Vancomycin Minimum Inhibitory Concentration and Outcome in Patients With *Staphylococcus aureus* Bacteremia: Pearl or Pellet?

Thomas L. Holland and Vance G. Fowler Jr

Department of Medicine, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina

(See the article by Holmes et al, on pages 340–7.)

For decades, vancomycin has been the mainstay of treatment for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Recently, a debate has arisen over its continued utility for this purpose [1], fueled by a steady stream of reports linking a worse clinical outcome of MRSA-infected patients and a higher vancomycin minimum inhibitory concentration (MIC) of the infecting pathogen (Table 1). In fact, 13 of the 16 peer-reviewed publications addressing the topic to date have found that patient outcomes are worse when the vancomycin MIC of the infecting MRSA strain is higher, even if it still falls in the susceptible range. This association between poor patient outcome and high vancomycin MIC has been attributed to difficulty achieving an optimal vancomycin area under curve (AUC)/MIC ratio [2, 3], which is widely regarded as the best predictor of successful vancomycin therapy [4]. Clinicians have responded to this association by either increasing the vancomycin dose or switching to an alternative antibiotic. However, recent practice guidelines from the Infectious Diseases Society of America (IDSA) for treatment of MRSA infections do not recommend using a vancomycin alternative based on an elevated MIC alone, provided that the isolate has an MIC in the susceptible range [5].

In this issue of the *Journal*, Holmes et al add another wrinkle to this story. In their prospective multinational cohort of 532 patients with *S. aureus* bacteremia, elevated vancomycin MIC was associated with increased 30-day mortality in patients with MRSA bacteremia [6]. The truly exciting aspect of the article, however, was unveiled by the investigators' ingenious decision to consider the same association in patients infected with methicillin-susceptible *S. aureus* (MSSA)—most of whom never received vancomycin. When the investigators evaluated vancomycin MIC values of the isolates from patients with MSSA bacteremia who were treated exclusively with flucloxacillin, they found that the same association existed between higher vancomycin MIC and worse overall clinical outcomes. In these patients, of course, a low vancomycin AUC/MIC ratio cannot be invoked as the explanation for worse patient outcome. How, then, are we to explain this link between MIC and mortality? And what should clinicians do when faced with the increasingly common dilemma of how to treat patients with MRSA infection and a vancomycin MIC >2 μg/mL? This study provides insights into both of these key questions.

Strengths of the study include its robust sample size and its prospective, multinational design. With well over 500 patients, it is the largest of the prospective cohorts yet assembled to tackle this issue. It provides further evidence to support the association between higher vancomycin MIC and worse patient outcome in MRSA-infected patients. For the first time, however, the investigators present novel, compelling evidence that this association may not be causal, by demonstrating it in the bloodstream isolates of MSSA-infected patients who were not treated with vancomycin. The authors speculate that the vancomycin MIC could be a marker of as yet unidentified host or organism factors that affect treatment outcome. For example, factors that alter the biology of the *S. aureus* cell wall or cell membrane could

Received and accepted 12 April 2011.

Potential conflicts of interest: none reported. V. F. completed the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Correspondence: Vance G. Fowler Jr, MD, MHS, Department of Medicine, Duke University Medical Center, Box 102359 Medical Center, Durham, NC, 27710 (fowle003@mc.duke.edu).

The Journal of Infectious Diseases 2011;204:329–31

0022-1899 (print)/1537-6613 (online)/2011/2043-0001$14.00
DOI: 10.1093/infdis/jir275

Table 1. Summary of Published Studies Evaluating Association Between Vancomycin Minimum Inhibitory Concentration (MIC) of Infecting Pathogen and Patient Outcome

Study	Year	MIC comparison (All Units ug/mL)	MIC test method	Infection type	Study design	Clinical outcome
Studies that have shown a worse outcome with higher vancomycin MIC						
Moise-Broder et al [11]	2004	0.5 vs 1.0 vs 2.0	BMD	All MRSA infections	Retrospective cohort	Higher rate of treatment failure with increasing MIC
Sakoulas et al [12]	2004	0.5 vs ≥1	BMD	MRSA bacteremia	Prospective cohort	Higher treatment failure with higher MIC
Hidayat et al [13]	2006	<2 vs ≥2	Etest	MRSA from any site	Prospective cohort	Lower end-of-treatment response and higher infection-related mortality in high-MIC group
MacClayton et al [14]	2006	≤0.5 vs 2	BD	MRSA bacteremia in hemodialysis patients	Retrospective case-control study	Higher mortality in high-MIC group
Neoh et al [15]	2007	1.0 vs 2.0	BMD	MRSA bacteremia	Retrospective cohort	Poor outcome associated with higher MIC
Lodise et al [8]	2008	<1.5 vs ≥1.5	Etest	MRSA bacteremia	Retrospective cohort	Higher rate of failure in high-MIC group
Soriano et al [16]	2008	1.0 vs 1.5 vs 2.0	Etest	MRSA bacteremia	Prospective cohort	Higher mortality with MIC = 2 μg/mL
Musta et al [17]	2009	1.0 vs 1.5 vs 2.0	Etest	MRSA bacteremia	Retrospective cohort	Higher mortality with MIC ≥2 μg/mL
Haque et al [9]	2010	0.75 vs 3	Etest	MRSA nosocomial pneumonia	Prospective cohort	Increasing 28-d mortality with increasing MIC
Wang et al [18]	2010	<2.0 vs 2.0	BMD	MRSA bacteremia	Prospective cohort	Higher mortality in high-MIC group
Yoon et al [10]	2010	<2.0 vs 2.0	Vitek card	MRSA bacteremia	Retrospective case-control study	MIC = 2 μg/mL was a risk factor for persistent MRSA bacteremia
Choi et al [19]	2011	≤1 vs ≥1.5	Etest	MRSA nosocomial pneumonia	Retrospective cohort	Slower clinical response and higher relapse rate in high-MIC group
Kullar et al [2]	2011	<1 vs ≥1	Etest and BMD	MRSA bacteremia	Retrospective cohort	Higher rate of vancomycin failure with higher MIC
Studies that have not showed an association between vancomycin MIC and clinical outcome						
Crompton et al [20]	2010	<2 vs ≥2	Not specified	MRSA SSTI, bacteremia, IE	Retrospective registry	No significant difference in clinical failure rates
Honda et al	2011	≤1 vs ≥2	BMD	MRSA bacteremia	Prospective cohort	Higher MIC not associated with mortality
Studies that have shown a better outcome with higher vancomycin MIC						
Price et al [21]	2009	<1 vs >1.5	Etest	*S. aureus* bacteremia	Prospective cohort	Lower 3-mo mortality with higher MIC

NOTE. BMD, broth microdilution; BD, broth dilution; IE, infective endocarditis; MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and skin structure infection.

conceivably both influence vancomycin MIC and enhance bacterial virulence. Indeed, changes such as increased cell wall thickness, decreased autolysis, and metabolic changes characterize *S. aureus* isolates with reduced susceptibility to vancomycin [7]. Thus, it is possible that these or similar changes might also influence treatment outcomes with β-lactam antibiotics. Alternatively, it may simply be that the link is driven by patient comorbidities and healthcare contact. Because of limitations of their database, Holmes et al were unable to provide data on these comorbid conditions or clinical variables such as APACHE II scores. We are, therefore, left with the possibility that "sicker" patients (both the chronically unwell and the acutely ill, hospitalized patients) who acquire nosocomial staphylococcal infection are simply more likely to be infected with hospital-resident strains of higher-MIC *S. aureus* and are more likely to die because of—or in spite of—their resultant infections.

With their discovery that high vancomycin MIC does not fully explain the higher mortality suffered by MRSA-infected patients, Holmes et al have made an important contribution to the field. A common inference from previous studies that focused solely on MRSA-infected, vancomycin-treated patients was that alternatives to vancomycin should be used when the

vancomycin MIC was above some cutoff value (but still ≤ 2 μg/mL) [1, 8–10]. The findings reported in the Holmes et al article call such an assumption into question. At a minimum, the results of this study provide supporting evidence for the recommendations of the IDSA Treatment Guidelines for MRSA that vancomycin MIC alone should not guide the decision of whether to use vancomycin for isolates with MIC ≤2 μg/mL [5].

In summary, Holmes et al are to be commended for their work. Although there clearly appears to be a link between high vancomycin MIC and poor outcome in *S. aureus*–infected patients, Holmes et al show that this link is probably not causal. For this reason, the practice of systematically switching patients infected with MRSA exhibiting vancomycin MIC ≤2 μg/mL from vancomycin to an alternative antibiotic is probably often unnecessary. Vancomycin's long reign as first-line therapy for serious MRSA infections may be in its twilight, but there is still no proven heir to the throne.

Funding

Funding for this study was provided by by K24-AI093969 (VGF) and NO1-AI90023 (VGF).

References

1. Deresinski S. Counterpoint: Vancomycin and *Staphylococcus aureus*–An antibiotic enters obsolescence. Clin Infect Dis **2007**; 44:1543–8.
2. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: Support for consensus guidelines suggested targets. Clin Infect Dis **2011**; 52:975–81.
3. Patel N, Pai MP, Rodvold KA, Lomaestro B, Drusano GL, Lodise TP. Vancomycin: We can't get there from here. Clin Infect Dis **2011**; 52:969–74.
4. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis **2009**; 49:325–7.
5. Liu C, Bayer A, Cosgrove SE, et al. Infectious Diseases Society of America. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis **2011**; 52:e18–55.
6. Holmes N, Turnidge J, Munckhof W, et al. Antibiotic choice may not explain poorer outcomes in patients with high vancomycin MIC *Staphylococcus aureus* bacteremia. J Infect Dis **2011**; 204:340–7.
7. Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in *Staphylococcus aureus,* including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: Resistance mechanisms, laboratory detection, and clinical implications. Clin Microbiol Rev **2010**; 23:99–139.
8. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. Antimicrob Agents Chemother **2008**; 52: 3315–20.
9. Haque NZ, Zuniga LC, Peyrani P, et al. Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Relationship of vancomycin minimum inhibitory concentration to mortality in patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired, ventilator-associated, or health-care-associated pneumonia. Chest **2010**; 138:1356–62.
10. Yoon YK, Kim JY, Park DW, Sohn JW, Kim MJ. Predictors of persistent methicillin-resistant *Staphylococcus aureus* bacteraemia in patients treated with vancomycin. J Antimicrob Chemother **2010**; 65: 1015–8.
11. Moise-Broder PA, Sakoulas G, Elipopoulos GM, Schentag JJ, Forrest A, Moellering RC Jr. Accessory gene regulator group II polymorphism in methicillin-resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. Clin Infect Dis **2004**; 38:1700–5.
12. Sakoulas G, Moise-Broder PA, Schentag JJ, Forrest A, Moellering RC Jr, Elipopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol **2004**; 42: 2398–402.
13. Hidayat LK, Hsu D, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: Efficacy and toxicity. Arch Intern Med **2006**; 166:2138–44.
14. Maclayton DO, Suda KJ, Coval KA, York CB, Garey KW. Case-control study of the relationship between MRSA bacteremia with a vancomycin MIC of 2 microg/mL and risk factors, costs, and outcomes in inpatients undergoing hemodialysis. Clin Ther **2006**; 28:1208–16.
15. Neoh HM, Hori S, Komatsu M, et al. Impact of reduced vancomycin susceptibility on the therapeutic outcome of MRSA bloodstream infections. Ann Clin Microbiol Antimicrob **2007**; 6:13.
16. Soriano A, Marco F, Martínez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis **2008**; 46: 193–200.
17. Musta AC, Riederer K, Shemes S, et al. Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: Trends over 11 years. J Clin Microbiol **2009**; 47: 1640–4.
18. Wang JL, Wang JT, Sheng WH, Chen YC, Chang SC. Nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in Taiwan: Mortality analyses and the impact of vancomycin, MIC = 2 mg/L, by the broth microdilution method. BMC Infect Dis **2010**; 10:159.
19. Choi EY, Huh JW, Lim CM, et al. Relationship between the MIC of vancomycin and clinical outcome in patients with MRSA nosocomial pneumonia. Intensive Care Med **2011**; 37:639–47.
20. Crompton JA, North DS, Yoon M, Steenburgen JN, Lamp KC, Forrest GN. Outcomes with daptomycin in the treatment of *Staphylococcus aureus* infections with a range of vancomycin MICs. J Antimicrob Chemother **2010**; 65:1784–91.
21. Price J, Atkinson S, Llewelyn M, Paul J. Paradoxical relationship between the clinical outcome of *Staphylococcus aureus* bacteremia and the minimum inhibitory concentration of vancomycin. Clin Infect Dis **2009**; 48:997–8.