Meta-Analysis: Vancomycin Treatment Failures for MRSA Bacteremia Based on MIC Determined by E-test

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Abstract

Background: Vancomycin is used to treat serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). It is unclear whether MRSA isolates with minimum inhibitory concentration (MIC) 1.5 to 2 µg/mL are successfully treated with vancomycin. **Objective:** Evaluate vancomycin failure rates in MRSA bacteremia with an MIC <1.5 versus ≥1.5 µg/mL, and MIC ≤1 versus ≥2 µg/mL. **Methods:** A literature search was conducted using MESH terms vancomycin, MRSA, bacteremia, MIC, treatment and vancomycin failure to identify human studies published in English. All studies of patients with MRSA bacteremia treated with vancomycin were included if they evaluated vancomycin failures, defined as mortality, and reported associated MICs determined by E-test. Study sample size, vancomycin failure rates, and corresponding MIC values were extracted and analyzed using RevMan 5.2.5. **Results:** Thirteen studies including 2955 patients met all criteria. Twelve studies including 2861 patients evaluated outcomes using an MIC cutoff of 1.5 µg/mL. A total of 413 of 1186 (34.8%) patients with an MIC <1.5 and 531 of 1675 (31.7%) patients with an MIC of ≥1.5 µg/mL experienced treatment failure (odds ratio = 0.72, 95% confidence interval = 0.49–1.04, *P* = .08). Six studies evaluated 728 patients using the cutoffs of ≤1 and ≥2 µg/mL. A total of 384 patients had isolates with MIC ≤1 µg/mL, 344 had an MIC ≥2 µg/mL. Therapeutic failure occurred in 87 and 102 patients, respectively (odds ratio = 0.61, 95% confidence interval = 0.34–1.10, *P* = .10). As heterogeneity between the studies was high, a random-effects model was used. **Conclusion:** Vancomycin MIC may not be an optimal sole indicator of vancomycin treatment failure in MRSA bacteremia.

Keywords

vancomycin, bacteremia, treatment failure, methicillin-resistant *Staphylococcus aureus*, minimum inhibitory concentration

Study Rationale and Background

Vancomycin is recommended for the treatment of serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).¹ Most MRSA infections continue to be susceptible to vancomycin at a minimum inhibitory concentration (MIC) susceptibility breakpoint of ≤2 mg/L defined by the Clinical Laboratory Standards Institute.² However, the increased use of vancomycin has led to an increase in resistant isolates, resulting in further discussions as to whether the susceptibility breakpoint should be decreased further by the Clinical Laboratory Standards Institute. This has been studied extensively with MRSA bacteremia, where increased vancomycin MICs have been associated with decreased efficacy and increased mortality among those treated with vancomycin, especially when the observed MIC is ≥2 mg/L.^{3,4} Two prior meta-analyses have been performed among published studies of MRSA infections, and these meta-analyses showed worse outcomes in those with higher vancomycin MICs.^{5,6} However, these analyses

included both episodes of bacteremia as well as other infections. In addition, there was some variability in the susceptibility method used among the studies. As the traditional methods of susceptibility testing such as broth microdilution method appear to underestimate vancomycin MIC among *S aureus* isolates, the use of E-test is considered the optimal testing method.⁷ This meta-analysis will examine the effect of MIC using E-test on vancomycin failure rates as defined by mortality in cases of MRSA bacteremia.

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Figure 1. Search strategy. All search terms used were MESH terms.

Methods

Data Sources and Study Selection

A multimethod approach was used to identify relevant studies for this review. To identify all applicable publications, a systematic literature search of PubMed (1966-December 2013), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews was conducted by 2 investigators independently using the following Medical Subject Headings and key words to identify appropriate studies: vancomycin, MRSA, bacteremia, MIC, treatment and vancomycin failure. The resulting studies were further limited to human studies published in English. Retrospective and prospective studies of patients with MRSA bacteremia treated with vancomycin were included if they evaluated vancomycin failures, defined as mortality. Included studies also

reported MRSA MIC values determined by E-test <1.5 $\mu\text{g/L}$ and ≥ 1.5 $\mu\text{g/L}$, or ≤ 1.0 $\mu\text{g/L}$ and ≥ 2.0 $\mu\text{g/L}$. Studies were included only if vancomycin failures were reported stratified by the aforementioned MICs and all data were reported in a usable format. Studies were excluded if they included treatment of persistent bacteremia or immunocompromised patients.

Bibliographies of recent review articles and systematic reviews were hand searched to identify any additional trials. Figure 1 depicts the search strategy used in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁸

Data Extraction

Two investigators independently extracted data from all eligible studies using a standardized form and independently

Table 1. Characteristics of Included Studies.^{3,4,11-18,20,21}

Reference	Study Type	N	Primary Outcome	Power Analysis Performed	Endocarditis (n)	Osteomyelitis (n)
Lodise et al (2008) ³	R	92	Vancomycin failure including 30-day mortality	No	9	NA
Musta et al (2009) ¹¹	R	487	Patient outcomes including mortality	No	217	NA
Lalueza et al (2010) ¹³	R	63	Patient outcomes including mortality	No	4	NA
Neuner et al (2010) ¹²	R	222	Clinical, microbiological, genetic characteristics of persistent MRSA bacteremia	No	15	15
Yeh et al (2012) ¹⁴	R	140	Mortality	No	NA	NA
Rojas et al (2012) ¹⁵	R	309	Clinical failure including mortality	No	4	5
Wang et al (2013) ²¹	R	284	Effect of hVISA on patient outcomes including mortality	No	24	40
Lodise et al (2014) ²⁰	R	184	Patient outcomes including mortality	No	21	9
Soriano et al (2008) ⁴	P	414	Patient outcomes including mortality	No	NA	NA
Price et al (2009) ¹⁶	P	31	Patient outcomes including mortality	No	NA	NA
Miller et al (2012) ¹⁷	P	694	Hematogenous complications	No	25	47
Yoon et al (2013) ¹⁸	P	134	Patient outcomes including mortality	No	4	11

Abbreviations: R, retrospective; P, prospective; NA, not available; MRSA, methicillin-resistant *Staphylococcus aureus*.

examined the accuracy of the extracted data. Information was obtained regarding the following variables: sample size, vancomycin failure rates, and corresponding MIC values. Any discrepancy that developed regarding the inclusion or interpretation of data was resolved through consensus.

Data Synthesis

We report results as events for the dichotomous variable of vancomycin failure as mortality or no mortality. Summary effects estimates are presented as odds ratios (ORs) with 95% confidence intervals (CIs). For all analyses, $P \leq .05$ (2-sided) was considered as significant. Measures were also taken to assess the heterogeneity among studies. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). The Cochrane handbook suggests that a value greater than 50% may be considered substantial heterogeneity.⁹ As statistical heterogeneity was present, we utilized a random-effects model. Funnel plots were used to assess publication bias. Statistical analyses were performed using Review Manager (RevMan version 5.2.5) software (The Nordic Cochrane Centre, Copenhagen, Denmark).¹⁰

Results

An initial search of the literature with the MESH term vancomycin yielded 10 604 results, which were then screened

according to the PRISMA guidelines.⁸ After limiting the results to English language and human subjects, 7064 articles remained. Adding the MESH terms bacteremia or treatment failure, or the term vancomycin failure, yielded 626 potential publications. The addition of the MESH term minimum inhibitory concentration yielded 209 results. Limiting the results further with the MESH term methicillin-resistant *Staphylococcus aureus* yielded 83 results. Seventy-four of these were excluded due to no mortality data ($n = 21$), E-test method not used to establish MIC ($n = 11$), MIC data were unusable ($n = 29$), case reports ($n = 6$), were meta-analyses or systematic reviews ($n = 2$), review articles ($n = 4$), or animal model ($n = 1$). This yielded 9 articles for inclusion. An additional 4 articles were identified through hand searches of references of recent review articles resulting in a total of 13 articles to be included in the meta-analysis.^{3,4,11-21} Figure 1 illustrates the search strategy. Table 1 describes the characteristics of the included studies. None of the studies reported a power analysis.

Heterogeneity between the studies was present, indicated by an I^2 value higher than the prespecified threshold of 50% in either the subgroups or the overall analyses; therefore, a random-effects model was used. We assessed for publication bias within the 11 included studies using funnel plots of odds ratios of treatment failures versus standard error. The funnel plots for both comparisons appeared symmetrical, which suggests a lack of publication bias.

Eight retrospective studies and 5 prospective studies met all criteria. A total of 2955 patients were evaluated. In the

Figure 2. Vancomycin treatment failure with MIC <1.5 or MIC ≥1.5.

analysis, 413 of 1186 (34.8%) patients with an MIC <1.5 and 531 of 1675 (31.7%) patients with an MIC of ≥1.5 µg/mL experienced treatment failure (OR = 0.72, 95% CI = 0.49-1.04, $P = .08$; Figure 2). In a comparison of an MIC ≤1 µg/mL and ≥2 µg/mL, treatment failures occurred in 87 of 384 (22.7%) patients and 102 of 344 (29.7%) patients, respectively (OR = 0.61, 95% CI = 0.34-1.10, $P = .10$; Figure 3).

Subgroup analyses of retrospective and prospective trial data were completed for all MIC cutoff points. Retrospective trial data resulted in 131 of 439 (29.8%) patients with an MIC <1.5 and 359 of 1149 (31.2%) patients with an MIC of ≥1.5 µg/mL experiencing treatment failure (OR = 0.70, 95% CI = 0.45-1.08, $P = .11$).^{3,11-15,20,21} Prospective data resulted in 282 of 747 (37.8%) patients with an MIC <1.5 and 172 of 526 patients (32.7%) with an MIC of ≥1.5 µg/mL experiencing treatment failure (OR = 0.69, 95% CI = 0.32-1.49, $P = .34$; Figure 2).^{4,16-18} In a comparison of an MIC ≤1 µg/mL and ≥2 µg/mL in retrospective trials, treatment failures occurred in 23 of 82 (28.1%) patients and 42 of 127 (33.1%) patients, respectively (OR = 0.54, 95% CI = 0.17-1.75, $P = .30$).^{11,12,15} In prospective trials, 64 of 302 (21.2%) and 60 of 217 (27.7%) patients experienced treatment failure with MIC ≤1 µg/mL and ≥2 µg/mL, respectively (OR = 0.65, 95% CI = 0.3-1.44, $P = .29$).^{4,18,19}

Discussion

The current meta-analysis shows similar vancomycin treatment failure defined as mortality rates despite higher versus

lower MIC values in patients with MRSA bacteremia. There were no differences in mortality when comparing patients with MIC <1.5 versus ≥1.5 µg/mL. While there was a numeric difference when comparing patients with MICs ≤1 versus ≥2 µg/mL, these differences did not achieve statistical significance. Despite evaluating the data further based on the nature of the study (prospective vs retrospective), there remained no differences in mortality between patients with higher versus lower MIC values.

There are 2 other meta-analyses that have evaluated the effect of vancomycin MIC on outcomes in patients with MRSA bacteremia that have found that increased MICs correlated with increased mortality and treatment failure.^{5,6} In 2012, a meta-analysis sought to evaluate the significance of MIC in MRSA infections.⁶ In this analysis, 22 prospective and retrospective studies were included that evaluated a variety of infections due to MRSA including bacteremia, pneumonias, bone and joint infections, among others. Several different methods of determining the MICs of the isolates were included. The authors compiled the data and evaluated the outcomes using a variety of MIC breakpoints (1 µg/mL, 1.5 µg/mL, and 2 µg/mL). In this meta-analysis, there was an increase in mortality for MRSA infections with higher MIC values regardless of source of infection or method for MIC determination.

In 2013, another meta-analysis was performed to assess vancomycin treatment failure rates based on MIC values, determined by broth microdilution (BMD) or E-test, of MRSA infections.⁵ Treatment failure and mortality of all MRSA

Figure 3. Vancomycin treatment failure with MIC ≤ 1 or MIC ≥ 2.

infections comparing low versus high MIC, defined as an MIC <1 µg/mL and ≥1.5 µg/mL, respectively, were presented. When blood stream infections using E-test to determine MIC were analyzed specifically, a higher MIC was significantly associated with an increase in mortality (relative risk [RR] = 1.46, 95% CI = 1.04-2.03, $P = .03$), but not with overall treatment failure (RR = 1.27, 95% CI = 0.96-1.68, $P = .09$).

The results of the current meta-analysis differ compared to the previous 2 meta-analyses mainly due to methodological differences. In an effort to include a homogeneous population, studies were only included if they enrolled patients with MRSA bacteremia and MICs were determined exclusively by E-test. Additionally, studies including patients with persistent bacteremia or immunocompromised patients were excluded in an effort to maintain homogeneity among the study population. These stricter criteria resulted in minimal overlap of included studies compared with the other published meta-analyses. Only 5 of the 13 studies that were included in the current analysis were in common with the other 2 meta-analyses. Some of the studies excluded from our meta-analysis but included in the other 2 analyses contained large populations of heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA), which may affect clinical outcomes. The presence of hVISA has been associated with poor outcomes including treatment failure. In most of the trials included in this meta-analysis, the prevalence of hVISA among the included isolates was not specifically reported. Moreover, our analysis only included full-length published studies whereas abstracts were included in the other meta-analyses.

Variability between the meta-analyses may also be attributed to the variety of available methods to determine MIC and susceptibility of MRSA to vancomycin. BMD and

E-test were the most commonly used methods to determine MIC of MRSA isolates in the studies. E-test MIC results are often found to be higher than BMD results for vancomycin.²² We attempted to limit the effect of this variability by including only studies that report MIC by E-test.

There were several limitations to this meta-analysis. Most of the included trials did not explicitly identify and report the presence of hVISA strains. The selected studies may have included hVISA isolates but did not test for them. We did not adjust for severity of infections or comorbid conditions because the information was not included for all of the studies. In addition, we did not evaluate the effect of concomitant antimicrobials that may have an effect against MRSA as this information was not available. This analysis was limited by the definition of treatment failure (mortality) that was used in the included trials. Clinical failure was not included as an outcome in these studies. Moreover, we were limited by how the data were reported with respect to MIC cutoffs as these data were not reported in the studies. We were unable to define additional MIC cutoffs, which did not allow for analysis of treatment failure rates for MIC between 1.5 and 2 µg/mL. Finally, we could not evaluate the effect of duration of therapy as there were not standardized approaches to treatment duration.

Conclusion

The results of this meta-analysis indicate that there were no statistically significant differences in mortality rates in patients treated with vancomycin for MRSA bacteremia with MIC <1.5 versus ≥1.5 or ≤1.0 versus ≥2.0 µg/mL. Vancomycin MIC may not be an optimal sole indicator of

vancomycin treatment failure in MRSA bacteremia. Future studies evaluating the effect of vancomycin on MRSA bacteremia should include information on underlying conditions, source of infection, and duration of therapy in addition to the vancomycin MIC.

Authors' Note

At the time of writing this article, Nicholas Mariani was a Doctor of Pharmacy Candidate at Wayne State University.

Declaration of Conflicting Interests

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