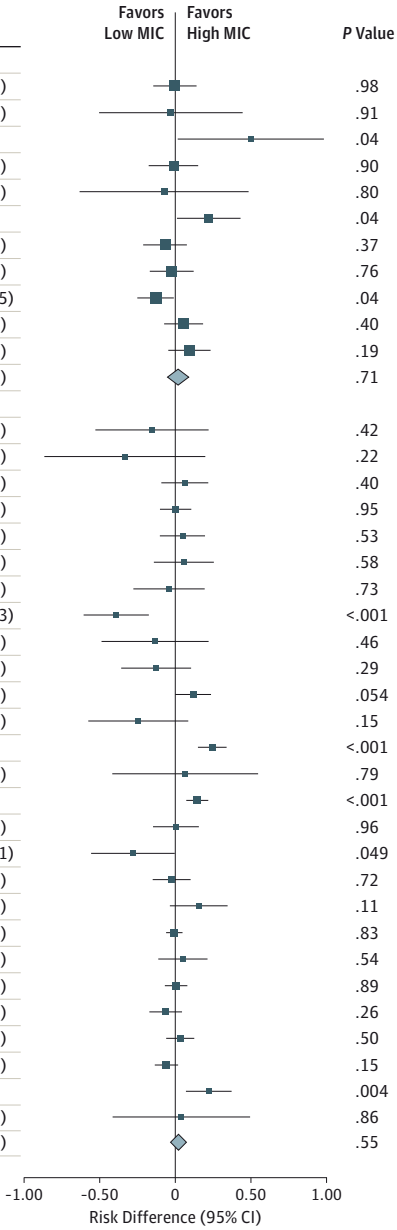
vancomycin MIC: n = 400; mortality, 30.0%), RD was 1.7% (95% CI, −7.1% to 10.5%), *P* = .71, and T^2 = 0. For studies in which vancomycin treatment status was not noted (high-vancomycin MIC: n = 61; mortality, 26.2% vs low-vancomycin MIC: n = 87; mortality, 26.4%), RD was 0.2% (95% CI, −14.6% to 14.2%), *P* = .98, and T^2 = 0.

Year of Publication and Mortality Outcome

To better assess whether evolving changes in the standard of care may have been associated with confounding, an analysis by year of study publication was performed. No significant changes in mortality outcome were observed with year of publication (eFigure 1 in the Supplement).

Figure 5. Mortality by Assay Type and Overall for High-Vancomycin MIC vs Low-Vancomycin MIC

Source	High MIC, No. Deaths	High MIC, No. Total	Low MIC, No. Deaths	Low MIC, No. Total	Risk Difference (95% CI)	P Value
BMD Assay						
Schwaber et al,[18] 2003	16	61	23	87	-0.002 (-0.146 to 0.142)	.98
Howden et al,[20] 2004	4	7	6	10	-0.029 (-0.505 to 0.447)	.91
Neoh et al,[22] 2007	2	2	8	16	0.500 (0.016 to 0.984)	.04
Liao et al,[23] 2008	13	40	46	137	-0.011 (-0.176 to 0.155)	.90
Jang et al,[28] 2009	1	3	13	32	-0.073 (-0.633 to 0.487)	.80
Wang et al,[38] 2010	13	26	27	97	0.222 (0.010 to 0.434)	.04
Lin et al,[34] 2010	24	60	78	167	-0.067 (-0.212 to 0.078)	.37
Khatib et al,[44] 2011	8	36	60	245	-0.023 (-0.169 to 0.123)	.76
van Hal et al,[46] 2011	8	47	66	221	-0.128 (-0.252 to -0.005)	.04
Honda et al,[43] 2011	26	112	9	51	0.056 (-0.075 to 0.186)	.40
Chen et al,[48] 2012	19	53	63	238	0.094 (-0.047 to 0.235)	.19
Overall (z score = 0.372; P value = .71; T^2 = 0.004)	134	447	399	1301	0.013 (-0.055 to 0.081)	.71
Etest Assay						
Charles et al,[19] 2004	1	5	17	48	-0.154 (-0.530 to 0.222)	.42
Maor et al,[21] 2007	2	4	10	12	-0.333 (-0.867 to 0.200)	.22
Lodise et al,[24] 2008	12	66	3	26	0.066 (-0.088 to 0.221)	.40
Soriano et al,[25] 2008	26	92	90	322	0.003 (-0.101 to 0.107)	.95
Musta et al,[30] 2009	14	43	67	242	0.049 (-0.102 to 0.200)	.53
Maor et al,[29] 2009	14	27	103	223	0.057 (-0.143 to 0.256)	.58
Bae et al,[26] 2009	13	37	11	28	-0.042 (-0.279 to 0.196)	.73
Price et al,[31] 2009	1	20	11	25	-0.390 (-0.607 to -0.173)	<.001
Fong et al,[27] 2009	5	10	19	30	-0.133 (-0.488 to 0.221)	.46
Lalueza et al,[32] 2010	2	13	14	50	-0.126 (-0.358 to 0.106)	.29
Neuner et al,[36] 2010	21	76	19	120	0.118 (-0.002 to 0.238)	.054
Lewis et al,[33] 2010	0	3	34	139	-0.245 (-0.576 to 0.087)	.15
Takesue et al,[37] 2010	33	97	62	662	0.247 (0.150 to 0.343)	<.001
Moore et al,[35] 2010	4	6	6	10	0.067 (-0.418 to 0.551)	.79
Holmes et al,[42] 2011	48	179	42	344	0.146 (0.073 to 0.220)	<.001
Walraven et al,[47] 2011	21	69	21	70	0.004 (-0.148 to 0.157)	.96
deSanctis et al,[41] 2011	0	4	26	93	-0.280 (-0.558 to -0.001)	.049
Clemens et al,[40] 2011	2	24	10	94	-0.023 (-0.150 to 0.104)	.72
Aguado et al,[39] 2011	6	23	8	76	0.156 (-0.037 to 0.348)	.11
Schweizer et al,[45] 2011	82	619	27	195	-0.006 (-0.061 to 0.049)	.83
Yeh et al,[52] 2012	27	62	30	78	0.051 (-0.113 to 0.215)	.54
Han et al,[49] 2012	21	134	39	258	0.006 (-0.070 to 0.081)	.89
Rojas et al,[51] 2012	102	240	59	121	-0.063 (-0.171 to 0.046)	.26
Miller et al,[50] 2012	36	111	170	583	0.033 (-0.062 to 0.127)	.50
Gasch et al,[53] 2013	69	237	110	315	-0.058 (-0.136 to 0.020)	.15
Yoon et al,[55] 2014	36	87	9	47	0.222 (0.069 to 0.375)	.004
Kan et al,[54] 2014	2	5	14	39	0.041 (-0.414 to 0.496)	.86
Overall (z score = 0.599; P value = .55; T^2 = 0.008)	600	2293	1031	4250	0.015 (-0.033 to 0.062)	.55



BMD indicates broth microdilution; Etest, epsilometer test. High-vancomycin minimum inhibitory concentration (MIC) was defined as greater than or equal to 1.5 ug/mL. The size of each data marker indicates the relative weight of each study.

Quality of Study Design and Mortality Outcome

In analysis in which studies were grouped according to the strength of study design, no mortality differences were noted between prospective cohorts, retrospective cohorts, case-controls, and case-series designs (eFigure 2 in the Supplement and see eReferences in the Supplement for eFigures references).

Sensitivity Analysis

Because the case-series design is known to be more prone to selection bias than cohort and case-control studies, an analysis was performed without studies that used case-series design (high-vancomycin MIC: n = 2722; mortality, 26.6% vs low-vancomycin MIC: n = 5483; mortality, 25.5%) in which the RD was 1.2% (95% CI, −2.7% to 5.1%), P = .54, and T^2 = 0.007. A sensitivity analysis was performed that excluded studies using either case-control or case-series methodology (high-vancomycin MIC: n = 2695; mortality, 26.3% vs low-vancomycin MIC: n = 5260; mortality, 24.6%) in which the RD was 1.0% (95% CI, −2.9% to 5.0%), P = .60; and T^2 = 0.008. Additionally, a study quality analysis found similar results when the analysis was restricted to the highest-quality studies (Newcastle-Ottawa scale based with scores of 8-9) (high-

vancomycin MIC: n = 2318; mortality, 26.2% vs low-vancomycin MIC: n = 4168; mortality, 27.8%) showing an RD of 0.9% (95% CI, −2.9% to 4.6%), $P = .65$, and $T^2 = 0.002$.

Meta-regression

Several factors that could have been associated with the mortality outcome (represented as the RD in the y-axis) were analyzed as continuous predictor variables (x-axis). The factor noted to be significantly related to mortality in the high-vancomycin MIC group was percent mortality in the low-vancomycin MIC group (eFigure 3 in the Supplement) in which y = −0.139 − 0.0045 (95% CI, −0.0075 to −0.0015)* ×; $P = .003$. Because disease severity scores were only reported in a few studies, the control group (low-vancomycin MIC) mortality was considered a surrogate measure of the baseline disease severity. Other factors of clinical importance analyzed as continuous variables were as follows: age ($P = .57$); Charlson score ($P = .08$); vancomycin MIC cutoff ($P = .54$); vancomycin exposure in the previous 6 months ($P = .88$); vancomycin trough levels ($P = .92$); duration of bacteremia ($P = .11$); proportion of patients with endocarditis ($P = .57$); proportion of patients hospitalized in the ICU ($P = .09$); and proportion of patients who received vancomycin treatment ($P = .24$). See eAppendix 2 in the Supplement for the metaregression equations and eTable 2 in the Supplement for the metaregression variables.

Publication Bias Analysis

No significant bias was detected by using Egger regression analysis: intercept = −0.472, standard error = 0.525, $P = .37$, or by Begg and Mazumdar rank correlation: $\tau = -0.045$, $z = 0.402$, $P = .69$.

Discussion

The main finding of this meta-analysis of 8291 episodes of SAB was that there were no statistically significant differences in the risk of death when comparing patients with *S aureus* isolates exhibiting high-vancomycin MIC (≥1.5 mg/L) to those with low-vancomycin MIC (<1.5 mg/L), although the findings cannot definitely exclude an increased mortality risk. This conclusion remained consistent independent of different MIC cutoffs, microbiological susceptibility assays, methicillin susceptibility status, vancomycin heteroresistance, presence of endocarditis, previous exposure to vancomycin, and treatment with vancomycin. The large sample size and the low degree of heterogeneity among studies further support this conclusion.

The primary potential explanation cited for the association of elevated vancomycin MIC values with outcomes focuses on pharmacokinetic indices. Elevations in vancomycin MIC may influence pharmacokinetic targets and studies have suggested that when MIC values are greater than 1 mg/L, achievement of area under the concentration-time curve (AUC) MIC target levels would be unlikely. Because the majority of persons with SAB are at least initially treated with vancomycin, it would be expected that as the MIC increases, outcomes would worsen.[56,57] In the present study, elevated vancomycin MICs were not significantly associated with increased mortality although the upper bound of the CI surrounding the point estimate for the RD was consistent with as much as a 5.6% increase in mortality risk associated with high-vancomycin MIC vs low-vancomycin MIC. There are several possible explanations for these findings.

First, despite the narrow 95% CI of the overall results in this study, the final interval shows that either increases or decreases in mortality could be associated with high-vancomycin MICs. One explanation for a possible increase in mortality that has been suggested is the difficulty in achieving adequate vancomycin AUC–MIC ratios when *S aureus* isolates have an elevated MIC value. However, the fact that the mortality outcome was not increased in patients with high-vancomycin MICs who received vancomycin compared with those who did not receive vancomycin suggests that achievement of pharmacokinetic targets may not be an accurate predictor of mortality. Importantly, the meta-regression showed no mortality dose-effect based on increasing MICs when control mortality was evaluated as a continuous variable. The other possibility, a mortality decrease with high-vancomycin MICs, could be explained by the fact that strains with high-vancomycin MICs could be less virulent than strains with low-vancomycin MICs. This mortality reduction has been observed by others,[46] as well as by this study's results of the hVISA subanalysis which suggested a lower mortality with higher MICs.

Second, the current Clinical and Laboratory Standards Institute (CLSI) vancomycin susceptibility breakpoints[58] are necessarily somewhat subjective and may not accurately correlate with clinical outcomes, or the MIC values reported in the literature may be erroneous due to testing methodology.[59] For example, MIC values have been shown to vary based on the testing method and duration of isolate storage.[60]

Third, outcomes of patients with SAB also are related to various clinical confounding factors such as source control (eg, removal of infected vascular catheters, drainage of abscesses) and these factors may be more important in determining mortality than the vancomycin MIC.[61] In the regression analysis of this present study, a correlation between the level of mortality in the patients with SAB due to low-vancomycin MIC and the overall mortality of all patients in the study was noted. For every 1% increase in mortality in the low-vancomycin MIC group, there was a 0.45% decrease in the absolute RD between low- and high-vancomycin MIC groups. This may suggest underlying differences in severity of illness in the study population or differences related to features of care such as source control.

Fourth, elevations in vancomycin MIC appear to be associated with alterations in *S aureus* cellular function such as cell wall changes and transcriptional alterations that may modulate virulence and microbiologic fitness. For example, Soriano et al[25] noted that patients infected with high-vancomycin MIC strains were less likely to experience hypotension and shock, while Holmes et al[42] observed that elevations in vancomycin MIC appeared to be associated with outcomes even in patients infected with MSSA who were treated exclusively with semisynthetic penicillins. In support of this, infections due to

hVISA, rather than being associated with increased mortality, may actually be associated with decreased mortality.[46] A recent systematic review of hVISA infections found that despite being associated with increased rates of treatment failure, there was no association between hVISA infection and increased mortality.[62] Thus, subtle increases in vancomycin MIC that continue to be within the susceptible range may be a surrogate marker for intrinsic microbiologic traits and not associated with worsened clinical outcomes.[63]

The findings of this meta-analysis differ from the findings from 3 previous ones.[6-8] The difference in conclusions from other published meta-analyses may be related to differences in study design. The previous meta-analyses evaluated outcomes in patients with staphylococcal infections from various sites including skin and soft tissue, urinary tract, lungs, abdomen, and bloodstream. This would be predicted to result in significant clinical heterogeneity because mortality outcomes vary greatly between sites such as skin and soft-tissue infections and pneumonia. The present study was the first, to our knowledge, to prospectively include only patients with SAB; this improved clinical homogeneity made analysis more comparable from both the pathogenesis and clinical perspectives. In addition, the present study included the largest number of studies (N = 38) and SAB infection episodes (N = 8291) to date, which increased the statistical precision as seen by the narrow CIs. Moreover, other meta-analyses have not evaluated and adjusted for the relationship between mortality and important clinical comorbidities that commonly accompany SAB such as ICU hospitalization, presence of endocarditis, duration of bacteremia, previous vancomycin exposure, vancomycin trough levels, treatment with vancomycin, and baseline disease severity.

The findings of this study may have implications for clinical practice and public health: (1) the Clinical and Laboratory Standards Institute (CLSI) interpretive standards for vancomycin MIC most likely do not need to be lowered; (2) routine differentiation of MIC values between 1 mg/L and 2 mg/L appears unnecessary; and (3) the use of alternative antistaphylococcal agents may not be required for *S aureus* isolates with elevated but susceptible vancomycin MIC values. These conclusions are consistent with current Infectious Disease Society of America treatment guidelines that recommend use of vancomycin for treatment of MRSA bacteremia with consideration for alternative agents based on the patient's clinical response and not the MIC.[64] Investigational drugs thought to be alternatives to vancomycin should be assessed in well-designed and appropriately powered clinical trials. Rather than focusing on MIC values, clinicians providing care for patients with SAB should ensure that patients are evaluated for occult sources of infection, have drainable and removable sources of infection eliminated, and are treated for the appropriate duration of therapy.

This study should be interpreted in the context of several limitations. First, the clinical response to treatment was not assessed. The authors prospectively agreed to this approach based on the observational nonblinded nature of this assessment and its susceptibility to bias. In addition, the criteria used to assess clinical response varied substantially among studies, precluding appropriate pooling of the data. The choice to avoid the use of more ambiguous outcomes (ie, clinical response) and to prioritize the evaluation of the most clinically relevant and precisely measured outcome (ie, mortality) may have contributed to more reliability and generalizability to its findings. Second, the possibility that nonmortality outcomes may be associated with vancomycin MIC cannot be excluded. Third, most studies were retrospective in design, and this may have introduced inherent selection bias into this report. Fourth, the use of stored *S aureus* isolates for MIC measurement may affect MIC values. Ludwig et al[65] found mean MIC values in 36 *S aureus* isolates decreased from 1.21 to 0.65 mg/L over 9 months of freezer storage. Changes such as these may affect MIC interpretation, particularly when values are within a narrow range of assessment (0.5-2.0 mg/L). Fifth, treatment choices were not standardized and varied between studies; however, when analyzed by use of vancomycin, this study found no association between vancomycin MIC values and mortality. Sixth, it was not possible to obtain severity of illness scores for all studies, but a clinically relevant surrogate marker—mortality rate in the low-vancomycin MIC group—was significantly associated with mortality in the high-vancomycin MIC group. Seventh, type 1 error cannot be excluded due to the multiple analyses performed for this study. Eighth, the 95% upper bound of CI of this study suggests that a potential higher mortality rate (≤5.6%) with high-vancomycin MIC may have not been detected by this study, and further studies are needed to evaluate the possibility of this increased risk and its potential clinical importance.

Some may reason that the best means to determine whether high-vancomycin MIC levels are associated with increased mortality would be by performing an adequately powered randomized clinical trial. However, such a clinical trial may not be advisable for the following reasons: (1) ethical issues: adding or withholding different antibiotic treatments based on arbitrary MIC cutoffs may not be permissible by ethical review committees; (2) logistical issues: a recent trial[66] evaluating the efficacy of daptomycin for SAB conducted in 44 hospitals in several countries required nearly 3 years to randomize 246 patients; hence to enroll several thousand patients in such a trial most likely would require years; and (3) financial issues: the costs to design and execute a trial with thousands of patients infected with *S aureus* would be prohibitive to both pharmaceutical and governmental funding agencies.

Conclusions

In this meta-analysis of SAB episodes, there were no statistically significant differences in the risk of death when comparing patients with *S aureus* exhibiting high-vancomycin MIC (≥1.5 mg/L) vs those with low-vancomycin MIC (<1.5 mg/L), although the findings cannot definitely exclude an increased mortality risk. These findings should be considered when interpreting vancomycin susceptibility and in determining whether alternative antistaphylococcal agents are necessary for patients with SAB with elevated but susceptible vancomycin MIC values.

ARTICLE INFORMATION

Author Contributions: Dr Kalil had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kalil.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Administrative, technical, or material support: All authors.

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