MAJOR ARTICLE

The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in *Staphylococcus aureus* Infections: A Systematic Review and Meta-analysis

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(See the Editorial Commentary by Deresinski, on pages 772–4.)

Background. Emerging data suggest that vancomycin may be less effective against serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections with minimum inhibitory concentration (MIC) values at the higher end of the susceptibility range. The purpose of this review is to examine the strength of these associations.

Methods. All relevant studies pertaining to treatment outcomes or mortality associated with vancomycin MIC were retrieved from the medical literature from January 1996 through August 2011 and analyzed according to Cochrane guidelines.

Results. Of the 270 studies identified, 48 studies were reviewed, with 22 studies included in the final meta-analysis. Vancomycin MIC was significantly associated with mortality for MRSA infection irrespective of the source of infection or MIC methodology (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.14–2.37; $P < .01$). This mortality association was predominantly driven by bloodstream infections (BSIs; OR, 1.58; 95% CI, 1.06–2.37; $P = .03$) and isolates with a vancomycin MIC of 2 μg/mL by Etest (OR, 1.72; 95% CI, 1.34–2.21; $P < .01$). Vancomycin MIC was significantly associated with treatment failure irrespective of source of infection or MIC methodology (OR, 2.69; 95% CI, 1.60–4.51; $P < .01$).

Conclusion. High vancomycin MIC was associated with a higher mortality rate in MRSA BSI. Thus, institutions should consider conducting Etest MICs on all MRSA BSI isolates. Although these data highlight concerns about vancomycin, currently, there are no data to support better survival rates with alternative antibiotics. Data are sorely needed to determine whether other agents can remedy these outcomes observed with vancomycin for MRSA infections with elevated vancomycin MIC values.

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are a major public concern. Hospital-acquired MRSA infection rates have steadily increased over the past 25 years, and the bacterial strain is making inroads to the community [1–6]. Vancomycin is currently the cornerstone of therapy for serious infections caused by this pathogen. Although vancomycin has been widely used in the treatment of MRSA infection for the past 2 decades [7], the majority of MRSA strains have remained susceptible to vancomycin at the current minimum inhibitory concentration (MIC) susceptibility breakpoint designated by the Clinical Laboratory Standards Institute (CLSI) [2]. It has taken approximately 40 years for the first isolates with reduced susceptibility to glycopeptides to emerge.

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Despite its sustained in vitro microbiologic inhibitory activity, researchers are beginning to question the continued clinical usefulness of vancomycin for MRSA infection. In particular, emerging data suggest that vancomycin may be less effective against serious MRSA infection with MIC values at the higher end of the susceptibility range. Although the CLSI susceptibility breakpoint has been reduced to 2 ug/mL (previously 4 ug/mL), the increased rate of failures reported for MRSA infection at 2 mg/L has prompted a debate about whether the MIC breakpoints should be decreased even further. The consequence of such a decision would be to reduce the role of vancomycin substantially, if not relegate it to the antibiotic scrapheap, especially in institutions documenting vancomycin MIC creep [8]. The purpose of this review is to examine the strength of these associations and identify the future role of vancomycin.

METHODS

Search Strategy and Selection Criteria

Studies were retrieved from PubMed, Embase, Cochrane Controlled Trial Registry, and Medline databases from January 1996 through August 2011. Search terms included "*Staphylococcus aureus*" or "*S. aureus*" or "methicillin resistant *Staphylococcus aureus*," "vancomycin" and "minimum inhibitory concentration" or "MIC" in combination with "mortality" or "death." Similar searches were performed for clinical or microbiological treatment failure with the terms "*Staphylococcus aureus*," "vancomycin," and "minimum inhibitory concentration" or "MIC" in combination with any one of the following: "treatment failure," "outcome," "persistent bacteremia," or "microbiological failure." References were also identified from the bibliographies of studies retrieved from the aforementioned literature search.

The abstracts of all studies were reviewed. A study was considered to be eligible for inclusion if outcomes of interest were presented for *S. aureus* infections by vancomycin MIC strata. The MIC methodologies considered to be appropriate included broth microdilution (BMD), automated BMD, and Etest. In contrast, studies using agar dilution and disc diffusion for vancomycin MIC measurements were excluded because these methods are no longer considered to be accurate [9]. In addition, authors were contacted (wherever possible) to provide further details on mortality, treatment failure, or MIC methodology used. Studies written in languages other than English and those presented solely as abstracts at scientific conferences were excluded.

Data Extraction, Outcomes, and Data Analysis

Data extracted from the identified studies included clinical setting, number of patients studied, *S. aureus* infection type, breakdown of *S. aureus* episodes by susceptibility pattern, MIC methodology used, vancomycin treatment duration, microbiological failure, treatment failure, and patient mortality. The bacteremic source was further classified into 3 mortality risk categories: high-risk (which included endovascular, lower respiratory tract, abdominal, and CNS foci), intermediate-risk (which included osteoarticular, soft-tissue, and unknown foci), and low-risk sources (which included intravenous catheter and urinary tract foci).

The primary outcome was all-cause 30-day mortality. Secondary predefined outcomes were treatment or microbiological failure. For treatment failure, the definition in each study was used. Heteroresistant vancomycin-intermediate *S. aureus* (hVISA) infections were excluded from the analysis when these details were present in the relevant studies.

Data analysis was performed using RevMan version 5.1 for Windows [10], and performed according to Cochrane guidelines. Odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables were calculated. Meta-analysis was performed using fixed-effects models, unless significant heterogeneity was observed, in which case random-effects models were used. Heterogeneity was assessed using the χ^2 test, with the extent of inconsistency assessed using I^2 statistics. A P value of .05 was regarded as statistically significant. Predetermined subgroup analyses were performed on the basis of MIC methodology, *S. aureus* infection type, and *S. aureus* characterized by susceptibility pattern.

RESULTS

Our literature search identified 270 studies (Figure 1), of which 48 studies were reviewed [11–58]. Of these, 25 studies were included in the meta-analysis (Table 1). Twenty-three studies were excluded for the following reasons: no MIC data were presented against outcomes (11 studies) [16, 24, 27, 29, 30, 31, 33, 46, 51, 56, 57], inappropriate MIC testing methodology was used (3 studies) [13, 35, 44], case reports (2 studies) [11, 38], and nonrelevance (7 studies) [14, 18, 20, 22, 28, 37, 40].

Of the 25 studies that made the preliminary eligibility cut, 3 were excluded from the meta-analysis because all used different MIC cutoffs [39, 48, 49]. The study by Rubenstein et al [48] did not have any isolates with a vancomycin MIC >1 μg/mL in the vancomycin-treated arm. The study by Sakoulas et al [49] combined isolates with vancomycin MICs of 1 μg/mL and 2 μg/mL into 1 group, and the data available did not allow for separation into 2 distinct categories. Thus, a total of 22 studies were included in this meta-analysis, subsets of which were also analyzed to answer specific inquiries as described next.

Overall 30-Day Mortality

Seventeen of the 22 studies provided data on mortality and vancomycin MICs involving 3332 MRSA-infected and 517

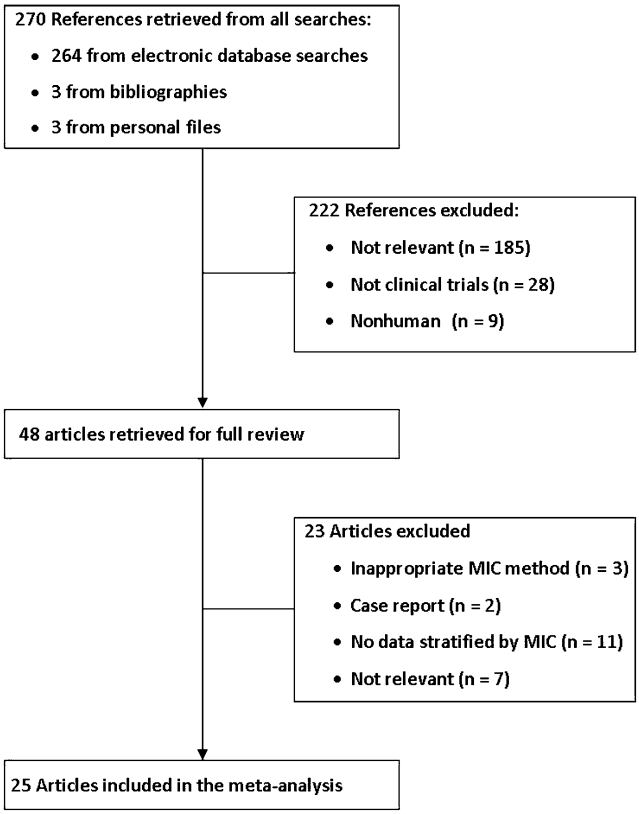

Figure 1. Quality of reporting of meta-analysis profile showing flow of studies included in the meta-analysis. Abbreviation: MIC, minimum inhibitory concentration.

methicillin-susceptible *S. aureus* (MSSA)–infected patients [12, 15, 19, 23, 26, 32, 34, 36, 43, 45, 47, 50, 52–55, 58]. From these episodes, there were 2383 MRSA and 507 MSSA bloodstream infections (BSIs), and 949 MRSA and 10 MSSA non-BSIs.

All 17 studies provided mortality data for high MIC (≥1.5 μg/mL) relative to low vancomycin MIC infections (<1.5 μg/mL; Table 1). When pooling all the data irrespective of the source of infection, antimicrobial susceptibility (MSSA and MRSA), or MIC methodology, vancomycin MIC was not associated with mortality among those with *S. aureus* infection (OR, 1.41; 95% CI, .95–2.10; $P = .09$). This finding did not change if data was pooled by source of infection: BSI (OR, 1.36; 95% CI, .86–2.1.5; $P = .19$), compared with non-BSI (OR, 1.47; 95% CI, .88–2.47; $P = .14$). Vancomycin MIC was not associated with increased mortality in MSSA BSI episodes (OR, 0.65; 95% CI, .65–10.49; $P = .76$).

Vancomycin MIC was significantly associated with mortality associated with MRSA infection irrespective of the source of infection or MIC methodology (OR, 1.64; 95% CI, 1.14–2.73; $P < .01$) (Figure 2) when patients with MSSA infection were excluded (study by Price et al [47] and the MSSA subsets from Schweizer et al [50] and Holmes et al [23]). This association was secondary to BSI (OR, 1.58; 95% CI, 1.06–2.37; $P = .03$), because vancomycin MIC was not a predictor of mortality associated with non-BSI (OR, 1.42; 95% CI, .82–2.43; $P = .21$).

Except for 2 studies [34, 55], Etest was the methodology used for MIC determination. After limiting the data to Etest vancomycin MIC testing only, MRSA BSI was no longer associated with increased mortality (OR, 1.52; 95% CI, .95–2.24; $P = .08$).

Eight studies, each of which used Etest, provided mortality data for high MIC infections stratified into 1.5 and ≥2 μg/mL categories [12, 19, 23, 43, 45, 47, 50, 52, 54] (Table 2). There was no statistically significant difference in mortality associated with *S. aureus* infection with a vancomycin MIC of 1.5 μg/mL compared with an MIC ≤1 μg/mL (OR, 1.11; 95% CI, .84–1.45; $P = .45$; Figure 3). However, an Etest MIC ≥2 μg/mL was significantly associated with an increased mortality (OR, 1.74; 95% CI, 1.34–2.21; $P < .01$; Figure 4). These associations remained when limiting the data to any MRSA infection or MRSA BSI only.

Although the proportion of high- and low-risk BSI sources was similar among studies (Table 1), no study stratified MIC data by source of bacteremia, thus it remains unclear whether a high MIC line-related BSI (low risk) has similar implications to a high MIC endovascular BSI (high risk).

Treatment Failure

Eleven of the 22 studies provided data on treatment failure and vancomycin MIC involving 1439 MRSA-infected (552 BSI; 887 non-BSI) and 0 MSSA-infected patients [12, 15, 17, 21, 25, 32, 36, 41, 42, 53, 58]. Although definitions varied among studies (Table 1), vancomycin MIC was significantly associated with treatment failure (OR, 2.69; 95% CI, 1.60–4.51; $P < .01$; Figure 5). This association did not change substantively when excluding studies enriched for vancomycin failure [41, 42] (OR, 2.22; 95% CI, 1.30–3.79; $P < .01$) or when excluding studies using non-Etest MIC methodology (OR, 2.12; 95% CI, 1.14–3.96; $P = .02$) [17, 41, 42, 58]. Likewise, the association between vancomycin MIC and treatment failure did not change substantially when pooling studies using similar treatment failure definitions. When limited to studies that examined persistent bacteremia [12, 32, 36, 41, 58], the OR for high vancomycin MIC was 2.44, but the 95% CI spanned zero (95% CI, .72–8.24; $P = .15$) [12, 32, 36, 41, 58]. Similarly, the OR was 2.81 (95% CI, 1.73–4.59; $P < .01$) when the analysis was restricted to studies that focused on clinical failure [15, 17, 21, 25, 42]. Similar to the mortality analysis, treatment failure was more likely to occur in MRSA BSI episodes (OR, 2.91; 95% CI, 1.26–6.72; $P = .01$) than in non-BSI episodes (OR, 1.96; 95% CI, 1.25–3.07; $P < .01$). Similar to the mortality analysis, treatment failure was more likely to occur in MRSA BSI episodes (OR, 2.91; 95% CI, 1.26–6.72; $P = .01$) than in non-BSI episodes (OR, 1.96; 95% CI, 1.25–3.07; $P < .01$).

Table 1. Characteristics of Eligible Studies Examining the Association Between Outcomes and Vancomycin Minimum Inhibitory Concentration

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Comments
Bae et al [12]	Prospective, multicenter study (ICE)	65 (0)	BSI High risk: 100%[c]	Etest	39% (11/28)	35% (13/37)	.24	Persistent bacteremia despite >3 d of antibiotics	43% (12/28)	49% (18/37)	.19	hVISA (detected by PAP-AUC method) present in 19 (29%) MRSA isolates
Choi et al [15]	Retrospective, single-center, vancomycin-treated (>48 h) cohort study	70 (0)	HAP	Etest	17% (6/36)	12% (4/34)	.62	Early treatment response (5 d): reduction in pulmonary infection score to <6 or ≥2 from baseline	36% (13/36)	65% (22/34)	.03	
Choi et al [15]								End of treatment response: resolution of clinical signs and symptoms	28% (10/36)	35% (12/34)	.61	
Ferry et al [17]	Retrospective single-center cohort study	52 (0)	ODI	BMD	…	…	…	Persistent infection, recurrence, limb loss or death	47% (9/19)	60% (9/15)	.54	
Haque et al [19]	Analysis of vancomycin-treated (>24 h) MRSA episodes selected from prospective multicenter IMPACT-HAP ICU study	158 (0)	HAP	Etest	23% (10/43)[b]	36% (41/115)[b]	ND		…	…	…	Propensity score analysis: 3-fold (OR 3.7; 95% CI, 1.45–9.62; $P < .01$) increase in mortality with 1 μg/mL increase in MIC

Table 1 continued.

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Comments
Hidayat et al [21]	Prospective, single-center, vancomycin-treated(>72 h) cohort study	95 (0)	Any 25% (24/95) BSI High- and low-risk BSI sources: ND	Etest	9% (4/44)	24% (12/51)	.9	No improvement or worsening of signs and symptoms of infection	16% (7/44)	39% (20/51)	.01	Greater number of patients with pneumonia and bacteremia in high vancomycin MIC group (≥1.5 μg/mL; *P* = .02) with greater failure in this subgroup vs other infection types
Holmes et al [23]	Prospective multicenter study cohort study	199 (0)	BSI High Risk: 32% Low Risk: 27%	Etest	15% (16/105)	30% (28/94)	<.05	Not studied				hVISA screening performed using GRD Etest on MIC 2 μg/mL isolates (0.4% positive)
Holmes et al [23]	Prospective multicenter study cohort study	0 (324)	BSI High risk: 24%[c] Low Risk: 19%	Etest	11% (26/239)	24% (20/85)	<.01	Not studied				
Hsu et al [25]	Prospective, single-center, vancomycin-treated (>72h) cohort study	83 (0)	Any 24% (20/83) BSI High- and low-risk BSI sources: ND	Etest	…	…	…	No improvement or worsening of signs and symptoms of infection	11% (4/38)	38% (17/45)	.03	Comparison of BMD, Etest, and automated platforms: Etest most reliable predictor of treatment re sponse
Huang et al [26]	Retrospective, single-center cohort study	24 (13)	CNS	Etest	67% (12/18)	82% (9/11)	.67	Not studied	…	…	…	8-year study examining patients with *S. aureus* meningitis; concurrent bacteremia in 10 (36%) cases.

Table 1 continued.

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Comments
Lalueza et al [32]	Retrospective, single-center cohort study	63 (0)	BSI High Risk: 6% Low Risk 44%	Etest	28% (14/50)	15% (2/13)	.57	Breakthrough bacteremia after 3 d of therapy	34% (17/50)	23% (3/13)	.67	High MIC isolates associated with less sepsis ($P = .005$)
Liao et al [34]	Retrospective single-center study	177 (0)	BSI High risk: 27% Low risk: 28%	BMD	34% (46/137)	33% (13/40)	ND	Not studied	…	…	…	
Lodise et al [36]	Retrospective, single-center, vancomycin-treated (>24 h) cohort study	92 (0)	BSI High- and low-risk sources: ND	Etest	12% (3/26)	18% (12/66)	.5	Microbiological failure: blood culture growing MRSA after 10 d of appropriate antibiotic therapy	0% (0/26)	9% (6/66)	.18	Composite endpoint (mortality, microbiological failure and 60-d recurrence) increased in high MIC (≥1.5 μg/mL) group ($P = .049$)
Moise et al [41]	Analysis of randomly selected (based on presence or absence of *agr*-II) MRSA isolates from compassionate access prospectively collected multicenter isolate re pository[b]	34 (0)	BSI High- and low-risk sources: ND	BMD	…	…	…	Eradication of MRSA from blood culture at end of treatment	25% (5/20)	79% (11/14)	.01	Treatment success and microbiological eradication was associated with increased vancomycin bactericidal activity at 24 h

Table 1 continued.

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Comments
Moise-Broder et al [42]	Analysis of randomly selected vancomycin-treated (≥5 days) MRSA episodes from compassionate access prospectively collected multicenter isolate repository[b]	63 (0)	Any 54% (34/63) BSI High- and low-risk sources: ND	BMD	…	…	…	Persistent, worsening, or appearance of new signs and symptoms of infection	58% (22/38)	92% (23/25)	.04	Non-*agr* group II polymorphism was associated with treatment success (OR 6.94; 95% CI, 1.77–27.11; $P = .005$)
Musta et al [43]	Retrospective, single-center, cohort study with MIC analysis in adequately (trough level ≥10 μg/mL) vancomycin-treated episodes	242 (0)	BSI High- and low-risk sources: ND	Etest	19%[b] (7/36)	29%[b] (60/206)	.05	Not studied	…	…	…	hVISA (determined by Macromethod Etest) episodes excluded from data.[b] Mortality not associated with hVISA
Neuner et al [45]	Retrospective, single-center, vancomycin-treated cohort study	196 (0)	BSI High risk: 18%[c] Low risk: 31%	Etest	10% (1/10)	21% (39/186)	.11	Not studied	…	…	…	High MIC (=2 μg/mL) associated with persistent bacteremia (>5 d) but not mortality

Table 1 continued.

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Comments
Price et al [47]	Prospective single-center study, all patients treated with vancomycin	31 (14)	BSI High- and low-risk sources: ND	Etest	36% (9/25)[b]	5% (1/20)[b]	.022	Not studied	…	…	…	Patients with low MIC (<1.5 μg/mL) were more likely to die at 3 months com pared with high MIC infections (OR 12; 95% CI, 1.7–83; $P < .01$)
Schweizer et al [50]	Retrospective, single-center study, including all MRSA episodes treated with vancomycin	312 (0)[c]	BSI High- and low-risk sources: ND	Etest	18% (3/17)	16% (46/295)	Not stated	Not studied	…	…	…	*agr* group II polymorphism associated with mortality ($P = .05$)
Schweizer et al [50]	Treated with vancomycin	0 (169)[b]	BSI High- and low-risk sources: ND	Etest	56% (5/9)	16% (25/160)	Not stated	Not studied	…	…	…	
Soriano et al [52]	Retrospective, single-center, with MIC analysis performed on vancomycin-treated episodes only	414 (0)	BSI High Risk: 26% Low Risk: 43%	Etest	28% (30/109)	28% (86/305)	Not stated	Not studied	…	…	…	Vancomycin MIC of 2 μg/mL was an independent predictor of mortality only in the subgroup of patients empirically treated with vancomycin (OR 6.39; 95% CI, 1.68–24.3; $P < .001$). Shock less likely to occur in episodes with MIC of 2 μg/mL

Table 1 continued.

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	*P* Value	Comments
Takesue et al [53]	Retrospective, single-center, vancomycin-treated cohort study	128 (0)	BSI High risk: 34% Low Risk: 51%	Etest	20% (17/87)	66% (27/41)	.001	Not stated	25% (22/87)	59% (24/41)	<.001	MIC of 2 μg/mL was an independent predictor of mortality (OR 6.05; 95% CI, 2.3–15.93; *P* < .001) on mutivariate analysis.
Takesue et al [53]		631 (0)	Non-BSI		8% (45/575)	11% (6/56)	.617	Not stated	11% (63/575)	18% (10/56)	.073	
Van Hal et al [54]	Retrospective, single center	353 (0)[b,d]	BSI High Risk: 18% Low Risk: 38%	Etest	31% (73/236)	32% (37/117)	.63	Not studied				hVISA in ST239 MRSA isolates was an independent predictor of reduced mortality (OR 0.27; 95% CI, .09–.83; *P* = .022)
Wang et al [55]	Retrospective, single-center, vancomycin-treated cohort study	123 (0)	BSI High risk: 37% Low Risk: 41%	BMD	28% (27/97)	50% (13/26)	.057	Not studied	…	…	…	High MIC = 2 μg/mL was an independent predictor of mortality (OR 2.39; 95% CI, 1.2–4.79; *P* = .014) on multivariate analysis
Yoon et al [58]	Retrospective, single-center case-controlled study to assess risk factors of persistent bacteremia	63 (0)	BSI High- and low-risk sources: ND	Vitek	…	…	…	Persistent bacteremia >7 d	38% (17/45)	78% (14/18)	.01	Bacteremic persistence associated with infection-related mortality (*P* = .002)

Table 1 continued.

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) *P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	Treatment Failure Vancomycin MIC (μg/mL) *P* Value	Comments
Studies using alternative vancomycin MIC cut-offs												
					Vancomycin MIC (μg/mL)				Vancomycin MIC (μg/mL)			
					≤0.5	2	*P* value		≤0.5	2	*P* value	
Maclayton et al [39]	Retrospective, single-center, vancomycin-treated cohort study in patients undergoing hemodialysis	50 (0)	BSI High- and low-risk sources: ND	Vitek	24% (8/33)	35% (6/17)	Not stated	Not studied	…	…	…	Hospitalization costs significantly greater in high MIC group
					Vancomycin MIC (μg/mL)				Vancomycin MIC (μg/mL)			
					≤0.5	≥1	*P* value		≤0.5	≥1	*P* value	
Rubinstein et al [48]	Multicenter, randomized, controlled double-blind phase III trial of telavancin vs vancomycin (ATTAIN study)	133 (0)	HAP	BMD[d]	…	…	…	Persistence or progression of signs and symptoms, or progression of radiological signs of pneumonia	79% (22/28)	74% (78/105)	Not stated	Monomicrobial *S. aureus* HAP episodes with MIC ≥1 μg/mL significantly more likely to be cured with telavancin compared with vancomycin (treatment difference 12.5%; 95% CI, .5–23; $P = .03$); no MIC 1.5 or 2 μg/mL isolates

Table 1 continued.

Reference	Study Population	Number of MRSA (MSSA) Isolates	Source	MIC Method	Overall Mortality % (n) Vancomycin MIC (μg/mL) <1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) ≥1.5	Overall Mortality % (n) Vancomycin MIC (μg/mL) *P* Value	Definition of Treatment Failure	Treatment Failure Vancomycin MIC (μg/mL) <1.5	Treatment Failure Vancomycin MIC (μg/mL) ≥1.5	Treatment Failure Vancomycin MIC (μg/mL) *P* Value	Comments
Sakoulas et al [49]	Analysis of randomly selected vancomycin-treated (≥5 days), persistently bacteremic MRSA episodes from compassionate access prospectively collected multicenter isolate repository	30 (0)	BSI High- and low-risk sourcses: ND[c]	BMD	…	…	…	Persistent, worsening, or appearance of new signs and symptoms of infection	44% (4/9)	90% (19/21)	.01	Treatment failure was associated with reduced vancomycin bactericidal activity

Abbreviations: *agr*, accessory gene regulator; BMD, broth microdilution; BSI, bloodstream infection; CI, confidence interval; CNS, central nervous system infection—meningitis; GRD, glycopeptide resistance detection Etest; HAP, hospital-acquired pneumonia; HAP ICU, hospital-acquired pneumonia intensive care unit; hVISA, heteroresistant vancomycin-intermediate *S. aureus*; ICE, International Collaboration on Endocarditis; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; ND, not described; ODI, orthopedic device infection; OR, odds ratio; PAP-AUC, population analysis profile area under the curve.

[a] The same isolate repository containing approximately 400 MRSA isolates from 200 patients were used for all 3 studies.

[b] Data obtained through communications with the relevant authors.

[c] A high-risk bacteremic source included endovascular sources, lower respiratory tract, abdominal sources, and CNS foci; while low-risk sources included intravenous catheters and urinary tract. The remaining BSI episodes are classified as intermediate-risk sources, which included osteoarticular sources, soft-tissue, and unknown sources. For further details see reference [52].

[d] All isolates underwent hVISA testing by population analysis—data represents vancomycin-susceptible *S. aureus* isolates only.

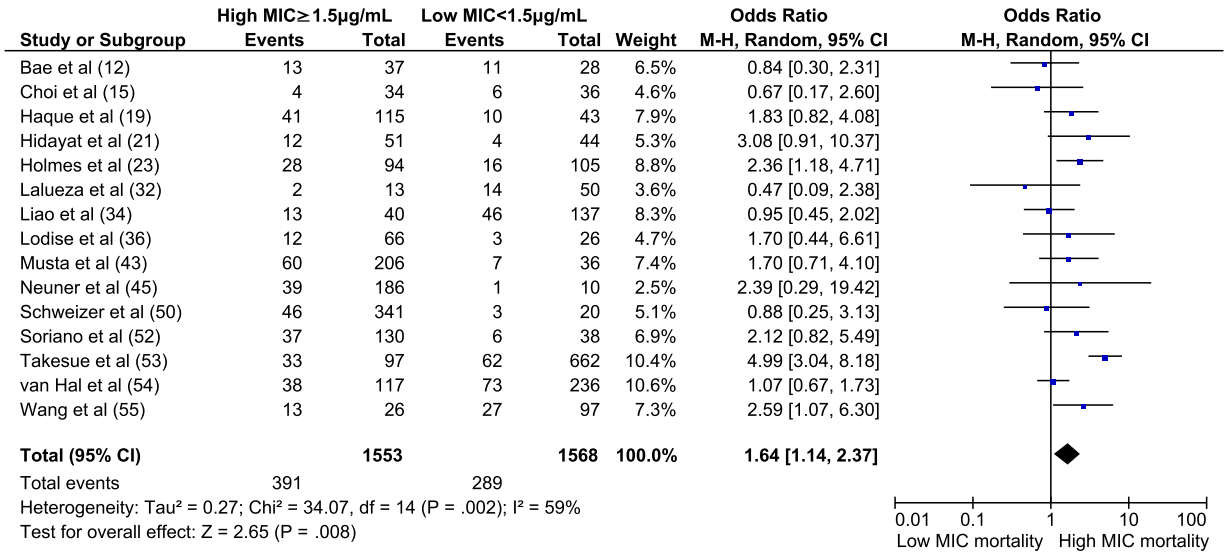

Figure 2. Forest plot (using Mantel-Haenszel analysis) of events denoting methicillin-resistant *S. aureus* mortality (irrespective of source of infection and minimum inhibitory concentration [MIC] methodology used) comparing high vancomycin MIC (≥1.5 µg/mL) with low MIC (<1.5 µg/mL) infections. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

Heterogeneity and Publication Bias

There was significant heterogeneity in mortality among the pooled studies, with the prevalence of high MIC (≥1.5 µg/mL) isolates ranging from 9% through 95%.

Because only 2 studies detailed *S. aureus* typing data [12, 54], it is unclear whether this heterogeneity is a consequence of specific MRSA clones. Similarly, hVISA infections may add to the heterogeneity among studies, with only 4 studies testing for heteroresistance [12, 23, 43, 54] and with hVISA episodes able to be excluded from only 2 studies [43, 54]. Furthermore, vancomycin prescribing differences and achieved targets could not be assessed, because no data were available from the relevant studies. With respect to treatment failure, heterogeneity among the pooled studies was marked secondary to the various different and nonstandardized definitions used for treatment failure.

DISCUSSION

Two notable findings emerged from this comprehensive literature review. First, high vancomycin MIC (≥1.5 µg/mL by Etest) was associated with a higher mortality rate associated with MRSA infection; this association predominantly occurred in BSIs with an Etest vancomycin MIC ≥2 µg/mL. Second, higher vancomycin MIC values (≥1.5 µg/mL), irrespective of MIC testing methodology and infection source, were predictive of treatment failure. Again, the relationship between high vancomycin MICs and treatment failure was more pronounced in patients with MRSA BSIs than in patients with non-BSIs.

There are several possible explanations for these findings. First, MIC is a surrogate marker for a pathogen-specific factor responsible for worse outcomes or enhanced virulence secondary to antibiotic resistance [23, 59]. Clinical data argue against this, because shock occurs less frequently with high-MIC infections [32, 52]. Nevertheless, it is still feasible that pathogen-specific factors influence outcomes because polymorphisms in the accessory gene regulator (*agr*) have been found to be independently associated with treatment outcomes [42].

Second, episodes may represent hVISA infections, especially at high MICs (2 µg/mL) [60] because high rates of treatment failure have been documented with heteroresistant isolates [61]. We attempted to exclude heteroresistance as a confounding variable by removing hVISA episodes. However, this is not feasible without formal testing of all isolates because heteroresistance can be detected at MICs as low as 0.5 µg/mL. Despite this, hVISA is unlikely to account for all our results, because the overall prevalence of this phenotype remains uncommon [61].

Third, vancomycin is a suboptimal antibiotic. The optimal pharmacodynamic parameter that predicts vancomycin activity is the area under the curve to MIC ratio, with a ratio >400 associated with treatment success in patients with pneumonia [62] and BSI [30]. However, the probability of achieving this target is extremely low when the MIC value reaches 2 µg/mL, even when maintaining vancomycin troughs of 15–20 µg/mL [63].

Finally, it is likely that not one but all of these factors are responsible for treatment outcomes and mortality. Therefore,

Table 2. Eligible Studies Examining the Association Between Mortality and Vancomycin Minimum Inhibitory Concentration (MIC) Classified by MIC Categories 1.5 μg/mL and 2 μg/mL Separately

	Study Population	Number of MRSA, (MSSA) Isolates	Source	MIC Method	Mortality% (n) Vancomycin MIC (μg/mL) ≤1	1.5	≥2	Comments
Bae et al [12]	See Table 1	65 (0)	IE	Etest	39% (11/28)	29% (9/31)	67% (4/6)	
Haque et al [19]	See Table 1	158 (0)	HAP	Etest	23%[a] (10/43)	30%[a] (26/86)	52%[a] (15/29)	
Holmes et al [23]	See Table 1	199 (324)	BSI	Etest	12%[a] (7/57)	13%[a] (35/272)	27%[a] (48/179)	Mortality rates were similar for MIC results 1 vs 1.5 μg/mL ($P = 1.0$)
Musta et al [43]	See Table 1	242 (0)	BSI	Etest	19%[a] (7/36)	27%[a] (50/185)	48% (10/21)	
Neuner et al [45]	See Table 1	196 (0)	BSI	Etest	10% (1/10)	17% (18/110)	28% (21/76)	
Schweizer et al [50]	See Table 1	312 (0)[a]	BSI	Etest	15%[a] (3/20)	12%[a] (28/230)	16%[a] (18/111)	
Soriano et al [52]	See Table 1	414 (0)	BSI	Etest	28% (30/109)	27% (60/213)	28% (26/92)	Vancomycin MIC independent predictor of mortality in empirically treated patients only (n = 168)
Van Hal et al [54]	See Table 1	353 (0)[a,b]	BSI	Etest	31% (73/236)	33% (32/96)	24% (5/21)	

Abbreviations: BSI, bloodstream infection; HAP, hospital-acquired pneumonia; IE, infective endocarditis; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a] Data obtained through personal communications with the relevant author.

[b] All isolates underwent heteroresistant vancomycinintermediate *S. aureus* testing by population analysis—data represents vancomycin-susceptible *S. aureus* isolates only.

our findings underscore the need for additional studies to better describe the mechanisms and factors leading to worse outcomes among patients with MRSA infection. Furthermore, additional clinical studies are needed to determine whether the adverse outcomes observed in patients with higher vancomycin values can be remedied by optimizing vancomycin treatment, switching to an alternative agent, and maximizing surgical management.

Our findings have implications for clinical practice. In particular, the results suggest that institutions should consider conducting Etest MICs on all MRSA BSI isolates to identify patients at greatest risk for mortality and treatment failure. On the basis of the limited clinical data and current laboratory studies, alternative MIC methods cannot be recommended as a surrogate for Etest because the correlation between MIC testing methods is moderate to poor [64]. Etest MIC results are

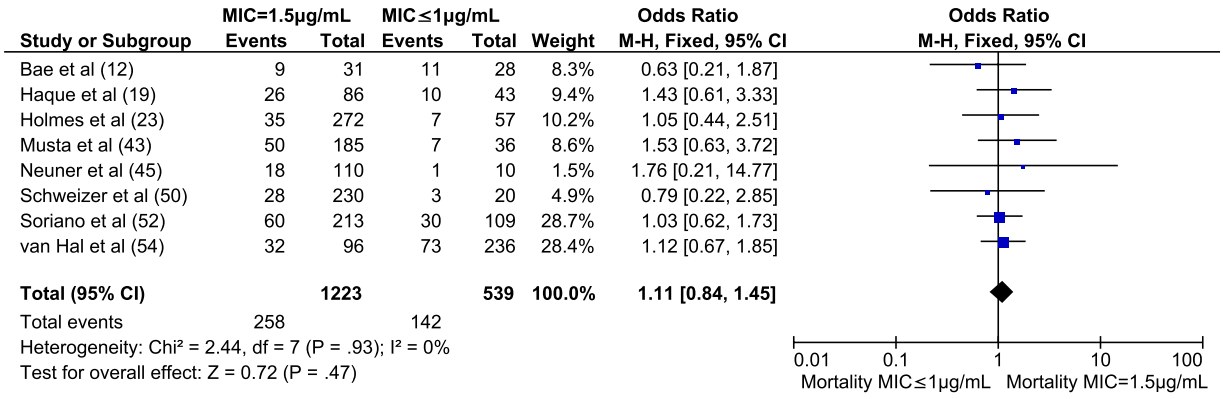

Figure 3. Forest plot (using Mantel-Haenszel analysis) of events denoting *S. aureus* mortality (irrespective of source of infection) comparing Etest vancomycin minimum inhibitory concentrations (MIC) of 1.5 μg/mL with MIC ≤1 μg/mL. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

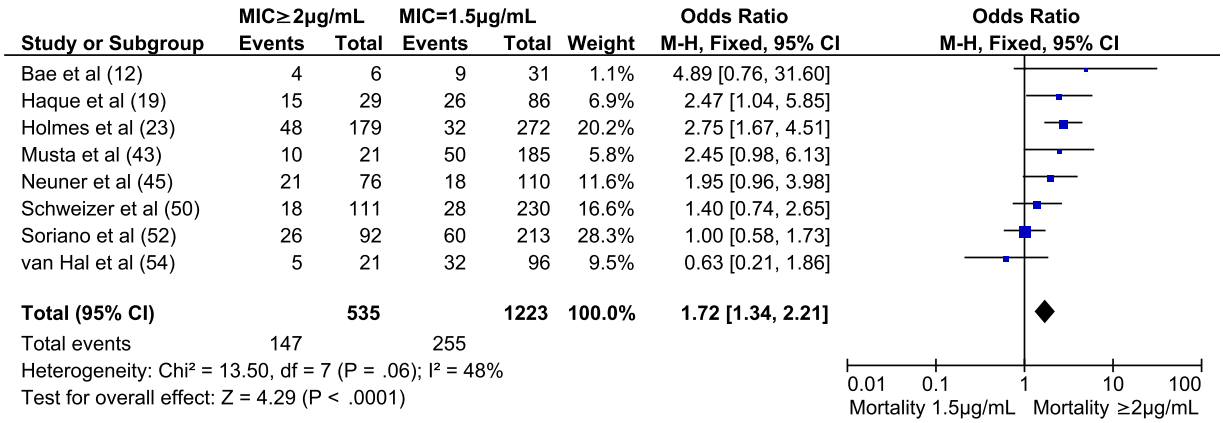

Figure 4. Forest plot (using Mantel-Haenszel analysis) of events denoting *S. aureus* mortality (irrespective of source of infection) comparing Etest vancomycin minimum inhibitory concentrations (MIC) of 1.5 μg/mL with MIC ≥2 μg/mL. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

generally 0.5–1 dilution higher than the gold standard BMD, whereas automated systems generally produce MIC results 1–2 dilutions lower than the gold standard [64, 65, 66]. Furthermore, these differences are not predictable and cannot simply be inferred [64]. Although the results indicate that higher vancomycin MIC values in the susceptibility window are associated with adverse outcomes, we do not support lowering the susceptibility breakpoint. Most of the vancomycin MIC outcomes studies involved Etest. As stated previously, Etest tends to be 0.5–1 $\log_2$ dilution higher than the gold standard BMD. Until data show that vancomycin MICs of 2 μg/mL by BMD predict mortality, we are not in favor of lowering the CLSI breakpoint.

These findings also suggest that alternative anti-MRSA agents should be considered for MRSA BSI with vancomycin MICs ≥2 μg/L by Etest, especially in patients with persistent disease [67]. Although these data highlight emerging failure concerns with vancomycin, there are currently no data to support better survival rates with alternative antibiotics for MRSA BSI. Only daptomycin has been licensed for the treatment of MRSA BSI and showed outcomes similar to vancomycin in these patients [68]. Furthermore, cross-resistance between high vancomycin MIC isolates and daptomycin has been noted and associated with daptomycin treatment failure [69]. Thus, care should be taken before substitution of vancomycin, and vancomycin should not be automatically relegated to second-line therapy.

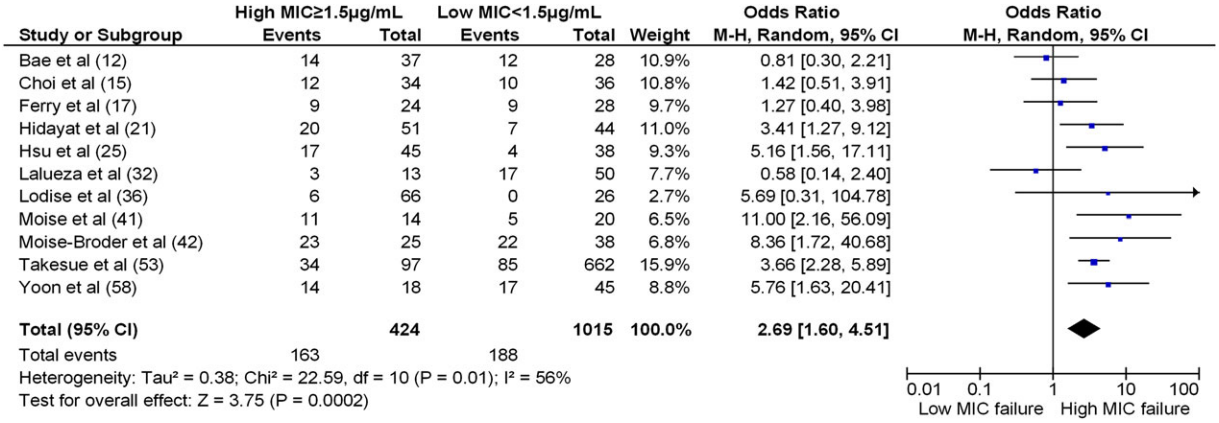

Figure 5. Forest plot (using Mantel-Haenszel analysis) of events denoting *S. aureus* vancomycin treatment failure (irrespective of definition, source of infection and minimum inhibitory concentration [MIC] methodology used) comparing high vancomycin MIC (≥1.5 μg/mL) with low MIC (<1.5 μg/mL) infections. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

In the absence of further comparative trials, we are unable to recommend the best alternative agent for treatment of these infections. Data are sorely needed to determine whether other agents can remedy the outcomes observed with vancomycin for MRSA infection with elevated vancomycin MIC.

Several points should be noted when interpreting these results. Outcomes were not stratified by the mortality risk associated with source of bacteremia [52] or by whether source control was adequate (eg, debridement, device removal, or line removal). In the absence of data, definitive conclusions regarding the impact of these variables on the observed outcomes cannot be inferred, and further studies should consider these key covariates as stratifying variables. Although we attempted to exclude hVISA-positive isolates from the analysis, hVISA testing was not performed in every study. Therefore, future studies should consider inclusion of hVISA testing to assess the relationship between vancomycin MIC values and outcomes among patients with *S. aureus* infection. Finally, limited information was available on vancomycin concentration profiles. Among studies that stratified outcomes by trough concentrations, it does not appear to affect the observed association between vancomycin MIC and mortality and treatment failure [21, 36]. Because of the recent Infectious Diseases Society of America MRSA recommendations for vancomycin therapy, the vancomycin exposure profile should be a key covariate in future analyses. At a minimum, studies should stratify the relationship between vancomycin MIC and outcomes by trough concentrations.

In conclusion, the results suggest that patients with MRSA BSI and higher vancomycin MIC values by Etest have a higher likelihood of mortality and treatment failure. The cause of increased adverse outcomes among patients with higher vancomycin MIC values is not well defined but most likely reflects an interaction among pathogen-specific variables, host responses, and suboptimal vancomycin exposure. On the basis of our findings, nonvancomycin anti-MRSA therapies should be considered for patients with MRSA BSI with high vancomycin MIC, especially for values $\geq$2.0 μg/mL by Etest. Although these data highlight emerging failure concerns with vancomycin, there are currently no data to support better survival rates with alternative antibiotics for MRSA BSI. Prospective studies are needed to determine whether optimizing vancomycin therapy can improve outcomes without subjecting patients to an increased risk of vancomycin-related toxicities.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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