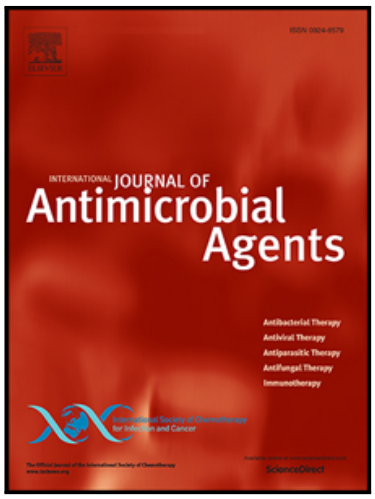

The dosing and monitoring of vancomycin – what is the best way forward?

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Highlights.

- Vancomycin remains an indispensable agent for the treatment of *S. aureus* infections
- Therapeutic drug monitoring can maximise the probability of successful outcomes
- Bayesian and log-linear methods or continuous infusions are superior to trough monitoring
- Variation in estimates of drug exposure and pathogen susceptibility must be considered for rational treatment individualization

The dosing and monitoring of vancomycin – what is the best way forward?

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Running Head: Vancomycin dosing and monitoring in adults

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Abstract

We have evaluated the literature to review optimal dosing and monitoring of intravenous vancomycin in adults, in response to evolving understanding of targets associated with efficacy and toxicity. The area under the total concentration-time curve (0 - 24 h) divided by the MIC (AUC_{24}/MIC) is the most commonly accepted index to guide vancomycin dosing for the treatment of *Staphylococcus aureus* infections, with a value of 400 h a widely recommended target for efficacy. Upper limits of AUC_{24} exposure of around 700 (mg/L).h have been proposed, based on the hypothesis that higher exposures of vancomycin are associated with an unacceptable risk of nephrotoxicity. If AUC_{24}/MIC targets are used, sources of variability in the assessment of both AUC_{24} and MIC need to be considered. Current consensus guidelines recommend measuring trough vancomycin concentrations during intermittent dosing as a surrogate for the AUC_{24}. Trough concentrations are a misleading surrogate for AUC_{24} and a poor end-point in themselves. AUC_{24} estimation using log-linear pharmacokinetic methods based on two plasma concentrations, or Bayesian methods are superior. Alternatively a single concentration measured during continuous infusion allows simple AUC_{24} estimation and dose-adjustment. All of these methods have logistical challenges which must be overcome if they are to be adopted successfully.

Keywords: Vancomycin; Staphylococcus aureus; drug monitoring; pharmacokinetics

1. Introduction

Dosing and monitoring strategies for intravenous vancomycin have been the subject of numerous international guidelines and literature reviews.(1–5) Recent contributions to the literature have highlighted the need for a re-evaluation of guideline recommendations, in

response to evolving understanding of targets for efficacy and toxicity in increasingly complex patient populations. The literature varies in suggested pharmacokinetic/pharmacodynamic targets and how these should be achieved, which is a source of confusion. In this commentary, we review important aspects of the dosing and monitoring of intravenous vancomycin for the treatment of infections caused by *Staphylococcus aureus*. We aim to summarise fundamental principles of vancomycin TDM which may serve as a basis for rational dose individualisation for any patient and any therapeutic target, focusing on issues relevant to adult inpatients without critical organ dysfunction. Following this we outline possible strategies for application of these principles in routine clinical practice.

The area under the total concentration-time curve (0 - 24 h) divided by the MIC (AUC_{24}/MIC) is a pharmacokinetic/pharmacodynamic target that is recommended for the treatment of *S. aureus* infections with intravenous vancomycin, based on *in vitro*, animal and human studies. (1) The first human study to suggest an AUC_{24}/MIC target of 400 h derived this value from observational data from patients with *S. aureus* lower respiratory tract infections where the vancomycin MIC by broth microdilution (BMD) was ≤ 1 mg/L. (6) The expression AUC_{24}/MIC should be amended to AUC_{24}/MIC_{BMD} to reflect the method of MIC determination, since different validated methods of MIC determination are not interchangeable. Guidelines and observational studies are in general agreement that this target has some validity and thus is a useful starting point for discussion about different approaches to dosing and monitoring. (1, 7) More recent observational studies have recognised that risk of toxicity also needs to be considered and have attempted to identify AUC_{24} thresholds associated with nephrotoxicity, leading to a proposed AUC_{24} upper limit

of 700 (mg/L).h (8–10). Other factors include characteristics of the infection in individual patients (e.g. site, severity, bacterial subtype, MIC), physiological state (e.g. renal function), and clinical progress. Choosing an appropriate AUC_{24}/MIC_{BMD} target in individual patients should increase the chances of maximising the probability of clinical cure without subjecting the patient to excessive drug exposure and resultant toxicity. Other targets have been proposed, such as the AUC_{24} to minimum bactericidal concentration ratio (AUC_{24}/MBC). One small observational study has suggested that this index may be superior to the AUC_{24}/MIC in predicting treatment mortality in MRSA bacteraemia.(11) Alternative indices such as this warrant further evaluation, however their potential clinical application is contingent on the feasibility of introducing more specific antimicrobial susceptibility testing methods into clinical practice.

A target AUC_{24} range should be considered as a guide only, e.g. one might accept a lower value for a simple infection that has responded well to initial therapy, or a higher target in a complicated infection. In order to achieve targets associated with efficacy, many guidelines, including those published in 2009 by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists (ASHP/IDSA/SIDP guidelines) recommend trough vancomycin concentrations of 15-20 mg/L as an "accurate and practical" method of achieving the target AUC:MIC when the MIC of the pathogen is 1 mg/L or lower. This recommendation was based on the assumption that trough concentrations can be used to accurately infer the AUC_{24}. This assumption may not be widely appreciated, and in practice trough concentrations often become the target in themselves. As we will discuss, such an approach is flawed because the correlation between trough concentration and AUC_{24} is not strong enough to justify

trough-based monitoring in the population of adult patients who are routinely treated with vancomycin. Trough based monitoring therefore carries the risk of inappropriate dosing.(12–14) Our view is that the AUC_{24} must be estimated using a more accurate method.

For intermittent dosing, the AUC_{24} can be estimated via log-linear calculations based on plasma concentrations taken at two time-points within the dosing interval ('two-point estimation') or by Bayesian methods (preferred if available) using one or two concentrations. The AUC_{24} estimation is much simpler if dosing is by continuous infusion, as it can be estimated by multiplying a single steady-state concentration taken at any time (which represents ő$_{ححة}$) by 24 i.e. öˆŸő.٢ ά῎ΩϮΰ ΅῎Ω سي ő$_{ححة}$ ά῎ΩϮΰ عي ςτ ῎Ω . The following discussion emphasises the assumptions and variability inherent in each component of the AUC_{24}/MIC target, and offers a pragmatic way forward for vancomycin dosing and monitoring. Key principles are illustrated in relation to a target AUC_{24}/MIC_{BMD} of 400 h, but apply equally to any chosen target.

2. Key pharmacokinetic-pharmacodynamic concepts for vancomycin dosing and monitoring

2.1 MIC

In clinical practice, the MIC is most commonly used to determine whether an isolate is reported as susceptible or resistant to a particular antimicrobial, and hence whether that antimicrobial should be used. Given that numerous studies suggest that the AUC_{24}/MIC is an important therapeutic target for *S. aureus* infections treated with vancomycin,(7) a

natural tendency is to use the measured MIC of a clinical isolate to derive an individualised AUC_{24}/MIC target for dose adjustment. There are numerous validated methods for determining the MIC. BMD is a reference method commonly used for MIC determination in observational studies that have investigated the association between vancomycin AUC_{24}/MIC and clinical outcomes for patients with *S. aureus* infection.(6, 7, 15) Commercial methods which are less labour-intensive, and therefore preferred in clinical settings include the Etest®, and automated methods that are modifications of BMD.(15) Two issues which must be considered when interpreting the suitability of the MIC as a tool for dose individualisation are the *bias* and *precision* of the method of measurement.

Bias refers to the systematic difference in the mean MIC of an organism (e.g. *S. aureus*) to an antimicrobial when tested using a commercial method, relative to the reference method. Bias is evident in vancomycin MICs for *S. aureus* measured using the commercial methods, particularly for the Etest®, where the mean vancomycin MIC is reported to be 0.5 to 1.5 log_2 dilutions higher than the MIC_{BMD}.(16–19) This explains the disparate findings of a recent meta-analysis of observational studies, where proposed optimal AUC_{24}/MIC ratios for seven studies that determined MIC using BMD ranged from 345 - 451 h (median 399 h), while in two studies that used Etest® the ratios were 211 and 293 h.(7)

Precision refers to the inherent variability of measured MICs upon repeated testing of a single isolate using the same method. The accepted precision in BMD is ± one log_2 dilution, when a bacterial strain is re-tested within the same laboratory using the same assay (intra-laboratory variability) or at different laboratories (inter-laboratory variability). (20–22) A standard method of comparison between the reference BMD and commercial methods is

113 *essential agreement*, defined as a measured MIC using the commercial method falling within
114 a ± one $\log_2$ dilution of the reference.(15) *Categorical agreement* is defined as the
115 proportion of isolates which are correctly classified as sensitive or resistant by the
116 commercial method compared to the reference determination. Both essential agreement
117 and categorical agreement of the commercial methods is high, which justifies their use
118 clinically for the categorical determination of isolates as sensitive or resistant. However, all
119 methods of MIC testing limited have limited precision, and unlike bias, this cannot be easily
120 managed by simply choosing different AUC_{24}/MIC targets for different methods. (16)

121 Observational studies of mortality and treatment failure demonstrate that, at the
122 population level in the range of infections studied, there is an increase in the probability of
123 successful treatment if the AUC_{24}/MIC_{BMD} is greater than ~400 h.(7) The repeated
124 identification of this ratio in studies with heterogeneous patient groups and infectious
125 syndromes suggests that the methods for measuring the MIC (and AUC_{24}) are sufficiently
126 accurate for a useful signal to emerge. This does not mean that the target can be
127 interpreted simplistically in the individual patient because variability in measured MICs
128 (using any method) could lead to erroneous dose adjustments in response to what may
129 simply be random variation due to the limited precision of MIC assays.

130 The EUCAST distribution of MICs to vancomycin for *S. aureus* aggregates MICs contributed
131 by reference laboratories that may use different validated methods which all have limited
132 precision. This distribution is therefore remarkable for its narrow range, with >99% of
133 strains within 0.5 – 2 mg/L. As Mouton *et al* recently pointed out, this MIC distribution is
134 narrower than that reported for many other bacteria-drug combinations. (20, 23) This

suggests that a substantial amount of the observed variability in S. aureus to vancomycin may be due limited assay precision, rather than true variation in phenotypic susceptibility. The problem of imprecision in MIC measurement is amplified by the magnitude of the dose-adjustment that would be required if the measured MIC is used as the denominator for an AUC_{24}/MIC target. This is because the scale of MIC measurement performed using standard methods is discrete and logarithmic rather than continuous and linear: over an MIC range of 0.5 – 2 mg/L the standard BMD method measures MICs step-wise as 0.5, 1 or 2 mg/L. Compared to an AUC_{24}/MIC_{BMD} target of 400 h for an MIC of 1 mg/L, adjusting dosage according to the given MIC_{BMD} would thus require a halving (to 200 (mg/L).h) or doubling (to 800 (mg/L).h) of the target AUC_{24} if the MIC was 0.5 or 2 mg/L, respectively. The Etest®, has similar although less severe issues due to the more finely-graded MICs reported (0.5, 0.75, 1, 1.5 and 2 mg/L over this range).

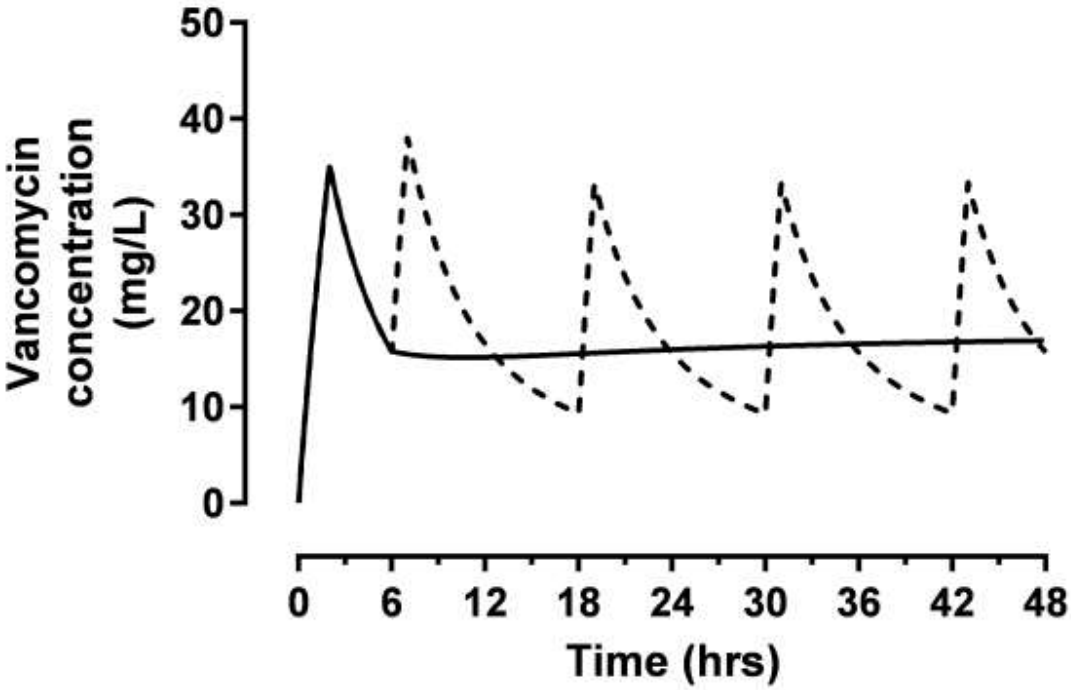
Given these issues, it is not clear whether adjusting dosage based on a measured MIC is better or worse than simply assuming a population value for the MIC (e.g. 1 mg/L for *S. aureus*). We recommend that the decision to use measured MICs should be individualised, considering not only the imprecision of MIC testing methods, but also the patient's clinical progress, risk of treatment failure, and any observable toxicity. Further, the 'starting' value of 400 h is best considered as a guide rather than rigid target. Further research is required to understand the best way to incorporate estimates of phenotypic antimicrobial susceptibility into therapeutic targets for individual patients.

2.2 AUC

The AUC is a measure of a patient's total exposure to a drug over a given period of time. It is often misunderstood, especially when its units of measurement and the time period over which it is estimated are not stated explicitly. In pharmacokinetic studies, AUC is usually measured after a single dose from 0 hours to 'infinity' ($AUC_{0-\infty}$), as this represents total exposure. In such studies, the AUC is usually measured until the lowest detectable concentration, and an extrapolation made to 'infinity' by adding the final concentration divided by the terminal elimination rate constant (ö خ ة ز/ ٢ ٣ ٦). In clinical practice, with regular intermittent dosing, the AUC is measured over the dose interval (ز), and the steady-state AUC ($AUC_{0-\tau}$) equals the $AUC_{0-\infty}$ after a single dose. A dose-rate (i.e. dose per dose interval) can be calculated to achieve the $AUC_{0-\tau}$. The AUC is equivalent to the mean concentration multiplied by the time period (i.e. ö ح ة ا ج في ز), has units of (mg/L).h, and is often averaged over 24 h for convenience. It is clear that any discussion of AUC should state the time period involved, such as $AUC_{0-\tau}$ or AUC_{0-24}, or AUC_{24} for a generic 24 hour period at steady-state.

For vancomycin, the common guideline recommendation of an AUC_{24}/MIC_{BMD} of 400 h is for a time period of 24 hours. This AUC (i.e. AUC_{24}) is explicitly stated as such in the article from which the value of 400 is recommended.(6) The subscript '24' has often been omitted in subsequent references.(2, 3, 16) As this causes confusion, we believe that this ratio should always be stated as AUC_{24}/MIC_{BMD}. This AUC_{24} is equivalent to the mean steady-state concentration multiplied by 24 h. An AUC_{24} target of 400 (mg/L).h has a mean concentration of 16.7 mg/L (400/24 = 16.7). It should be noted that the value of 16.7 mg/L is for the *total* concentration, which needs to be corrected for protein binding to derive the

613 **Figure 1** Predicted median total vancomycin concentration-time curves associated with
614 fixed target trough concentration of 15mg/L for a) continuous infusion (solid line), b) 12-
615 hourly intermittent infusion (dot-dashed line), c) 6-hourly intermittent infusion (dashed
616 line), for a 70kg person with a GFR of 120mL/min based on the two-compartment
617 population pharmacokinetic model of Thomson et al. (44) Associated median steady state
618 AUC_{24} is 370 (mg/L).h, 500 (mg/L).h, and 630 (mg/L).h respectively.



619

620 **Figure 2** Predicted median total vancomycin concentration-time curves associated with
621 2000 mg loading dose followed 6 hours later by a) continuous infusion of 2500 mg
622 vancomycin over 24 h (solid line), b) 12-hourly intermittent infusion of 1250 mg
623 vancomycin (dashed line). Associated $AUC_{0\text{-}24}$ and $AUC_{24\text{-}48}$ for a) are 411 and 397 (mg/L)/h
624 and for b) are 494 and 413 (mg/L)/h respectively.

625