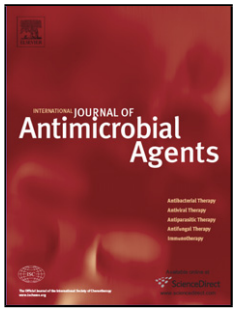
Is vancomycin redundant for serious staphylococcal infection?

Ian M. Gould



Title: Is vancomycin redundant for serious staphylococcal infection?

Author: Ian M. Gould

PII: S0924-8579(10)00466-8
DOI: doi:10.1016/j.ijantimicag.2010.11.005
Reference: ANTAGE 3459

To appear in: *International Journal of Antimicrobial Agents*

Please cite this article as: Gould IM, Is vancomycin redundant for serious staphylococcal infection?, *International Journal of Antimicrobial Agents* (2010), doi:10.1016/j.ijantimicag.2010.11.005

Is vancomycin redundant for serious staphylococcal infection?

Ian M. Gould*

Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, AB25 2ZN, UK

*Tel.: +44 (0)1224 554954; fax: +44 (0)1224 550632.

E-mail address: i.m.gould@abdn.ac.uk.

Abstract

Vancomycin's clinical utility is under serious threat. Intensive use has created selective pressure and many databases record modal minimum inhibitory concentrations (MICs) of ≥1 mg/L. Although the current breakpoint is 2 mg/L this is reasonably well established as having no clinical relevance. Unfortunately, setting a clinical breakpoint of 0.5 or 1 mg/L, which is argued persuasively by the available clinical data, would lead to a loss of reproducibility and frequent misclassification of susceptibility in the laboratory. Moreover, MIC testing is method-dependent and this adds further confusion when trying to ascertain the place of an antibiotic with such a narrow therapeutic window. The optimal pharmacokinetic/pharmacodynamic target of a total area under the curve (AUC)/MIC ratio of 400, although based on only a small number of publications, is backed up by the available clinical studies, albeit that they are non-randomized cohorts, often retrospective. Unfortunately, the toxicity of vancomycin would seem to prevent us from prolonging its useful life by increasing doses. Even if the AUC/MIC ratio 400 were reached, it is not clear that such doses would be more efficacious, as a raised MIC also heralds other changes in the organism, such as altered accessory gene regulation and tolerance, which may further diminish the drug's performance. Unless vancomycin use can be seriously reduced, continued selective pressure is quite likely to lead to further elevations in MICs and increased numbers of strains with intermediate or reduced susceptibility. The same conclusions almost certainly apply to teicoplanin.

Keywords:

Meticillin-resistant *Staphylococcus aureus*

MRSA

Vancomycin

Teicoplanin

Breakpoint

Minimum inhibitory concentration

1. Introduction

Much debate has recently centred around whether vancomycin is redundant for the first-line treatment of serious staphylococcal infection, but it is fair to say that it is still generally perceived as the gold standard and is the usual comparator in clinical studies of new drugs for meticillin-resistant staphylococci [1]. Ever since its introduction into clinical use, however, it has been perceived as both toxic and poorly effective and was rapidly returned to the shelf when the semi-synthetic penicillins were developed [2]. With the advent of meticillin-resistant *Staphylococcus aureus* (MRSA) as a major worldwide epidemic it was rehabilitated, and remarkably seems to have maintained a first-line place over the past 20 years, particularly for the treatment of serious MRSA infections.

A long history of clinical, albeit usually non-randomized, comparative trials against β-lactam antibiotics consistently shows a poorer outcome for vancomycin-treated patients infected with meticillin-sensitive *S. aureus* (MSSA), and there is little doubt that this lesser clinical efficacy explains, at least in part, the consistently poorer outcomes reported for serious MRSA infections against comparable MSSA infections [3]. This is also still a serious issue for MSSA infections if vancomycin is used as sole empirical therapy for possible MRSA infections, as many of these patients will have MSSA and would do better on a β-lactam agent.

2. Minimum inhibitory concentration ‘creep’ or ‘leap’

The case for ceasing the routine use of vancomycin is strengthened by data emerging in the past few years that describe rising minimum inhibitory concentrations (MICs) for vancomycin in both MRSA and MSSA [4]. This is by no means a uniform observation and, where and if it occurs, it is uncertain whether it is due to strain evolution (MIC creep) or strain change (MIC leap) under continuous selective pressure. What is more important, however, in terms of whether vancomycin is likely to be efficacious, is the modal MIC in the locality, community or hospital and what is clear is that this is both variable and method-dependent [5]. Large databases such as EUCAST [6] have a modal MIC of 1 mg/L for both MSSA and MRSA using broth microdilution reference methods.

3. Pharmacokinetic/pharmacodynamic (PK/PD) targets

Several studies suggest that the area under the curve (AUC)/MIC ratio is the best predictor of outcome with vancomycin [7] but I am aware of only two studies, one of them in abstract form only, that have studied the optimal PK/PD target ratio [8,9]. The first study, in a neutropenic mouse model [9], suggested that total AUC/MIC ratios of around 500 might be optimal. The second study, in staphylococcal pneumonia, established a total AUC/MIC ratio of >345 as predicting good clinical outcome, although even higher levels might have been associated with a further improved outcome e.g. in high-inoculum infections with a ratio of 850 needed for microbiological eradication. Subsequent reviews and expert statements seem to have settled on an AUC/MIC figure of 400 as the

target to attain for an optimum outcome, but clearly more studies would be helpful [7].

Other studies [9-17] have assessed the efficacy of attaining a target unbound serum trough level of four to five times the MIC. This can be correlated quite well with AUC/MIC ratios and, as we shall see, similar outcome data can be extracted from these studies, adding some weight to the total AUC/MIC ratio of 400 as the correct target.

4. Clinical studies

As is usual in this field there are no randomized studies, and many are retrospective cohorts (Table 1) [9–17]. Nevertheless, there is a consistency both in the type of patient and the results. Most patients are bacteraemic, although rarely diagnosed with infective endocarditis, some have pneumonia and all the studies describe poorer outcome with higher MICs, although all isolates studied were considered fully susceptible, even by the new EUCAST and Clinical and Laboratory Standards Institute breakpoints of ≤2 mg/L [18].

[Table 1 here]

One critical aspect of the studies is which method they use to ascertain the vancomycin MIC, and here we can make a potentially very interesting observation. The studies using the reference method of broth dilution (macro or micro) usually report a breakpoint of 0.5 mg/L, above which there is poorer outcome. On the other hand, studies using the Etest consistently report a

breakpoint of 1 mg/L, above which there is a poorer outcome. This discrepancy can be convincingly explained by the systematic higher reading of MICs when the Etest is compared with the reference methods, with an approximate doubling of the MIC when read by the Etest [5,19,20]. The data are confounded, however; the studies using the reference method (broth micro- or macrodilution) are older and tend to have lower serum levels of vancomycin than those using the Etest (or VITEK).

There seems, however, to be a limit to the degree to which higher dosing schedules can compensate for raised MICs. Higher doses also increase the risk of nephrotoxicity. Thus it seems unrealistic to dose patients to achieve an AUC/MIC ratio of 400 for strains with an MIC of 2 mg/L, even by the Etest.

Clearly these studies do not begin to address glycopeptide-intermediate *S. aureus* (GISA) or even heterogeneous (h)GISA, which fortunately remain relatively rare but are also clearly related to poor outcome on treatment with glycopeptides. GISA were one of the reasons for the recent lowering of the vancomycin MIC from 4 to 2 mg/L, so these strains can now be classified as resistant. Clearly though, a breakpoint of 2 mg/L is still too high. Why was it not set lower and what should it actually be, based on our current knowledge?

5. What should the vancomycin breakpoint be for *S. aureus*?

When setting breakpoints it is normal to allow at least a couple of doubling dilutions between the breakpoint and the MICs of the susceptible (or resistant)

population because of day-to-day variability in the testing procedure. It is clear that there were too many clinical failures in infections by isolates with an MIC 4 mg/L, even with high-dose vancomycin, so the breakpoint was lowered to 2 mg/L. Arguably the breakpoint should have been lowered to 0.5 mg/L (sensitive) or 1 mg/L (intermediate) but this would, overnight, have designated many strains as vancomycin-resistant (or at best intermediate, perhaps responding to high-dose vancomycin) and thus made vancomycin redundant. So at the moment we just have one breakpoint (sensitive/resistant), which accommodates all GISA as resistant but misclassifies many hGISA as susceptible and ignores the fact that many infections with an MIC of 2 and even 1 mg/L will fail therapy.

Although the breakpoint setting should be based on reference data methodology, the clinical data, imperfect as it is, argues for a sensitive breakpoint of 0.5 mg/L and perhaps a higher, intermediate, breakpoint of 1 mg/L. But if the Etest is used then the sensitive breakpoint should be 1 mg/L. There are no data to suggest that an intermediate breakpoint of 2 mg/L by the Etest is appropriate, although 1.5 mg/L may be a possibility. This is problematic for the reproducibility of the susceptibility test as the breakpoint is now firmly in the middle of the MIC distribution curve. Given the innate lack of reproducibility of such tests (conventionally ± one doubling dilution), they will not be able to give reliable data to the clinician. One day the isolate may be susceptible, with an MIC of 0.5 or 1 mg/L, the next day it might test as 2 mg/L and resistant. The automated

systems are no help, seemingly being unable to reliably detect MICs <2 mg/L [20].

We can thus conclude that the breakpoint of 2 mg/L is a microbiological one only, set for reasons of test reproducibility. If vancomycin is to be used at all for serious staphylococcal infection then a sensitive, resistant or intermediate result is of little use to clinicians. Not only must they be told the actual MIC but also the method used to ascertain it.

6. A strategy for choosing the appropriate antibiotic

In conclusion we can be certain that the current breakpoint is incorrect for clinical purposes. It is also likely that the breakpoint will be method-dependent if Etests are to continue to be used. Clearly they are very convenient for the average clinical diagnostic laboratory, so this is probable.

In many hospitals most *S. aureus* strains are probably fully susceptible to vancomycin, if only just, with an MIC of 1 mg/L by the Etest. But judging by the published literature, others are not in such a fortunate situation. What will be critical to the future of vancomycin is whether MIC creep or leap continues apace. Perhaps control of MRSA might come just in time to save vancomycin, if this is associated with significantly reduced use and thus reduced selective pressure.

[Table 2 here]

A possible strategy for coping with the current dilemma is seen in Table 2. Although there is a lack of clinical evidence, the same conclusions almost

certainly apply to teicoplanin. It remains to be seen whether new glycopeptides such as telavancin and oritavancin will offer a clinical advantage. Certainly their microbiological activity against GISA seems good [21].

Funding: The author received an honorarium for writing this article. The funds for the honorarium were provided by Novartis AG, Switzerland and were handled by the organizing committee of the 4th European Conference on Bloodstream Infections for the publication of this supplement.

Competing interests: The author has received consultancy fees, lecture fees and research grants from all companies currently marketing novel MRSA treatments.

Ethical approval: Not required.

References

1. Fowler VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006;355:653–65.

2. Mohr JF, Murray BE. Point: Vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 2007;44:1536–42.

3. Lodise TP, McKinnon PS, Levine DP, Rybak MJ. Impact of empirical therapy selection on outcomes of intravenous drug users with infective endocarditis caused by methicillin-susceptible *Staphyloccus aureus*. Antimicrob Agents Chemother 2007;51:3731–3.

4. Gould IM. Clinical relevance of increasing glycopeptide MICs against *Staphylococcus aureus*. Int J Antimicrob Agents 2008;31:1–9.

5. Sader HS, Rhomberg PR, Jones RN. Nine-hospital study comparing broth microdilution and Etest method results for vancomycin and daptomycin against methicillin-resistant *Staphylococcus aureus.* Antimicrob Agents Chemother 2009;53:3162–5.

6. European Committee on Antimicrobial Susceptibility Testing – EUCAST. http://www.eucast.org [accessed 16 July 2010].

7. Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious

Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66:82–98.

8. Craig WA, Andes DR. In vivo pharmacodynamics of vancomycin against VISA, heteroresistant VISA (hVISA) and BSSA in the neutropenic murine thigh-infection model. Abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; 27–30 September 2006; San Francisco, CA, A-644.

9. Moise-Broder PA, Sakoulas G, Eliopoulos GM, Schentag JJ, Forrest A, Moellering RC. Accessory gene regulatory group II polymorphism in methicillin-resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. Clin Infect Dis 2004;38:1700–5.

10. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Eliopoulos GM. Relationship of MIC and bacteriocidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 2004;42:2398–402.

11. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections. Arch Intern Med 2006;166:2138–44.

12. MacLayton DO, Hall RG. Pharmacologic treatment options for nosocomial pneumonia involving methicillin-resistant *Staphylococcus aureus*. Ann Pharmacother 2007;41:235–44.

13. Maclayton DO, Suda KJ, Coval KA, York CB, Garey KW. Case–control study of the relationship between LMRSA bacteremia with a vancomycin MIC of

2 μg/ml and risk factors, costs and outcome in inpatients undergoing hemodialysis. Clin Ther 2006;28:1208–16.

14. Moise PA, Sakoulas G, Forrest A, Schentag JJ. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother 2007;51:2582–6.

15. Lodise TP, Graves J, Evans A, Graffunder E, Helmecke M, Lomaestro BM, et al. Antimicrob Agents Chemother 2008;52:3315–20.

16. Soriano A, Marco F, Martinez JA, Pisos E, Almela M, Dimova VP, 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. Yoon YK, Kim JY, Park DW, Sohn JW, Kim MJ. Predictors of persistent methicillin-resistant *Staphylococcus aureus* bacteremia in patients treated with vancomycin. J Antimicrob Chemother 2010;65:1015–18.

18. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A7. Wayne, PA: Clinical and Laboratory Standards Institute; 2006.

19. Prakash V, Lewis JS 2nd, Jorgensen JH. Vancomycin MIC's for methicillin-resistant *Staphylococcus aureus* isolates differ based upon the susceptibility test method used. Antimicrob Agents Chemother 2008;52:4528.

20. Hsu DI, Hidayat LK, Quist R, Hindler J, Karisson A, Yusof A, et al. Comparison of method-specific vancomycin minimum inhibitory concentration values and their predictability for treatment outcome of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Int J Antimicrob Agents 2008;32:378–85.

21. Saravolatz LD, Pawlak J, Johnson LB. In vitro activity of oritavancin against community-associated meticillin-resistant *Staphylococcus aureus* (CA-MRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA) and daptomycin-non-susceptible *S. aureus* (DNSSA). Antimicrob Agents Chemother 2010;36:69–72.

Table 1

Published clinical studies of clinical vancomycin breakpoints vs the minimum inhibitory concentration (MIC) method

Study [ref]	MIC test method	Clinical breakpoint (mg/L)	Target serum vancomycin trough (mg/L)	Infection type/outcome
Mosse-Broder et al. 2004 [9]	BMD[a]	≤0.5	NA	Clinically significant infection[b]
Sakoulas et al. 2004 [10]	BMD	≤0.5	10–15	MRSAB/treatment failure
Hidayat et al. 2006 [11]	Etest	≤1.0	15–20	MRSA infections incl. pneumonia, bacteraemia, SSTI/initial response, end-of-treatment response, infection-related mortality
Maclayton and Hall 2006 [12]	BD	≤0.5	? 5–10	Pneumonia
Maclayton et al. 2006	BD	≤0.5	5–10	MRSAB haemodialysis

[13]				
Moise et al. 2007 [14]	BMD	≤0.5[c]	8–12	MRSAB/clearance from blood[c]
		≤1.0		
Lodise et al. 2008 [15]	Etest	≤1.0	9–16	MRSAB/treatment failure
Soriano et al. 2008	Etest	≤1.0	>10	MRSAB/mortality
[16]				
Youn et al. 2010 [17]	VITEK	≤1.0	15–25	MRSAB/persistent MRSAB

BD, broth dilution (reference method); BMD, broth microdilution (reference method); MRSA, meticillin-resistant *Staphylococcus aureus*; MRSAB, MRSA bacteraemia; NA, not available; SSTI, skin and soft tissue infection.

[a] Stated as BM in paper, checked with one of the authors (J.J. Schentag).

[b] 40 of the 87 were in an intensive care unit. Infections included MRSAB, bone and joint, respiratory, intra-abdominal and SSTI.

[c] Breakpoint 0.5 for days to eradication and 1.0 for eradication rate by end of therapy.

Table 2

Algorithm for minimum inhibitory concentration (MIC)-based treatment of severe meticillin-resistant *Staphylococcus aureus* (MRSA) infections[a]

1. Risk assess for MRSA colonization in septic patients
2. Rapid screen for MRSA colonization

If 1 or 2 positive

3. Include MRSA cover in empirical treatment
4. Use glycopeptides* (trough 20 mg/L) if
    (a) Sepsis not life-threatening and
    (b) MIC ≤0.5 mg/L or not known, or
    (c) Modal glycopeptide MIC for your hospital is ≤0.5 mg/L

* Change to daptomycin or linezolid according to licensed indications if patient becomes septic, slow to respond or has prolonged bacteraemia. Check daptomycin MIC if previously glycopeptide-treated.

5. Use linezolid or daptomycin according to licensed indications if
    (a) Sepsis life-threatening
    (b) MIC ≥0.5 mg/L to glycopeptide (check daptomycin MIC)
    (c) Previous glycopeptide therapy (check daptomycin MIC)

[a] MIC measured by a reference method.