Point-Counterpoint: Should Clinical Microbiology Laboratories Report Vancomycin MICs?

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INTRODUCTION With numerous reported challenges to reporting MICs for vancomycin, clinical laboratories are attempting to identify accurate methods for MIC testing. However, the issues of poor reproducibility, accuracy, and clinical utility remain a challenge. In this Point-Counterpoint, Dr. Sara Revolinski discusses the pros of reporting MICs for vancomycin, while Dr. Christopher Doern argues for the use of caution.

POINT

Reporting vancomycin MICs is important. Vancomycin, a glycopeptide antibiotic developed in the 1950s, is considered the gold standard therapy for resistant Gram-positive infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA); however, recent studies have called this into question, especially for isolates for which MICs are elevated (1–3). Additionally, despite over 50 years of market presence, debate continues about how to optimize clinical outcomes and dosing while minimizing adverse effects and toxicity. Guidelines published by the Infectious Diseases Society of America (IDSA) in 2020 suggest that vancomycin dosing should aim to achieve an area under the concentration-time curve (AUC)/MIC ratio of 400 to 600 for optimal effectiveness and safety in patients with presumed or confirmed serious MRSA infections (1). However, calculating this ratio to optimize dosing often requires multiple serum levels, complex calculations or computer programs, and accurate measurement of the MIC, potentially decreasing its utility and implementation in clinical practice. To account for this, previous IDSA guidelines for vancomycin dosing published in 2009 suggested that a trough level of 15 to 20 µg/ml could be a surrogate marker for an AUC/MIC ratio of >400 (1), but recent studies have not demonstrated this correlation, suggesting that AUC/MIC determination may be necessary (4, 5). This is further supported by the updated 2020 vancomycin dosing guidelines, which recommend against trough-based monitoring.

In order to optimize vancomycin dosing and maximize clinical outcomes for patients, it is imperative that clinicians have an accurate MIC to guide treatment and dosing decisions.

An accurate MIC measurement may prove more difficult than expected. In a majority of U.S. clinical laboratories, MICs are determined by an automated testing system. A study conducted by Rybak and colleagues in 2013 compared MIC values obtained by automated systems to those determined by broth microdilution (BMD), the gold standard of MIC determination (6). The authors found the BD Phoenix system (Franklin Lakes, NJ) to be the most concordant with BMD, with a 66.2% concordance. The MicroScan WalkAway (Dade Behring, Deerfield, IL) turbidity method, Vitek 2 (bioMérieux, Hazelwood, MO) system, and Etest (bioMérieux) demonstrated concordance rates of 61.8%, 54.3%, and 36.7%, respectively. In addition, Etest overcalled the MIC by 1 to 2 dilutions compared to BMD. The MicroScan prompt method was found

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to overcall MIC values greater than 0.5 $\mu\text{g/ml}$, and the BD Phoenix and Vitek 2 systems undercalled MICs of 2 $\mu\text{g/ml}$. These deviations are important to keep in mind when analyzing studies describing outcomes based on vancomycin MIC, as studies use various methodologies. This inaccurate MIC reporting makes it difficult to associate outcomes with a specific MIC, difficult to draw conclusions based on MIC value, and difficult to determine courses of therapy based on an MIC. Clinicians need accurate MICs to guide treatment decisions, and if automated systems and the Etest cannot provide this, clinical microbiology laboratories should evaluate using BMD to identify MICs.

At the time of publication of the 2009 IDSA vancomycin dosing guidelines, data supporting AUC/MIC-based dosing were scarce. Since that time, more data evaluating the use of AUC/MIC-based dosing have emerged. In 2016, Men and colleagues conducted a systematic review and meta-analysis to evaluate the clinical impact of AUC/MIC-based vancomycin dosing (7). A total of 9 cohort studies were analyzed; all trials evaluated deep-seated MRSA infections. Seven trials used BMD methods to determine the MIC, with the remaining 2 studies utilizing Etest. All but one trial was retrospective in nature. Four trials assessed the impact of AUC/MIC-based dosing on mortality, finding a significantly lower risk of 30-day all-cause mortality with an AUC/MIC of >400 , compared to those with a ratio under 400 (relative risk [RR] = 0.47, 95% confidence interval [CI] = 0.31 to 0.70, $P < 0.001$). Similarly, six studies evaluated the risk of treatment failure and found that an AUC/MIC ratio of >400 was associated with a lower risk of failure (RR = 0.47, 95% CI = 0.30 to 0.73, $P = 0.001$).

While the 2009 IDSA guidelines suggest that a vancomycin trough of 15 to 20 $\mu\text{g/ml}$ increases the probability of attaining an AUC/MIC of >400 , some patients are able to achieve this ratio at lower troughs (8). Targeting higher vancomycin trough levels in these patients may result in increased toxicity (8). A quasi-experimental study conducted by Finch and colleagues in 2017 evaluated the impact of AUC/MIC-based vancomycin dosing on nephrotoxicity, compared to trough-based dosing, with a goal trough of 15 to 20 $\mu\text{g/ml}$ (9). AUC/MIC-based dosing was found to be independently associated with a reduced risk of nephrotoxicity after controlling for confounding variables when analyzed by logistic regression (odds ratio [OR] = 0.52, 95% CI = 0.34 to 0.80, $P = 0.003$) and Cox proportional hazards regression (hazard ratio = 0.53, 95% CI = 0.35 to 0.78, $P = 0.002$).

The results of these studies suggest that AUC/MIC-based vancomycin dosing, in conjunction with MIC determination by BMD, improves clinical outcomes for patients with deep-seated MRSA infections and support an AUC/MIC goal of >400 . Additionally, employing AUC/MIC dosing strategies reduces the risk of nephrotoxicity. In order to ensure dosing optimization, an accurate MIC is imperative to achieve the target AUC/MIC ratio.

It is also important to note that the 2020 IDSA vancomycin dosing guideline recommendations are based on a presumed vancomycin MIC of 1 $\mu\text{g/ml}$ or below. Some early literature suggested that treatment failure and increased mortality may be seen when vancomycin is used to treat *S. aureus* infections caused by isolates for which vancomycin MICs are 2 $\mu\text{g/ml}$, which is considered a susceptible MIC (10, 11). Three meta-analyses, published in 2012 to 2013, sought to analyze the impact of vancomycin MIC on clinical outcomes in *S. aureus* infections (12–14). Both methicillin-resistant and methicillin-sensitive isolates were analyzed from a variety of sources, and MICs of $>1 \mu\text{g/ml}$ were found to be significantly associated with increased mortality and treatment failure (12–14). The majority of trials included in these analyses utilized Etest methodology to determine MICs (12–14). However, two of these meta-analyses analyzed clinical outcomes stratified by testing methodology and showed that higher MICs detected by BMD or agar dilution were significantly associated with mortality and treatment failure (13, 14). Studies utilizing the Etest had various results, with some studies showing an increased risk of mortality and failure, while others did not (13, 14). As previously described, Etests overcall MICs compared to BMD (6).

More recently, in 2014, Kalil and colleagues conducted a systematic review and

meta-analysis analyzing mortality in 8,291 cases of *S. aureus* bloodstream infections based on the MIC (15). Thirty-eight studies were included, with 71% of studies utilizing the Etest and the remainder using BMD. Cases were stratified by MIC, with high MICs classified as 1.5 $\mu\text{g/ml}$ or greater. Of note, the Etest is the only testing methodology that can identify an MIC of 1.5 $\mu\text{g/ml}$, as automated systems and BMD use sequential doubling dilutions, making an MIC of 1.5 $\mu\text{g/ml}$ difficult to interpret. Patients infected with isolates for which the MIC was high demonstrated a mortality rate of 26.8%, compared to 25.8% for patients infected with isolates for which the MIC was low ($P = 0.43$). When only MRSA isolates were analyzed, mortality rates were 27.6% and 27.4% for high- and low-MIC groups, respectively ($P = 0.41$). The authors also did not find an association between MIC testing assay and mortality; however, with the majority of studies utilizing the Etest methodology, vancomycin MICs were likely overcalled, and organisms placed into the high-MIC groups may truly have had lower MICs, diluting the mortality impact on patients.

Since publication of these four meta-analyses, Baxi and colleagues prospectively evaluated 418 *Staphylococcus aureus* bloodstream infections and found no difference in 30- or 90-day mortality, infection recurrence, or hospital readmission rates between patients infected with organisms for which the MICs were $\geq 2 \mu\text{g/ml}$ and those infected with organisms for which MICs were less than 2 $\mu\text{g/ml}$ (16). The MIC was determined via the MicroScan Walkaway automated system, which similarly overcalls MICs compared to those determined by BMD, which may have resulted in patients being falsely placed into the high-MIC group and may have reduced the overall mortality in this group (6, 16).

The impact of the MIC on mortality remains controversial, and the literature to date has analyzed this impact with various testing methodologies, the majority of which are unreliable, with poor reproducibility. In order to truly ascertain the impact of the MIC on clinical outcomes, a more reliable MIC testing methodology, such as BMD, should be utilized. The meta-analyses described demonstrate increased mortality with elevated MICs, as identified by BMD, with equivocal results with other methodologies. Based on this, it is important for clinical microbiology laboratories to identify an accurate MIC, preferably utilizing BMD, to help determine mortality risk with elevated vancomycin MICs for *S. aureus* infections.

While vancomycin is considered the gold standard antibiotic for the treatment of MRSA, alternative antibiotics have also been evaluated. Several studies found an increased risk of treatment failure and mortality when vancomycin was used for the treatment of MRSA bloodstream isolates for which vancomycin MICs were greater than 1 $\mu\text{g/ml}$ (11, 17, 18). Two trials compared outcomes for patients who remained on vancomycin therapy and those who were started on or switched to daptomycin upon identification of an MIC of $>1 \mu\text{g/ml}$ (17, 18). Most patients received initial therapy with vancomycin, dosed to achieve a goal trough of either 10 to 20 $\mu\text{g/ml}$ (11, 18) or 15 to 20 $\mu\text{g/ml}$ (17). Median troughs obtained in patients ranged from 10 $\mu\text{g/ml}$ (18) to 17.6 $\mu\text{g/ml}$ (17). While therapeutic troughs were achieved in the study by Murray and colleagues (17.6 $\mu\text{g/ml}$), these authors also evaluated the AUC/MIC ratio in vancomycin-treated patients and found that only 12.2% of patients achieved the goal of >400 (17). The median AUC/MIC ratio obtained was 211.7 (interquartile range, 155.1 to 279.9) (17). These studies suggest that vancomycin may not be appropriate for MRSA isolates for which the vancomycin MIC is $\geq 1 \mu\text{g/ml}$, especially if the therapeutic AUC/MIC target cannot be reached. Because of this, it is important for clinicians to identify isolates for which MICs are elevated so therapy changes can be assessed.

A retrospective matched-cohort study by Claeys and colleagues evaluated treatment outcomes for patients with MRSA bacteremia treated with either vancomycin or daptomycin, regardless of the vancomycin MIC (3). Patients were defined as daptomycin treated if daptomycin was started within 72 h of initial anti-MRSA therapy, with a median time to daptomycin initiation of 48.4 h. Vancomycin was the initial therapy in 80.9% of patients. Vancomycin troughs of 15 $\mu\text{g/ml}$ were achieved in only 55% of

patients, suggesting that some patients may not have been optimally treated with vancomycin. AUC/MIC values were not determined. The authors found that receipt of vancomycin was an independent predictor of treatment failure at any MIC, with treatment failure defined as a composite of the 30-day mortality, persistent bacteremia at 7 days of therapy, and the need to change therapy due to persistent or worsening signs of infection (adjusted OR = 2.16, 95% CI = 1.24 to 3.76) (3). While this study suggests that vancomycin may be a suboptimal treatment for MRSA bacteremia regardless of MIC, we are unable to determine if vancomycin dosing was optimized, as AUC/MIC-based dosing was not evaluated in this trial. Suboptimal dosing may have contributed to treatment failure in the vancomycin group. As many institutions still utilize trough-based dosing for vancomycin, the data published to date support switching to alternative antibiotic therapy in patients with serious MRSA infections demonstrating a vancomycin MIC greater than 1, as trough-based dosing cannot ensure that adequate vancomycin exposure is achieved. Because of this, it is imperative that clinicians know accurate MIC values to prompt for potential therapy changes. More data are needed to evaluate treatment outcomes in this population when AUC/MIC-based dosing is utilized; however, knowledge of the MIC in these situations is paramount to ensure that the goal AUC/MIC ratio is achieved.

Identifying an accurate MIC of vancomycin is essential to ensure optimal treatment for patients. There also needs to be a uniform recommendation for clinical microbiology laboratories to determine the vancomycin MIC, especially for infections caused by *S. aureus*. With the various methods available and the limitations of each previously described, it is difficult to determine effective dosing or the impact on patient outcomes. Current studies utilize various testing methodologies, which makes identifying a therapeutic target difficult; these methodologies may also impact clinical outcomes. The literature suggests that MICs for *S. aureus* of $>1 \mu\text{g/ml}$ are associated with treatment failure when vancomycin is utilized for treatment, and when identified, this MIC should prompt the use of an alternative antibiotic therapy. As vancomycin remains the mainstay of therapy for empirical and confirmed *S. aureus* infections, it is essential that clinicians have MIC data to assist with therapeutic decisions. Experts suggest that our best option for targeting optimal outcomes is an AUC/MIC ratio of 400 to 600. As the new IDSA vancomycin dosing guidelines support AUC/MIC-based dosing, I anticipate that clinical centers will continue to transition to this methodology. Only when we have reliable MIC values will we be able to truly determine the appropriate therapeutic target that optimizes clinical outcomes and minimizes toxicity for patients.

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COUNTERPOINT

Vancomycin MICs lack utility. A large body of evidence now shows that patients with *Staphylococcus aureus* bloodstream infections (BSI) caused by isolates for which MICs are near the susceptible breakpoint (2 $\mu\text{g}/\text{ml}$) have poorer outcomes than patients infected with isolates for which vancomycin MICs are lower. The studies demonstrating this phenomenon have prompted many microbiology laboratories to report vancomycin MICs in an effort to help clinicians identify which patients are likely to fail therapy (1). In some cases, laboratories may even include therapeutic comments warning clinicians that isolates for which MICs are 2 $\mu\text{g}/\text{ml}$ are likely to fail vancomycin therapy and suggest that alternative therapies be considered.

This approach, although evidence based, is problematic for a variety of reasons, which will be discussed below. The argument most commonly made against reporting of vancomycin MICs relates to the variability that exists between and within test methods. In short, antimicrobial susceptibility testing (AST) methods are not reliable enough to justify reporting absolute MIC values. Although the issue of method variation will be addressed, there are other, often overlooked, reasons that vancomycin MICs should not be reported.

Several of the points that will be made here run contrary to commonly accepted tenants of vancomycin use as well as to a large body of evidence suggesting that MICs of 2 $\mu\text{g}/\text{ml}$ predict poorer patient outcomes. Specifically, this discussion will challenge two important arguments for reporting vancomycin MICs. The first argument is that an AUC/MIC target of 400 is predictive of successful therapy; it probably is not. The second argument is that alternatives to vancomycin are superior for the treatment of isolates for which MICs are 2 $\mu\text{g}/\text{ml}$, but not for isolates for which MICs are <2 $\mu\text{g}/\text{ml}$. The reality is that alternatives to vancomycin are superior regardless of the vancomycin MIC. I hope to convince readers that the reporting of vancomycin MICs is not only inaccurate, it is misleading.

An AUC/MIC of ≥ 400 : is it the right number? It is commonly accepted that the pharmacokinetic/pharmacodynamic (PK/PD) model that best predicts vancomycin therapeutic success is an AUC/MIC ratio target of 400. A central point supporting the conclusion that isolates for which vancomycin MICs are 2 $\mu\text{g}/\text{ml}$ are unlikely to respond to vancomycin therapy is that it is not physiologically possible to achieve a target of 400 if the MIC is 2 $\mu\text{g}/\text{ml}$ or greater (2). Despite the fact that this assertion is now virtually unchallenged in the literature and that targeting AUC/MIC ratios of 400 is now entrenched in clinical practice, there is little evidence to support it.

To the best of my knowledge, the first human study which led to the conclusion that an AUC/MIC value of 400 was predictive of successful treatment was a 2004

publication that studied vancomycin treatment of *S. aureus* lower respiratory tract infections (3). Of note, most of the data which demonstrate poor outcomes for vancomycin MICs of 2 $\mu\text{g/ml}$ come from the study of BSI, not pneumonia. That fact notwithstanding, the 2004 Moise-Broder study (3) found that patients who achieved treatment success had an average AUC/MIC of 463.1, while those who failed treatment had an average ratio of 323.0. Although these values were not statistically different ($P = 0.193$), the authors found that exceeding an AUC/MIC of 350 had an odds ratio of 7.19 in favor of success, and that finding did achieve significance ($P = 0.0036$). Thus, the AUC/MIC of 400 was established.

Since that initial study, little human data have been provided to definitively confirm its findings. In fact, the data that have been provided, in many cases, contradict their findings. In some cases, the findings support a lower target, while other studies suggest a higher target (4–12). A summary of these studies, their conclusions, and their limitations can be found in Table 1. As we assess the validity of making therapeutic decisions based on a vancomycin MIC value and, by extension, AUC/MIC ratio targets, it is critical that we understand the limitations of the data that are being used to drive these practices. As will be discussed in detail below, vancomycin susceptibility testing is method dependent and can have a significant impact on AUC/MIC calculations. Some studies account for this limitation, but most do not and in fact use an MIC method (Etest), which is well known to falsely elevate the vancomycin MIC (10). The AUC/MIC conversation is particularly relevant, as new guidelines will recommend that patient-specific AUC/MIC calculations be used to dose vancomycin with an AUC/MIC target of 400. It is worth noting that the references included in guideline documents supporting AUC/MIC targets of 400 do not actually support that claim (13–15). This perpetuates the conclusion and drives the design of subsequent scientific investigations, which are then based on the assertion that an AUC/MIC of 400 is the right metric for success. These publications go on to reference those guideline documents as supporting “evidence” for their study design. Thus, despite its now unchallenged status, a critical review of the literature will lead one to conclude that the AUC/MIC target of 400 is little more than dogma and could very likely be wrong.

An excellent review by Rybak highlights the limitations of the human data supporting an AUC/MIC target of 400 and includes references to several unpublished abstracts which found no correlation between an AUC/MIC of 400 and therapeutic success (16). Table 1 highlights some of the studies which have been performed to evaluate target attainment in vancomycin therapy for *S. aureus*.

Alternative antibiotics are superior regardless of vancomycin MIC. The literature has clearly demonstrated that when the Etest and vancomycin treatment are used, patient outcomes are worse for isolates for which MICs are 2 $\mu\text{g/ml}$ than they are for isolates for which MICs are $<2 \mu\text{g/ml}$ (1). The question that is not answered by these Etest-based studies is whether an alternative antibiotic would improve outcomes for isolates for which MICs are 2 $\mu\text{g/ml}$. This is an important distinction, because what is being inferred from these studies, and in fact what is being recommended by several different groups (2, 14, 15), is that alternative therapies should be considered when vancomycin MICs are $\geq 2 \mu\text{g/ml}$. Alternative therapies do improve outcomes for isolates for which vancomycin MICs are $\geq 2 \mu\text{g/ml}$, but they improve outcomes for isolates for which MICs are $<2 \mu\text{g/ml}$ as well. In other words, regardless of vancomycin MIC, there are superior alternatives to vancomycin, namely, daptomycin.

The finding that daptomycin is superior to vancomycin regardless of the vancomycin MIC is not surprising given the numerous studies which have been published and demonstrate the superiority of daptomycin. Table 2 summarizes these studies and shows that, regardless of outcome definition, be it in-hospital mortality, clinical failure, or 30-day or 60-day mortality, daptomycin is a better option for the treatment of *S. aureus* bacteremia. To be clear, there is insufficient data to draw a conclusion about the relevance of vancomycin MICs for conditions other than BSI, and the statement that daptomycin is superior to vancomycin should obviously not be applied to pneumonia.

TABLE 1 Summary of select studies evaluating vancomycin AUC/MIC targets

Study (reference)	Study design (human vs animal)	No. of patients	Vancomycin AST method(s)	Infection type(s)	Outcome(s) assessed	AUC/MIC findings	Study limitation(s)
Gawronski et al. (4)	Retrospective adult	59	Etest and MicroScan	Bacteremia and osteomyelitis	Bacterial clearance	>293 predictive of treatment success	Did not specify which AST method was used to calculate AUC/MIC, did not use reference broth microdilution
Martirosov et al. (5)	Retrospective adult	71	Etest	Bacteremia	30-day all-cause mortality, bacterial clearance, recurrence	>550 predictive of treatment success	Etest MICs were used to calculate AUCs, only isolates for which MICs were ≥ 1.5 $\mu\text{g/ml}$ were included
Holmes et al. (6)	Observational >12 yrs	182	Etest and broth microdilution (not defined)	Bacteremia	30-day all-cause mortality	>400 not predictive of treatment success	
					30-day all attributable mortality, recurrence, prolonged bacteremia	>373 predictive of treatment success	
Castaneda et al. (7)	Rabbit endocarditis	NA ^a	Etest and broth microdilution (not defined)	Endocarditis	Reduction in bacterial density	>400 not predictive of treatment success	Animal model
Kullar et al. (8)	Retrospective adult	320	Etest and reference broth microdilution	Bacteremia	30-day all-cause mortality, persistent symptoms at completion of vancomycin therapy, recurrence	>421 predictive of treatment success	Etest MICs used to calculate AUCs
Neuner et al. (9)	Retrospective adult	222	Etest	Bacteremia	Persistent bacteremia	No AUC/MIC target was predictive of treatment success	Etest MICs used to calculate AUCs
Lodise et al. (10)	Retrospective adult	123	Etest and reference broth microdilution	Bacteremia	30-day all-cause mortality, persistent bacteremia, recurrence	>300 (Etest) predictive of treatment success, >600 (BMD) predictive of treatment success	
Casapao et al. (11)	Retrospective adult	139	Broth microdilution	Infective endocarditis	30-day attributable mortality, persistent bacteremia	>600 (BMD) predictive of treatment success	
Brown et al. (12)	Retrospective adult	58	Etest	Bacteremia and infective endocarditis	30-day attributable mortality	>211 (Etest) predictive of treatment success	Etest MICs used to calculate AUCs
Hahn et al. (42)	Retrospective pediatric	365	Vitek and Etest	Bacteremia	30-day all-cause mortality, persistent bacteremia, recurrence	Relationship between AUC/MIC and treatment failure could not be established	Low MICs, likely due to use of Vitek

^aNA, not available.

TABLE 2 Summary of select studies comparing outcomes between vancomycin and daptomycin for the treatment of *S. aureus* bacteremia

Study (reference)	Outcome	% vancomycin failure	% daptomycin failure (P value)	Infection type
Rehm et al. (43)	Clinical failure	45	27	Complicated bacteremia
Moore et al. (36)	Clinical failure	31	17 (0.084)	BSI
	60-day mortality	20	8 (0.046)	
Murray et al. (37)	Clinical failure	48.20	20.0 (<0.001)	BSI
	30-day mortality	12.90	3.5 (0.47)	
Kullar et al. (44)	Clinical failure	59	25 (<0.001)	BSI
Weston et al. (35)	In-hospital mortality	35	16 (0.015)	BSI
Claeys et al. (21)	Composite failure	45	29 (0.007)	BSI
	30-day mortality	15.30	6.1 (0.01)	

Unfortunately, the obvious alternative to vancomycin and daptomycin treatment of *S. aureus* infection is ceftaroline, which has been extensively compared only to vancomycin in skin and soft tissue infections (17, 18).

Two studies have compared ceftaroline to vancomycin for the treatment of BSI. Arshad et al. conducted a retrospective analysis comparing outcomes in 30 patients treated with ceftaroline, 46 patients treated with daptomycin, and 56 patients treated with vancomycin (19). No differences in 30-day mortality, 42-day relapse, or 30-day readmission were observed. A second study compared combination therapy with ceftaroline and daptomycin ($n = 17$) to monotherapy with vancomycin ($n = 21$) or daptomycin ($n = 2$) (20). Unfortunately, due to the combination with daptomycin, it is impossible to draw a conclusion about the efficacy of ceftaroline alone; however, it is remarkable that the study had to be prematurely terminated due the significantly better outcomes in the combination arm, for which there were no deaths, compared to the 26% mortality in the vancomycin-only arm.

A number of studies have come to the conclusion that daptomycin is superior to vancomycin for the treatment of *S. aureus* BSI and are summarized in Table 2. Of particular interest is the study by Claeys et al. entitled "Daptomycin Improves Outcomes Regardless of Vancomycin MIC in a Propensity-Matched Analysis of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections" (21). In this retrospective, propensity-matched study, 262 patients were included (vancomycin, $n = 131$; daptomycin, $n = 131$) and outcomes were assessed and then stratified by vancomycin MIC. Overall, daptomycin resulted in lower rates of clinical failure according to the investigators' initial analysis (45% versus 29%, $P = 0.007$), as well as when a panel blind to the treatment analyzed the data (59.6% versus 42.6%, $P = 0.014$). Lower rates of clinical failure were also found when data were stratified by isolates for which the vancomycin BMD MIC was $0.5 \mu\text{g/ml}$ (54.5% versus 32.0%, $P = 0.027$). Thus, even at the lowest of vancomycin MICs, daptomycin proved to be a superior choice.

A related point can be made with the findings of studies which evaluate the treatment of methicillin-susceptible *S. aureus* (MSSA) and stratify outcomes by vancomycin MIC. In 2011, Holmes et al. compared 30-day all-cause mortality for MSSA isolates treated with flucloxacillin with that for isolates treated with vancomycin (22). Outcomes for both groups were stratified by vancomycin MIC. The vancomycin treatment arm replicated the findings of others, showing that outcomes were better when vancomycin MICs were $<1.5 \mu\text{g/ml}$. The key finding, though, was that outcomes in the flucloxacillin group were also significantly better for MSSA isolates for which vancomycin MICs were $<1.5 \mu\text{g/ml}$ than for MSSA isolates for which vancomycin MICs were $\geq 1.5 \mu\text{g/ml}$.

Taken together, the Holmes et al. (22) and Claeys et al. (21) studies raise serious questions about whether elevated vancomycin MICs are predictors of vancomycin failure or whether they are indicative of other, unknown pathogenic factors which lead to poorer outcomes. Importantly though, they show that vancomycin MICs of $2 \mu\text{g/ml}$ do not predict vancomycin failure; they predict poor outcomes regardless of the antibiotic

used. A critical conclusion here is that, at least for bloodstream infection, daptomycin is a better option than vancomycin at all vancomycin MICs. As a result, it is misleading to suggest that alternative therapies be considered only for isolates for which MICs are 2 $\mu\text{g/ml}$.

Variability in vancomycin MIC methods. There is now momentum for the real-time calculation of AUC/MIC values to guide vancomycin dosing in patients infected with *S. aureus*. This practice, of course, would necessitate the reporting of vancomycin MICs for all isolates to facilitate these calculations. This recommendation is based in large part on strong data demonstrating that risks of nephrotoxicity can be minimized by considering AUC/MIC targets (23, 24). However, this recommendation would also be based on the conclusion that an AUC/MIC target of 400 correlates with successful clearance of infection, and as was discussed above, the literature has not proven this point.

A secondary problem in making such a recommendation is that generating vancomycin MICs for *S. aureus* is highly method dependent, which brings up the most compelling reason that laboratories should not report MICs. A study by Chen et al. nicely compares vancomycin MIC values generated by commonly used test methods (25). In this study, 393 MRSA bloodstream isolates were tested, and it showed that reference broth microdilution (BMD), agar dilution, MicroScan, Vitek 2, and BD Phoenix all generate consistently lower MIC values than the Etest (25). Prakash et al. found that in comparison to BMD, the Etest shifted nearly all (88% to 98%) MICs for *S. aureus* to 2 $\mu\text{g/ml}$ (26).

In addition, one has to be careful in interpreting Etest data that are presented in less than doubling dilution increments. Many studies present MICs of 1.5 $\mu\text{g/ml}$ as though they are meaningfully different than MICs of 2 $\mu\text{g/ml}$ (27–32). This is microbiological nonsense. MIC methods, and especially the Etest, are not accurate enough to report such values (33, 34). It is well known that the allowable error of an MIC value is 1 doubling dilution, and thus, when a laboratory reports an MIC of, for example, 1 $\mu\text{g/ml}$, what they are really reporting is an MIC of 0.5 to 2 $\mu\text{g/ml}$. The Etest, or any method for that matter, simply is not accurate enough to report such a value.

Although variability in MIC determination is a well-known limitation of susceptibility testing, it is frequently dismissed by those who would use the MIC as an absolute value. It is not; it represents a range, and to use it on a patient-by-patient basis overinterprets the data. To illustrate the point, we need look no further than laboratory quality control (QC) data.

For those who are unfamiliar, microbiology laboratories perform regular QC susceptibility testing with known laboratory strains to ensure that all systems perform as expected. QC is performed by medical technologists under the most reproducible and rigorous conditions. Laboratories use exactly the same strain every time and under exactly the same testing conditions. If ever there was a system designed to reproduce the same result every time, antimicrobial susceptibility testing QC is it, and yet, even in this highly controlled setting, laboratories generate a range of results from day to day. Table 3 presents actual vancomycin QC data generated by several College of American Pathologists (CAP)-accredited clinical microbiology laboratories in the United States. Note that when using the Vitek 2 test, not a single result from 4 laboratories and 105 events generated an MIC result of 2 $\mu\text{g/ml}$. Conversely, 93% of Etest MICs were 2 $\mu\text{g/ml}$ for exactly the same strain. More to the point, notice the variability produced by the non-Etest AST methods. Using Vitek 2, 47% of tests yielded an MIC of 1 $\mu\text{g/ml}$ and 53% yielded an MIC of 0.5 $\mu\text{g/ml}$. Results were similar using the MicroScan test and *S. aureus* strain BAA-977.

For real-time AUC/MIC calculations, imagine the confusion that will be generated by the changing MICs that are produced from day to day by our AST methods. If AST methods cannot reliably reproduce MICs in QC testing, one cannot expect them to do so for patient-derived isolates that have been exposed to variables such as biofilm growth, patient immune response, antibiotic exposure, and heterogeneous populations.

TABLE 3 2019 vancomycin quality control results for 6 clinical microbiology laboratories

Lab	Organism	Method	QC range ($\mu\text{g/ml}$)	Total no. of tests	QC result (%) with the following MIC ($\mu\text{g/ml}$):		
					≤ 0.5	1	2
1	<i>S. aureus</i> 29213	Vitek 2	≤ 0.5 –2	20	10 (50)	10 (50)	0
2	<i>S. aureus</i> 29213	Vitek 2		18	13 (82)	5 (18)	0
3	<i>S. aureus</i> 29213	Vitek 2		47	13 (28)	34 (72)	0
6	<i>S. aureus</i> 29213	Vitek 2		20	0	20 (100)	0
3	<i>S. aureus</i> 29213	Etest		4	0	0	4 (100)
4	<i>S. aureus</i> 29213	Etest		50	0	6 (12)	44 (88)
5	<i>S. aureus</i> 29213	Etest		21	0	0	21 (100)
6	<i>S. aureus</i> 29213	Etest		20		1 (5)	19 (95)
5	<i>S. aureus</i> 29213	MicroScan	0.5–2	20	0	20 (100)	0
5	<i>S. aureus</i> BAA-977	MicroScan	None	20	13 (65)	7 (35)	0

As a result, reporting of vancomycin MICs, or any MIC for that matter, is misleading and should not be done, ever.

The Etest phenomenon. It is interesting that nearly all of the studies demonstrating a correlation between vancomycin MICs of 2 $\mu\text{g/ml}$ and treatment failure use the Etest. For a thorough review of this subject, see the meta-analysis published by van Hal and colleagues (1). Of the 29 manuscripts included in their review, only 7 used a vancomycin susceptibility testing method other than Etest. Among the non-Etest-based studies, a variety of treatment failure definitions were used, but 4 showed a correlation with elevated MICs and failure, while the other 3 did not. In contrast, the Etest-based studies consistently showed poorer outcomes in both mortality and treatment failure when the Etest MIC was elevated. Taken together, these data suggest that the Etest MICs are better predictors of poor outcome than MICs determined by all other AST methods, including the gold standard AST method, reference broth microdilution.

The consensus finding that only the elevated Etest MIC is predictive of poor outcomes has led some to conclude that the Etest is the best method for performing vancomycin MICs. Given the Etest's predilection for falsely elevating MIC values, this might simply reflect the fact that vancomycin just is not a very good antibiotic for treating *S. aureus* infections. In support of this conclusion, the van Hal et al. meta-analysis (1) included some 4,883 evaluable episodes across all MICs and all infection types, with a mortality of 22% for patients treated with vancomycin. Obviously, mortality rates will vary by institution, patient population, and therefore by study, but the one consistent finding in all studies that included a comparator for the treatment of *S. aureus* BSI is that there are better options than vancomycin. The Etest correlation with mortality is likely an artifact of its tendency to generate MICs of 2 $\mu\text{g/ml}$ for >90% of isolates.

Summary. For laboratories reporting vancomycin MICs, especially those that include warnings about treatment failure when the MIC is 2 $\mu\text{g/ml}$, the implication is that these isolates should be managed differently than isolates for which MICs are <2 $\mu\text{g/ml}$. This rationale is flawed, as it suggests that other therapies would be beneficial only when MICs are 2 $\mu\text{g/ml}$. There is no evidence that this is true, and Claeys et al.'s study showed that alternative therapies would be beneficial regardless of vancomycin MIC.

Put another way, those who would be inclined to use alternative therapies when MICs are 2 $\mu\text{g/ml}$ but not lower would have to argue that it is important to reduce mortality rates from 25% to 18% (the composite mortality rates for isolates for which vancomycin MICs are 2 $\mu\text{g/ml}$ or <2 $\mu\text{g/ml}$ [1]) but that it is not important to reduce mortality rates from 18% to 8.3% (the composite mortality rates for isolates for which vancomycin MICs are <2 $\mu\text{g/ml}$ [1] versus daptomycin treatment [35–37]). By these

numbers, there is a greater benefit to switching to daptomycin when vancomycin MICs are 1 $\mu\text{g/ml}$ or less.

As the pharmacy and infectious disease community considers guidelines that recommend vancomycin dosing based on patient-specific AUC/MIC calculations, the discussion about reporting of vancomycin MICs is critically important. This recommendation will drive requests to report vancomycin MICs, which, for all of the reasons discussed above, would be a mistake. For those making such a recommendation, the following question needs to be asked: which MIC method should be performed to facilitate the AUC/MIC calculation? If my laboratory uses the Etest (effectively doubling the MIC), the AUC/MIC calculation will be double or quadruple that of a laboratory testing the very same isolate with Vitek 2 and somewhere in between for those using MicroScan. This concept was studied by Eum and colleagues and discussed in detail by Heil and colleagues (38, 39).

Fortunately, there is an easy solution to this problem that should allow us to move forward with patient-specific AUC/MIC calculations. If the *S. aureus* vancomycin AST interpretation is susceptible, regardless of method, assume that the MIC is 1 $\mu\text{g/ml}$. For decisions about whether a patient is responding to vancomycin therapy, follow the 2011 recommendations of the Infectious Diseases Society of America, which states that “a patient’s clinical response should determine the continued use of vancomycin, independent of the MIC” (40). They make this recommendation because “current susceptibility testing methods are unable to reliably distinguish MICs of 1 $\mu\text{g/ml}$ from MICs of 2 $\mu\text{g/ml}$ ” (40). For decisions about AUC/MIC-based dosing calculations, for isolates testing as susceptible, the MIC should be considered to be 1 $\mu\text{g/ml}$. Globally, this is the “right” vancomycin MIC for susceptible *S. aureus*, a point that is nicely proven by the study of nearly 200,000 *S. aureus* isolates from all over the world (41). In this study, using reference broth microdilution, the MIC₅₀ and the MIC₉₀ was 1 $\mu\text{g/ml}$. This was true regardless of whether an isolate was methicillin susceptible or resistant, and it is worth noting that, using a gold standard AST method, for <3% of isolates, the MIC was 2 $\mu\text{g/ml}$, which does not correlate with poorer outcomes.

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SUMMARY

Points of agreement

1. Many of the commercially available antimicrobial susceptibility testing systems lack the ability to accurately report vancomycin MICs, which can greatly impact dosing strategies.
2. The variation in the performances of antimicrobial susceptibility testing systems compared to broth microdilution has resulted in a number of studies evaluating the utility of vancomycin MICs that are difficult to interpret or apply to clinical practice.
3. Clinical laboratories that report vancomycin MICs should consider reverting to broth microdilution or another methodology with a high degree of accuracy.
4. Alternate agents, such as daptomycin and/or ceftaroline, may offer superior outcomes to those of vancomycin in managing *S. aureus* bacteremia, although further research is needed.
5. In health systems that implement the AUC/MIC approach to vancomycin dosing, an evidence-based approach may be needed. When using the AUC/MIC approach for vancomycin dosing, health systems should recognize the need for multiple vancomycin levels, the education of clinicians on antibiotic dosing strategies, and the need for embedded calculations within the electronic medical record to facilitate the determination of the AUC/MIC ratio.

Points requiring further consideration

1. Several studies suggest that the risk of treatment failure increases when the vancomycin MIC is 2 $\mu\text{g/ml}$, and these isolates should be managed differently than isolates for which MICs are $<2 \mu\text{g/ml}$. Our authors disagree that alternate therapy is beneficial only when the vancomycin MIC is 2 or greater, with Dr. Doern suggesting alternate therapy can be beneficial for all patients.
2. If MICs are to be reported, the infectious disease community together with breakpoint-setting organizations should develop a uniform standard for determining vancomycin MICs.

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