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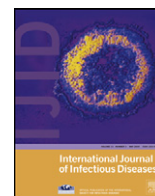
High vancomycin minimum inhibitory concentration and clinical outcomes in adults with methicillin-resistant *Staphylococcus aureus* infections: a meta-analysis

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S U M M A R Y

Background: Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections caused by isolates with a high but 'susceptible' minimum inhibitory concentration (MIC) to vancomycin may suffer poor outcomes. The aim of this study was to determine the association of high compared to low vancomycin MICs and clinical outcomes (treatment failure and mortality) in patients with MRSA infections.
Methods: PubMed, the Cochrane Library, and electronic abstracts from meetings were queried from January 2000 to July 2010. Two reviewers independently screened titles and abstracts of studies evaluating outcomes of patients with MRSA infections, using broth microdilution (BMD) or the Etest to determine MIC, for full-text review. Patients participating in included studies were classified into two mutually exclusive groups: high MIC or low MIC. High MIC was defined as MIC $\geq$1 mg/l by BMD or $\geq$1.5 mg/l by Etest. Study-defined failure and mortality were assessed in each group.
Results: Fourteen publications and six electronic abstracts met the inclusion criteria, with 2439 patients (1492 high MIC and 947 low MIC). There was no evidence of publication bias or heterogeneity. An increased risk of failure was observed in the high MIC group compared to the low MIC group (summary risk ratio (RR) 1.40, 95% confidence interval (CI) 1.15–1.71). The overall mortality risk was greater in the high MIC group than in the low MIC group (summary RR 1.42, 95% CI 1.08–1.87). Sensitivity analyses showed similar findings for failure (summary RR 1.37, 95% CI 1.09–1.73) and mortality (summary RR 1.46, 95% CI 1.06–2.01) for patients with bacteremia. The study quality was poor-to-moderate, and study-defined endpoints were variable.
Conclusions: A susceptible but high MIC to vancomycin is associated with increased mortality and treatment failure among patients with MRSA infections.

1. Introduction

The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the late 1970s dramatically increased the use of vancomycin.[1] For over 20 years, intravenous vancomycin has been the standard of care for serious MRSA infections. By 1996, the first isolate of MRSA with reduced susceptibility to vancomycin was reported.[2] Although frank resistance to vancomycin is rare in *S. aureus*, intermediate resistance is more common.[3] In 2006 the Clinical and Laboratory Standards Institute lowered the minimum inhibitory concentration (MIC) breakpoint for vancomycin susceptibility from >4 mg/l to >2 mg/l, partially based on reports of

clinical failures in patients with infections caused by MRSA isolates with MICs of $\geq$4 mg/l.[4,5] However, based on growing clinical experience of treatment failure against MRSA with vancomycin MICs in the higher end of the new 'susceptible' range, clinicians have begun to question the efficacy of vancomycin in patients with serious MRSA infections.[6]

The current literature provides inconsistent information on clinical outcomes of patients with infections caused by MRSA with high 'susceptible' MICs to vancomycin compared to low 'susceptible' MICs. Some studies have shown no significant association between higher MICs and poor outcomes,[7,8] but others have suggested an association with increased treatment failures and higher mortality.[9–13] Unfortunately, there are many differences in variables between individual studies (different patient populations, laboratory methods, outcome measures, etc.) making it difficult to interpret their findings and adding fuel

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to the ongoing debate regarding the efficacy of vancomycin against MRSA isolates with MICs at the higher end of the 'susceptible' range.

In order to comprehensively assess the available evidence addressing the question of whether high 'susceptible' vancomycin MICs are associated with poor clinical outcomes in patients with serious MRSA infections, we performed a systematic review and meta-analysis.

2. Methods

2.1. Data sources and searches

Studies reported between January 2000 and July 2011 in Medline and the Cochrane Library were identified by two infectious diseases subspecialists (JTJ, CAD); three search strategies were used, all applying the Boolean connector 'and' with the term 'microbial sensitivity tests': (1) 'methicillin resistance' and 'staphylococcal infections'; (2) 'methicillin resistance' and '*Staphylococcus aureus*'; and (3) 'methicillin-resistant *Staphylococcus aureus*'. Results were limited to 'Humans' and 'All Adults' (age ≥18 years) without any restriction on language. References in these studies were also reviewed to identify further sources. In addition, the electronic abstracts of the 2007, 2008, and 2009 Infectious Diseases Society of America (IDSA) annual meetings were reviewed using a similar methodology. The search was last run on August 12, 2011.

2.2. Study selection

Studies evaluating outcomes (failure and/or mortality) of patients with MRSA infections, stratified by MIC determined using broth microdilution (BMD) or the Etest, were considered candidates for inclusion; study designs that addressed this question, including case–control studies, cohort studies, and randomized control trials, were evaluated. Studies using only automated instruments were excluded, as were those exclusively focused on vancomycin-intermediate *S. aureus* (VISA) or hetero-resistant VISA (hVISA), or comparing isolates at extreme ranges of MIC (i.e., ≤0.5 vs. ≥2).

2.3. Data extraction and quality assessment

Data in tables, figures, or the text from included studies were independently extracted by two reviewers (JTJ, CAD); if estimates of outcome were not provided in the available study reports (abstracts, posters, or manuscripts), authors were contacted by e-mail at least twice in an attempt to obtain the required information. Differences in opinion between reviewers were resolved by consensus. Patients were classified into two mutually exclusive groups: low MIC or high MIC. Patients with MRSA isolates with a vancomycin MIC <1 mg/l by BMD or <1.5 mg/l by Etest were categorized in the low MIC group; patients with MRSA isolates with a vancomycin MIC ≥1 mg/l by BMD or ≥1.5 mg/l by Etest were classified into the high MIC group.

For the primary outcomes of treatment failure and mortality, individual study definitions were adapted for the review. If mortality was the only outcome assessed in a particular study, all deaths were included as treatment failures for the assessment of the treatment failure outcome. Whatever the mortality estimate provided by a study (hospital mortality, 14-day mortality, 30-day mortality, etc.), this was used for the assessment of the mortality outcome in the review. Similarly, whatever the treatment failure outcome defined by a study, this was used for the assessment of the treatment failure outcome in the review.

2.4. Data synthesis and analysis

Publication bias was explored graphically using funnel plots. Individual study quality was assessed by exploration of possible selection and misclassification bias, as well as confounding. Heterogeneity was assessed with the heterogeneity test and I^2 estimation. A *p*-value of ≤0.05 for the heterogeneity Chi-square test or an I^2 ≥50% were considered evidence of heterogeneity.

Three predetermined different sensitivity analyses were performed: (1) studies that reported failure in patients with MRSA bloodstream infection (BSI); (2) studies that reported mortality in patients with MRSA BSI; and (3) studies that used the Etest for MIC classification and reported mortality of patients with MRSA BSI. Risk ratios (RR) with 95% confidence intervals (CI) were calculated
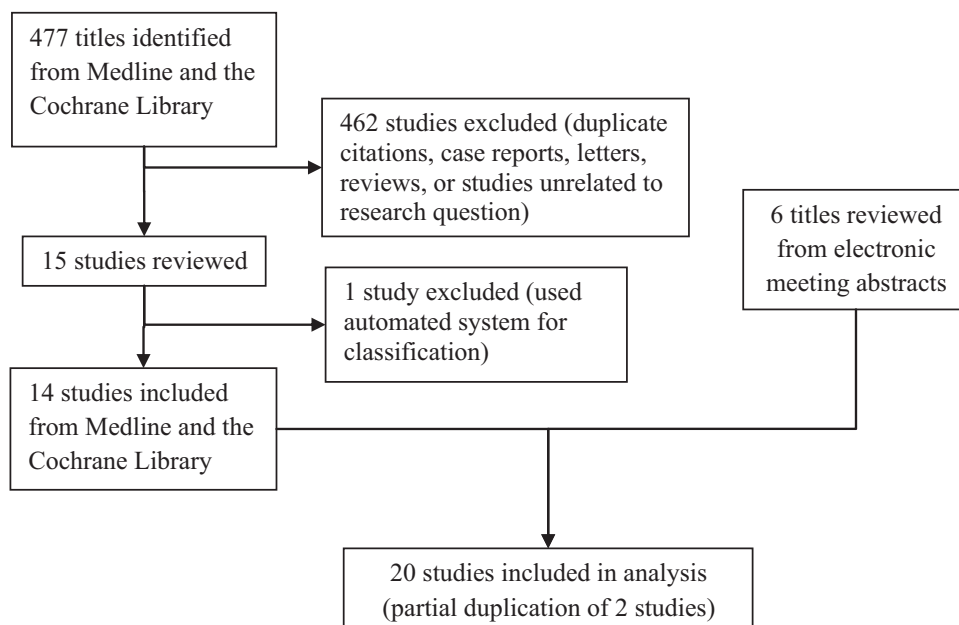

Figure 1. Results of the search strategy for the meta-analysis.

using random-effects models (DerSimonian and Laird).[14] Review Manager (RevMan) 5.1 software was used for the analysis and to create funnel and Forest plots.[15]

3. Results

Of the 477 studies identified from Medline and the Cochrane Library, 462 were excluded because they were case reports, letters, reviews, studies not related to the research question, or duplicates (Figure 1). One study was subsequently excluded because it used an automated system alone for MIC classification. Of the 14 remaining studies identified,[10,12,13,16–32] two studies had partial duplication of data,[10,12] but only one set of data from the overlapping studies was used in each analysis. Review of the electronic abstracts of meetings yielded another six studies.[27–32] No randomized control trials were identified. Overall study quality was poor-to-moderate since most studies were retrospective (Table 1) and therefore perceived to have a moderate-to-high risk of bias.

Among the 20 studies included, there was a total of 2439 unique patients, of whom 1492 (61.2%) had a high MIC and 947 (38.8%) had a low MIC. The funnel plot did not suggest publication bias (Figure 2). Most patients (1783/2439, 73.1%) in the meta-analysis came from published studies. There was no evidence of heterogeneity in all analyses.

An increased risk of failure (Figure 3A) was observed in the high MIC group compared to the low MIC group (summary RR 1.40, 95% CI 1.15–1.71). The overall mortality risk was greater in the high MIC group compared to the low MIC group (summary RR 1.42, 95% CI 1.08–1.87; Figure 3B). Sensitivity analysis showed similar findings for failure (summary RR 1.37, 95% CI 1.09–1.73) and mortality (summary RR 1.46, 95% CI 1.06–2.01) in patients with BSI (Figure 4, A and B). Although there was variation in the precision of the estimates, the results were generally consistent in subgroup analyses restricted to each antimicrobial susceptibility testing method (Etest vs. BMD; Figures 3 and 4).

4. Discussion

This meta-analysis supports previous individual studies suggesting poorer outcomes in patients with serious MRSA infections with vancomycin MICs at the higher end of the current 'susceptible' range.

These findings have potential implications for clinicians involved in the management of serious MRSA infections. Some would consider the use of alternative agents for empiric treatment of suspected MRSA infections, arguing that administration of an active antimicrobial during the first 48–72 h of therapy is essential to prevent poor outcomes. However, in the authors' opinion, current evidence is insufficient to support empiric use of alternative agents such as linezolid, daptomycin, telavancin, or quinupristin/dalfopristin for suspected serious MRSA infections for the following reasons: (1) broader use of these alternative agents will likely lead to increasing resistance to them; (2) frank vancomycin resistance remains rare; and (3) only a fraction of the patients with suspected MRSA infections are proven to have

Table 1
Summary of included studies

Authors	Study type	Year	Published	Site of isolation	MIC method	Eligible patients	High MIC group (n)	Low MIC group (n)	Failure outcome[a]	Mortality outcome
Choi et al.[16]	Retrospective	2011	Yes	Lung	Etest	70	34	36	Clinical non-response	28-day mortality
Ferry et al.[17]	Retrospective	2010	Yes	Bone/joint	BMD	41	40	1	Re-do surgery, relapse, limb loss, death	End of follow-up
Haque et al.[18]	Retrospective	2010	Yes	Lung	Etest	158	115	43	Clinical non-response	28-day mortality
Hidayat et al.[19]	Prospective	2006	Yes	Lung, blood, wound, urine	Etest	95	44	51	Clinical non-response	End of follow-up
Kullar et al.[20]	Retrospective	2011	Yes	Blood	Etest	320	122	198	Persistent infection, death	30-day mortality
Lewis E et al.[27]	Retrospective	2008	No	Blood	BMD	106	25	81	Persistent infection, relapse, death	-
Lewis T et al.[25]	Retrospective	2011	Yes	Blood	Etest	142	3	139	-	30-day mortality
Lodise et al.[21]	Retrospective	2008	Yes	Blood	Etest	92	66	26	Persistent infection, relapse, death	30-day mortality
Lustberg et al.[30]	Retrospective	2008	No	Blood	Etest	113	66	47	Relapse	In-hospital mortality
Moise-Broder et al.[10,b]	Retrospective	2004	Yes	Blood	BMD	63	42	21	Persistent infection	-
Moore et al.[31]	Retrospective	2008	No	Blood	Etest	122	116	6	Clinical non-response	In-hospital mortality
Musta et al.[22]	Retrospective	2009	Yes	Blood	Etest	285	249	36	-	In-hospital mortality
Neuner et al.[26]	Retrospective	2010	Yes	Blood	Etest	195	185	10	-	In-hospital mortality
Price et al.[23]	Prospective	2009	Yes	Blood	Etest	31	8	23	-	3-month mortality
Sakoulas et al.[12,b]	Retrospective	2004	Yes	Blood	BMD	30	21	9	Persistent infection	-
Soriano et al.[13]	Prospective	2008	Yes	Blood	Etest	168	130	38	-	30-day mortality
Swami et al.[28]	Retrospective	2008	No	Blood	Etest	97	52	45	-	30-day mortality
Wang et al.[24]	Prospective	2010	Yes	Blood	BMD	123	120	3	-	30-day mortality
Wilhelm et al.[29]	Retrospective	2008	No	Blood, lung	Etest	38	18	20	-	?In-hospital mortality
Yamaki and Wong-Beringer[32]	Retrospective	2008	No	Lung, wound, blood	Etest	180	57	123	Clinical non-response	?In-hospital mortality

BMD, broth microdilution; MIC, minimum inhibitory concentration.
[a] Mortality outcome used for failure outcome if not specified.
[b] Partial duplication of data.
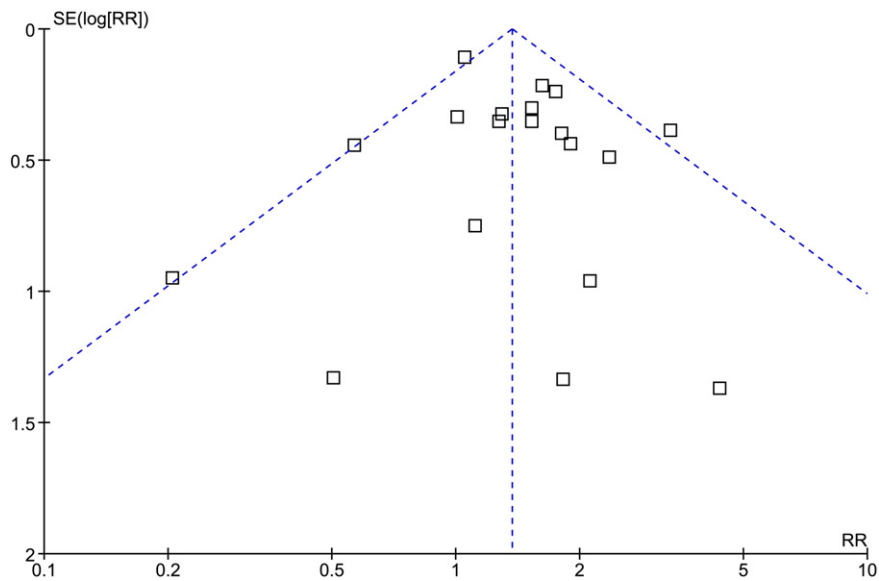
Figure 2. Funnel plot comparing the standard error (SE) of the logarithm of the risk ratio (RR) to the RR.

MRSA, and an even smaller proportion of these will be caused by organisms with a vancomycin MIC in the high-susceptible range.
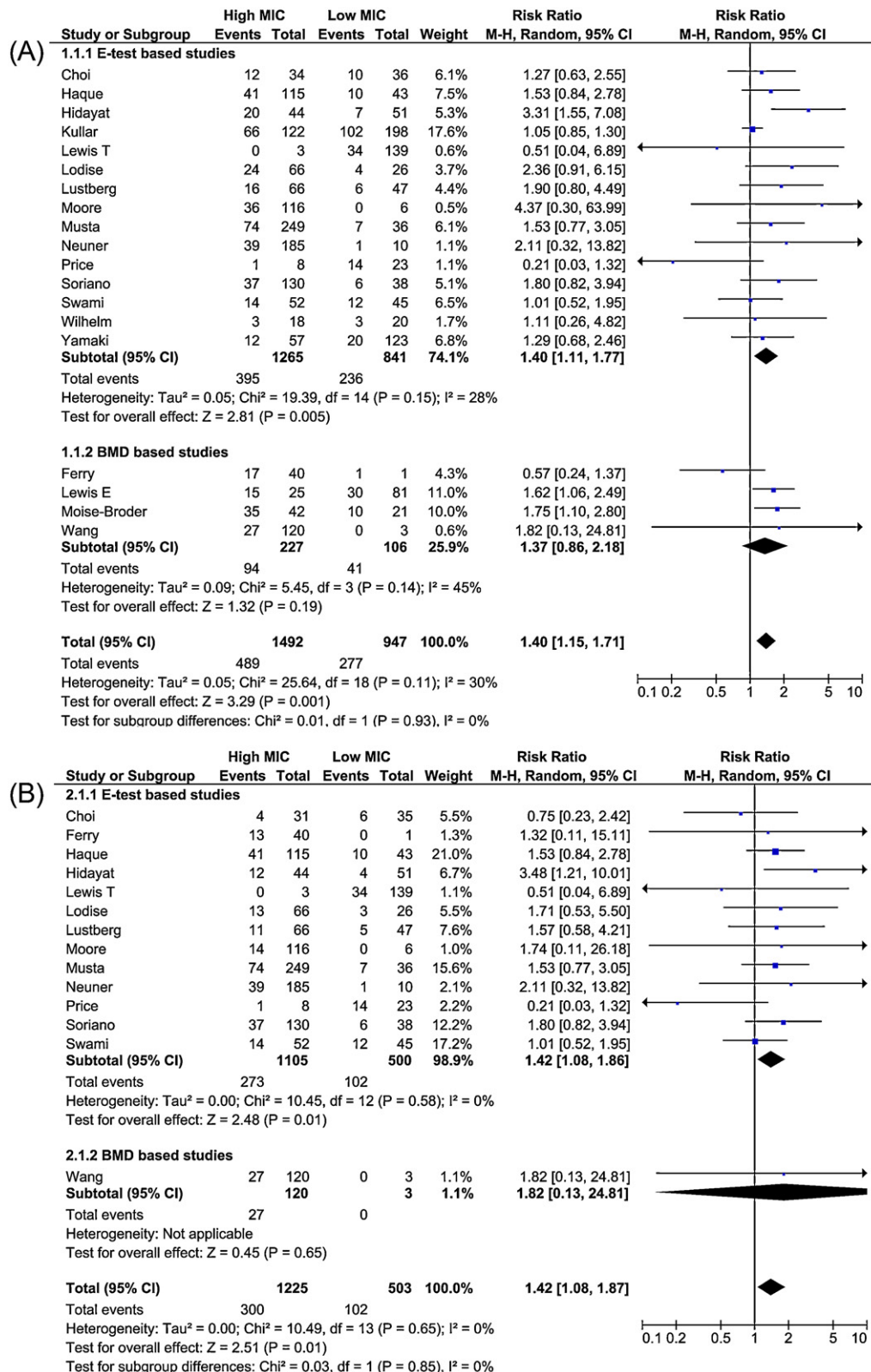
Although some studies suggest that alternative antimicrobials may have therapeutic advantages over vancomycin, no definitive evidence from randomized trials indicates the superiority of any other agent.[33–36] Unfortunately, few investigational agents are in the drug pipeline, and for the foreseeable future, clinicians will need to rely on currently available agents.[37] Evidence assessing the effectiveness of antimicrobials other than vancomycin for the treatment of serious infections caused specifically by isolates with vancomycin MICs in the high 'susceptible' range is even more limited. Only a few of the reviewed studies, all with methodological limitations, attempted to address the question. Soriano et al. concluded that a MIC >1 mg/l by Etest was one of several risk factors for increased mortality, but only in patients treated empirically with vancomycin.[13] Hidayat et al. reported that 12 out of 15 patients (80%) with MRSA infections with high vancomycin MICs and failing vancomycin therapy had successful outcomes when switched to other antimicrobial agents.[19]

A recently published study questions the therapeutic relevance of the association of poor outcomes and high vancomycin MIC: the association was demonstrated for *S. aureus* isolates overall, but there was no association with methicillin resistance or vancomycin therapy, suggesting that the poor outcomes may not actually be caused by an antibiotic failure.[38] In contrast, the above-mentioned study by Soriano et al. suggests the opposite, given that increased mortality was found only in patients who received empiric therapy with vancomycin. In addition, the study by Kullar et al. indicates that antibiotic therapy failure may be at least partially responsible for poor outcomes, given that a pharmacodynamic parameter specific to vancomycin and difficult to overcome in the presence of isolates with higher vancomycin MICs (an area under the curve (AUC)/MIC of <421) was found to be associated with failure according to a classification and regression tree (CART) analysis.[20] Finally, the observation from several studies that vancomycin MIC is associated with poor outcomes despite controlling for other possible determinants of failure or mortality, may further suggest that the association of these outcomes with high 'susceptible' MICs to vancomycin may be due to antibiotic treatment failure as opposed to other variables; only a randomized controlled trial would allow for adequate control of potential known and unknown confounders.

Because of the limitations of the available evidence, professional societies play an especially important role in guiding physicians in practice. To date, two US guidelines have addressed the management of serious MRSA infections caused by isolates with vancomycin MICs in the high 'susceptible' range. The vancomycin therapeutic monitoring guidelines from the American Society of Health-System Pharmacists, IDSA, and the Society for Infectious Disease Pharmacists recommend considering alternative therapies for MRSA infections if the MIC is ≥2 mg/l.[39] In contrast, the more recent IDSA guidelines for the treatment of MRSA infections recommend that for isolates with a vancomycin MIC ≤2 mg/l, the patient's clinical response should determine the continued use of vancomycin, independent of the MIC.[40] The two guidelines give, therefore, potentially discordant recommendations for the management of infections caused by isolates with a MIC of 2 mg/l. Given that the manufacturer recommends that "an Etest MIC value which falls between standard two-fold dilutions must be rounded up to the next upper two-fold value before categorisation",[41] and that according to this review a large proportion of recent MRSA isolates (around 60%) have a MIC ≥1.5 mg/l, many serious MRSA infections may be classified nowadays as caused by isolates for which consistent therapeutic guidance from professional societies is lacking.

In the authors' opinion, rational decision-making should take into account clinical response, severity of illness, and potential side effects, as well as the other principles of antibiotic stewardship. An evaluation of the patient should include clinical factors and ensure that the appropriate interventions, such as adequate drainage and repeat cultures if appropriate, are performed. Awaiting further evidence from more methodologically sound studies, the authors suggest that a known vancomycin MIC of ≥1.5 mg/l by Etest (or ≥1 mg/l by BMD) should lower the clinician's threshold to switch to alternative therapies in moderately to severely ill MRSA-infected patients without a rapid clinical or microbiological response to adequate vancomycin therapy and source control (if applicable).

A recently published meta-analysis on vancomycin MIC in *S. aureus* infections by van Hal et al. used different search terms, excluded abstracts from scientific conferences, and included studies using MIC determined by automated broth microdilution and patients with methicillin-susceptible *S. aureus* (MSSA) in their

(A)

Study or Subgroup	High MIC Events	Total	Low MIC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 E-test based studies						
Choi	12	34	10	36	6.1%	1.27 [0.63, 2.55]
Haque	41	115	10	43	7.5%	1.53 [0.84, 2.78]
Hidayat	20	44	7	51	5.3%	3.31 [1.55, 7.08]
Kullar	66	122	102	198	17.6%	1.05 [0.85, 1.30]
Lewis T	0	3	34	139	0.6%	0.51 [0.04, 6.89]
Lodise	24	66	4	26	3.7%	2.36 [0.91, 6.15]
Lustberg	16	66	6	47	4.4%	1.90 [0.80, 4.49]
Moore	36	116	0	6	0.5%	4.37 [0.30, 63.99]
Musta	74	249	7	36	6.1%	1.53 [0.77, 3.05]
Neuner	39	185	1	10	1.1%	2.11 [0.32, 13.82]
Price	1	8	14	23	1.1%	0.21 [0.03, 1.32]
Soriano	37	130	6	38	5.1%	1.80 [0.82, 3.94]
Swami	14	52	12	45	6.5%	1.01 [0.52, 1.95]
Wilhelm	3	18	3	20	1.7%	1.11 [0.26, 4.82]
Yamaki	12	57	20	123	6.8%	1.29 [0.68, 2.46]
Subtotal (95% CI)		1265		841	74.1%	1.40 [1.11, 1.77]
Total events	395		236			

Heterogeneity: Tau² = 0.05; Chi² = 19.39, df = 14 (P = 0.15); I² = 28%
Test for overall effect: Z = 2.81 (P = 0.005)

Study or Subgroup	High MIC Events	Total	Low MIC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 BMD based studies						
Ferry	17	40	1	1	4.3%	0.57 [0.24, 1.37]
Lewis E	15	25	30	81	11.0%	1.62 [1.06, 2.49]
Moise-Broder	35	42	10	21	10.0%	1.75 [1.10, 2.80]
Wang	27	120	0	3	0.6%	1.82 [0.13, 24.81]
Subtotal (95% CI)		227		106	25.9%	1.37 [0.86, 2.18]
Total events	94		41			

Heterogeneity: Tau² = 0.09; Chi² = 5.45, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 1.32 (P = 0.19)

Study or Subgroup	High MIC Events	Total	Low MIC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		1492		947	100.0%	1.40 [1.15, 1.71]
Total events	489		277			

Heterogeneity: Tau² = 0.05; Chi² = 25.64, df = 18 (P = 0.11); I² = 30%
Test for overall effect: Z = 3.29 (P = 0.001)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

(B)

Study or Subgroup	High MIC Events	Total	Low MIC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 E-test based studies						
Choi	4	31	6	35	5.5%	0.75 [0.23, 2.42]
Ferry	13	40	0	1	1.3%	1.32 [0.11, 15.11]
Haque	41	115	10	43	21.0%	1.53 [0.84, 2.78]
Hidayat	12	44	4	51	6.7%	3.48 [1.21, 10.01]
Lewis T	0	3	34	139	1.1%	0.51 [0.04, 6.89]
Lodise	13	66	3	26	5.5%	1.71 [0.53, 5.50]
Lustberg	11	66	5	47	7.6%	1.57 [0.58, 4.21]
Moore	14	116	0	6	1.0%	1.74 [0.11, 26.18]
Musta	74	249	7	36	15.6%	1.53 [0.77, 3.05]
Neuner	39	185	1	10	2.1%	2.11 [0.32, 13.82]
Price	1	8	14	23	2.2%	0.21 [0.03, 1.32]
Soriano	37	130	6	38	12.2%	1.80 [0.82, 3.94]
Swami	14	52	12	45	17.2%	1.01 [0.52, 1.95]
Subtotal (95% CI)		1105		500	98.9%	1.42 [1.08, 1.86]
Total events	273		102			

Heterogeneity: Tau² = 0.00; Chi² = 10.45, df = 12 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.48 (P = 0.01)

Study or Subgroup	High MIC Events	Total	Low MIC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.2 BMD based studies						
Wang	27	120	0	3	1.1%	1.82 [0.13, 24.81]
Subtotal (95% CI)		120		3	1.1%	1.82 [0.13, 24.81]
Total events	27		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

Study or Subgroup	High MIC Events	Total	Low MIC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		1225		503	100.0%	1.42 [1.08, 1.87]
Total events	300		102			

Heterogeneity: Tau² = 0.00; Chi² = 10.49, df = 13 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%

Figure 3. Forest plot comparing risk ratios for the outcomes of (A) failure, and (B) mortality, comparing patients in the high minimum inhibitory concentration (MIC) group to patients in the low MIC group stratified by method of testing for MIC (Etest vs. broth microdilution (BMD)).

analysis.[42] van Hal et al. classified MICs using a single breakpoint (1.5 μg/ml) regardless of the method of determination, whereas this analysis used established breakpoints that differ between the Etest and BMD, based on previous reports indicating that there is inconsistent correlation, compared to reference BMD, of MIC using different testing modalities, especially with automated instruments.[43,44] These methodological differences led to variation in the studies included in the mortality analysis (both included twelve
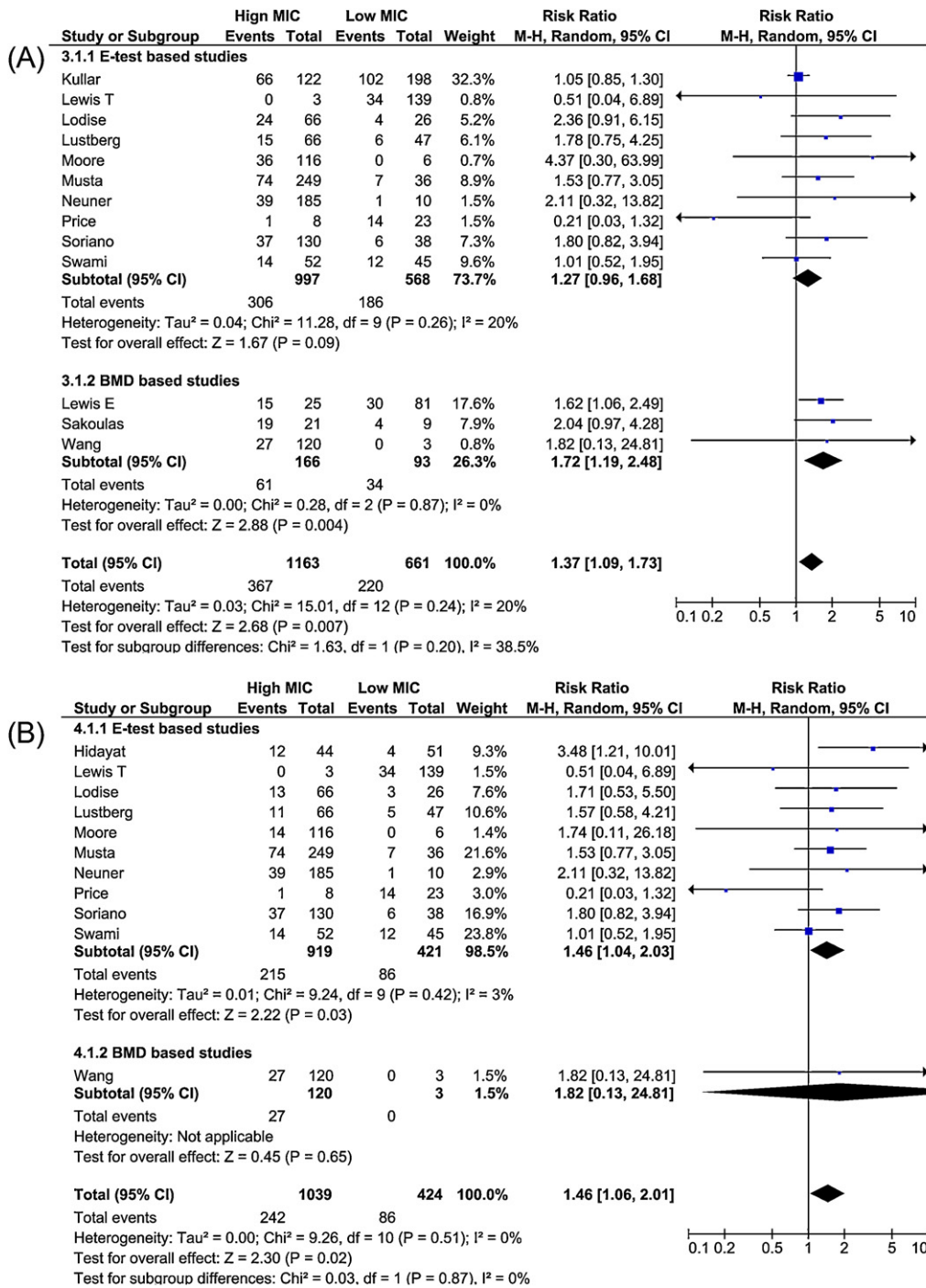
Figure 4. Forest plot for the sensitivity analysis assessing only bloodstream infections, comparing risk ratios for the outcomes of (A) failure, and (B) mortality, comparing patients in the high minimum inhibitory concentration (MIC) group to patients in the low MIC group stratified by method of testing for MIC (Etest vs. broth microdilution (BMD)).

studies,[10,12,13,16,18,19,21–24,26] but van Hal et al. selected twelve MRSA studies[7,9,23,45–53] not in this review, and the current review incorporated eight studies[17,20,25,27–32] that Van Hal did not). Despite these differences, it is reassuring that these two independently performed reviews both found the same associations between high vancomycin MIC and treatment failure and mortality.

This study has several limitations. Despite the lack of heterogeneity in our statistical analysis, studies included used different patient populations, different definitions of failure, or different time-points for the assessment of mortality. Many of the studies were retrospective in nature, all were observational, and most were assessed to have at least a moderate risk for bias and confounding. Additionally, some studies were reports from medical meetings (abstracts or posters) and were therefore not subjected to a judicious peer-reviewed process.

A large, multicenter randomized controlled trial is ideally needed for solving the question of whether serious infections caused by MRSA isolates with high (but still 'susceptible') MICs should be treated with vancomycin as opposed to other therapies; such a study will likely be extremely complex, requiring a large sample size, incorporating the optimal

pharmacodynamic dosing and monitoring, and assessing the toxicities possibly associated with the use of higher vancomycin doses. Unfortunately such a study is unlikely to be performed in the near future. In the absence of definitive evidence, the burden is on professional societies to provide clear overall recommendations for the management of MRSA infections and on clinicians to take responsibility for individualized therapeutic decisions at the bedside.

Acknowledgements

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