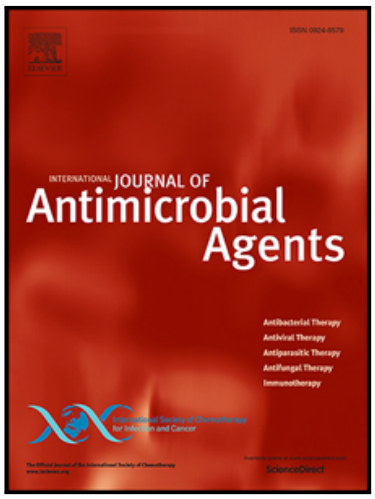

The dosing and monitoring of vancomycin – what is the best way forward?

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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 C_{mean}) by 24 i.e. $AUC_{24}\ [(mg/L).h] = C_{mean}(mg/L) \times 24\ (h)$. 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 (C_{last}/k). In clinical practice, with regular intermittent dosing, the AUC is measured over the dose interval (τ), 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. $C_{mean} \times \tau$), 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

biologically active *free* (unbound) concentration for meaningful interpretation against MIC values, which are based on unbound drug concentrations.(24) Observational studies relating vancomycin exposure to efficacy or toxicity have used *total* vancomycin concentrations (i.e. protein bound + free) and thus we will refer to the total drug AUC. The mean protein binding of vancomycin is around 0.3-0.5, but there is substantial inter-individual variation in hospitalised inpatients.(25–28) Thus variability in protein binding is an additional source of unexplained variability between total serum concentration and outcome in both observational studies and clinical practice. Further research is required to determine whether direct measurement of free vancomycin concentrations, or estimation using formulae, are of value in clinical or research settings, as suggested for antimicrobials with markedly higher protein binding such as flucloxacillin. (29)

2.3 Use of a loading dose

The routine use of a loading dose of vancomycin in patients with sepsis has a strong theoretical rationale: to rapidly attain effective drug exposure at the site of infection. Vancomycin is a hydrophilic drug, thus the volume of distribution (Vd) approximates the extracellular fluid volume. A loading dose of 25-30 mg/kg total body weight is commonly recommended(1–3), although more individualised approaches have also been proposed for critically-ill patients who may exhibit an increase in Vd, to maximise the probability of attainment of $AUC_{0\text{-}24}$ targets.(30) Obese patients have an increased Vd relative to the non-obese, however Vd does not scale in direct proportion to total body weight. (31) Patients who are morbidly obese may be subject to excessive loading doses if absolute body weight is used—loading dose strategies in these patients have been discussed in a recent review.(32)

A practical benefit of loading doses is that they result in the patient approaching the target steady-state AUC_{24} more rapidly, which will facilitate earlier estimates of drug exposure when the AUC_{24} is estimated using non-Bayesian methods. Small clinical studies also support the use of loading doses in order to optimise vancomycin exposure early in the course of therapy without increasing the risk of nephrotoxicity or other adverse events.(30, 33, 34)

2.4 Other sources of variability

There are numerous other sources of variability in the link between serum vancomycin concentration and clinical outcome that will not be discussed in detail. These include assay variability, immune status, site of infection, and variability in pathogen vancomycin susceptibility, inoculum, and virulence. For example, Ghosh et al. proposed AUC_{24}/MIC_{BMD} values associated with risk of mortality that differ according to site of infection.(35) In this study the AUC_{24}/MIC_{BMD} target for 'low risk' sites such as intravenous catheter-related infection was 330 h, versus 440 h for 'high-risk' sites such as pneumonia and endocarditis. This observation is consistent with observed variability in vancomycin tissue penetration.(35) More research is required to determine the settings in which these factors can usefully inform optimal vancomycin dosing.

3. Models for the estimation of AUC in individual patients

There are a number of different methods for estimating the AUC. Differences between these methods are a potential source of confusion when interpreting published studies and the application of therapeutic drug monitoring for individual patients. When first initiating vancomycin a useful 'best guess' for the AUC comes from a formula such as that of Rodvold

and Blum.(36) This is based on creatinine clearance, because renal function is the major determinant of vancomycin clearance. Following the first dose of vancomycin, there are several methods for estimating the AUC from measured vancomycin concentrations. These include approaches based on: 1. A trough concentration, 2. Two-point methods, such as the Sawchuk-Zaske method (originally described for gentamicin),(37) and 3. Bayesian methods using single or multiple concentrations. The AUC so calculated can be compared to the target AUC and a revised dose can be estimated proportionately. The precision of the estimated AUC will vary depending on the method used in its calculation. In general, simpler dosing methods use less (or no) patient specific information (e.g. a fixed dose for all patients), or dosing based on a single serum creatinine concentration measurement. They also require more assumptions than a model that includes more patient-specific information e.g. that the patient is assumed to be 'average' or that deviations from this are clinically unimportant and that the patient has stable renal function. The inclusion of patient-specific information should produce AUC estimates with higher precision, and result in dosing with lower probability of toxicity and higher probability of efficacy. The trade-off in using more complex models is that they require greater resources in terms of time, expense, software and expertise than simpler models. As discussed in the following sections, accumulating evidence suggests that individualised dosing methods for vancomycin are required for optimal efficacy.

3.1 Methods using estimated creatinine clearance

Many of the studies that advocate the target vancomycin AUC for the AUC_{24}/MIC_{BMD} ratio of 400 h did not calculate the AUC from measured vancomycin concentrations at all.(6, 38–41) Instead, they predicted the AUC using a formula based on a relationship between

vancomycin clearance and creatinine clearance (CL_{CR}, in mL/min/1.73m^2), previously derived by Rodvold and Blum:(36, 42)

$$AUC_{24} \frac{\text{Dose per 24 hours (mg)}}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$

This formula for predicting the AUC_{24} has been validated in adults and is useful for patients with stable renal function prior to any vancomycin concentrations being available.(42) There are numerous alternative approaches for initial dose calculations. Dosing nomograms have been described and externally validated for initial dosing in different patient groups.(41, 43) Another approach is to use population pharmacokinetic models integrated into Bayesian therapeutic drug monitoring software (discussed below). These predict exposures related to patient-specific covariates without any measured vancomycin concentrations. When actual vancomycin concentrations are available, an AUC_{24} can be estimated more accurately, by incorporating a direct measure of vancomycin exposure. Estimation of creatinine clearance using a single creatinine measurement is dependent on an assumption of stable renal function, which is frequently not the case in hospitalised patients. Such patients may be best served by early assessment of vancomycin exposure and appropriate dose adjustment using Bayesian methods which do not require the assumption of steady-state (see section 3.4).

3.2 Methods based on trough concentrations

Although appealing for their simplicity, trough concentrations should be considered important only to the degree that they inform estimation of the AUC_{24}. Some individuals with concentrations within the recommended range of 15 - 20mg/L have AUCs much

higher than 400 h, and many with lower trough concentrations also have AUCs above 400 h.(8, 13, 14) When vancomycin is given by intermittent infusion, patients with high vancomycin clearance will have a lower trough concentration for a given vancomycin AUC_{24} and may therefore be subject to unnecessary dose increases if dosing is adjusted to achieve a trough target.(12) Furthermore, for a given trough concentration, different dose intervals are associated with very different AUCs. This is illustrated in Figure 1. For a person with a 'normal' half-life of vancomycin of 6 h, a 12-hourly regimen adjusted to achieve a trough concentration of 15 mg/L will result in an AUC_{24} of 630 (mg/L).h, compared with 500 (mg/L).h with a 6-hourly regimen and 370 (mg/L).h) with a continuous infusion.(44) There is little evidence that the trough concentration is a useful predictor of clinical outcomes despite the suggestion from guidelines that this is an acceptable surrogate for the AUC_{24}. (45) More worrying is that patients achieving trough concentrations of 15 - 20 mg/L have an increased rate of nephrotoxicity compared to those with lower troughs,(46) which may be an indication of higher AUCs in this group.

The term 'trough concentration' implies that a blood sample is taken immediately before the next dose is due. In practice, there is a large variability in the timing of 'trough' sampling.(14) For a drug with a half-life of approximately six hours (as in normal renal function), variability in timing of blood sampling can add to imprecision to the estimated AUC if the blood sample is assumed to be a true trough concentration. This practical problem can be managed using more sophisticated methods as detailed below.

3.3 Two-point concentration methods

Vancomycin concentrations measured at two time points can be used to calculate AUC, most simply using a one-compartment pharmacokinetic model. This can be done using a hand-held calculator, but errors may be avoided with computer software. Pai et al. discuss modifications of the Sawchuk and Zaske method that perform well for vancomycin AUC estimation.(47) Centres that have implemented these two-point methods have observed improved AUC_{24} target attainment and lower nephrotoxicity compared with trough-based dosing.(13) A disadvantage of these methods is that they require two blood samples and accurate recording of the timing of both drug administration and blood sampling. In practice we have found that accurate recording will require significant education.

3.4 Methods using Bayesian models

There are a number of computer applications available for estimating AUC_{24} using Bayesian methods. (48, 49) These employ statistical models that combine 'prior' information about pharmacokinetic parameters and their distributions in the population with measured concentrations in an individual to estimate likely values of parameters for the patient, such as the AUC_{24}. Provided they are informed by population pharmacokinetic data that is relevant to the patient they can produce reliable estimates of AUC_{24} with as few as a one timed blood sample. Disadvantages include the need for trained practitioners and the cost of commercial software. Population pharmacokinetic models for vancomycin have been externally validated for use in a range of patient populations, including general inpatients, patients with critical illness, and those with obesity.(50–52) As with two-point estimation, a recent observational study from a centre which moved from trough based monitoring to a

Bayesian method noted a higher proportion of patients attaining the nominated target AUC_{24} and less nephrotoxicity.(14) The Bayesian method is also expected to be less sensitive to random variation in the vancomycin concentration assay than two-point methods as it shrinks random deviations towards the population parameter distributions. A limitation of the models currently implemented in Bayesian software (which is shared by all of the methods outlined above) is that they may not readily accommodate patients with rapidly changing physiology, and the resultant changing pharmacokinetic parameters such as clearance. Advances in covariate model structures, with the incorporation of covariates that are predictive of changes in physiology and therefore drug clearance will likely improve predictive performance. This is somewhat achieved in current Bayesian platforms, e.g. by incorporating changes in renal function over time, by assigning greater weight to more recent vancomycin concentrations, and by including additional covariates which can better characterise the patient's physiology. (53) Despite these limitations, the current models offer a significant improvement to trough-based monitoring and should be encouraged. Centres which adopt a Bayesian method will be well-placed to implement improved models in the future without major changes in workflow or clinician education.

3.5 Continuous infusion

There is some evidence that continuous infusion may decrease nephrotoxicity compared with intermittent infusion with trough monitoring.(54) It is not known however if continuous infusion causes less nephrotoxicity than intermittent infusion when the AUC is targeted accurately using two-point or Bayesian methods. Continuous infusion has the clear advantage over intermittent infusion that AUC estimation is simpler. At steady-state, a

vancomycin concentration obtained at any time during continuous infusion can be used to estimate an AUC_{24} by multiplying the concentration by 24 h. This obviates the need for specialised pharmacokinetic knowledge or software. As vancomycin concentrations should be constant over 24 hours at steady state (Figure 1), blood samples for concentration monitoring can be obtained during routine phlebotomy rounds. There are some practical considerations. A loading dose should be given to ensure rapid attainment of effective drug exposure, as illustrated by Figures 1 and 2. Continuous infusion generally requires a dedicated intravenous line/lumen due to the incompatibility of vancomycin with many other drugs. It is also recommended that continuously-infused vancomycin is administered via a central venous access device due to the risk of phlebitis with peripheral administration.(55) This is likely to limit the use of continuous infusion to patients in intensive care and in those with peripherally inserted central catheters. A third issue is that some patients may find continuous infusion inconvenient and disruptive, although elastomeric infusor devices counter this to some extent. Whether these potential disadvantages outweigh the advantages for dose adjustment will depend on specific patient and institutional circumstances.

4. Practical aspects of dosing to maximise efficacy and minimise toxicity

In this section we offer recommendations to achieve an AUC_{24}/MIC_{BMD} target — 400 h has been chosen for illustrative purposes.

4.1 MIC determination

If a measured MIC is not available, the local MIC_{90} *of S. aureus* strains (usually 1 mg/L) is a reasonable target. It is unclear whether using a single measured MIC to define an AUC_{24}/MIC target is better or worse than using a fixed population-based MIC. Care should be taken if considering adjusting the AUC_{24} target for an isolate with an MIC ±1 log_2 dilution either side of 1 mg/L since this may simply represent assay variation rather than phenotypic variation in susceptibility. If dosing to target a measured MIC, the method of MIC determination must be accounted for. The target AUC_{24}/MIC_{Etest} is likely to be lower than the corresponding AUC_{24}/MIC_{BMD} with approximate targets of 250 h and 400 h respectively.(7)

4.2 Loading dose

A loading dose of 25-30 mg/kg (total body weight) should be considered in most patients to facilitate rapid achievement of effective vancomycin exposure. The optimal time to commence maintenance dosing (continuous or intermittent infusion) is one half-life after the loading dose, as illustrated in figure 2.

4.3 Initial maintenance dose

It is simplest to consider the case of an organism with an MIC of 1 mg/L, measured by BMD and a target AUC_{24}/MIC_{BMD} of 400 h. To achieve the target AUC_{24}, the first maintenance dose is calculated using the formula of Rodvold and Blum (or equivalent) and the patient's estimated creatinine clearance. The initial maintenance dose is the same regardless of whether or not a loading dose is used, and for different methods of administration. Dosing

regimens based on validated population pharmacokinetic models implemented in Bayesian software are an attractive option for individualised dosing, but require appropriate software and expertise to be available to the clinician at the point of prescribing.

To check whether the target AUC_{24} has been achieved, it is easiest to wait until steady-state is approached. This occurs after approximately four half-lives of vancomycin, or 24 h with the half-life of around 6 h in patients with normal renal function. Bayesian estimation does not have the time requirement of waiting for steady-state to be achieved, and thus sampling can occur after completion of the first infusion.

4.4 Therapeutic Drug Monitoring during intermittent infusion

We reiterate that for the reasons noted above, trough concentration monitoring is not recommended unless its limitations are appreciated and better methods cannot be implemented. If trough concentration targets must be used, the targets should be based on a specific dose interval (e.g. 15 - 20 mg/L for 12-hourly dosing) that is likely to achieve the desired AUC_{24} and not used for other dose intervals, in order to avoid unnecessary increases in drug exposure and toxicity. For 12-hourly dosing, it should be appreciated that many patients with trough concentrations below 15 mg/L will have an adequate AUC_{24}, while 20 mg/L is a useful upper limit due to the association between higher trough concentrations and nephrotoxicity.

If dosing is by intermittent infusion, calculation of the AUC_{24} requires proficiency in pharmacokinetics. Bayesian software is the best for this, since it combines prior knowledge of population pharmacokinetics with the observed concentration(s) and dosing information from the individual patient. If Bayesian software is not available to allow

prediction from a single sample, two concentrations should be measured, usually a peak (30-60 minutes after the end of infusion) and a trough (just prior to next dose). The exact timing of the samples with respect to dose needs to be recorded accurately for useful dose calculations. It is possible to calculate the AUC_{24} using a handheld calculator, assuming a one-compartment model, but the potential for error is great. It is more reliable to use a simple computer program tailored for the purpose.

4.5 Therapeutic Drug Monitoring during continuous infusion

If dosing is by continuous infusion and steady-state has been achieved, a single concentration taken at any time is all that is needed to estimate the AUC_{24}. The measured concentration is simply multiplied by 24 to give the AUC_{24}. For example a concentration of 13 mg/L represents an AUC_{24} of 312 (mg/L).h (i.e. 13 x 24) if the MIC is 1 mg/L. The dose could be increased proportionately (400/312 or 1.3-fold) to achieve the desired target of 400 h.

4.6 Logistical considerations

Centres have different constraints on implementing precision dosing protocols. In centres with well-resourced therapeutic drug monitoring support, Bayesian methods may be relatively easily implemented. In settings that do not have these resources, continuous infusion is the easiest to monitor and probably should be the method of choice. In settings with sufficient technical support but without Bayesian software, two-point estimation of the AUC_{24} may be useful.

5. Conclusion

There is evidence to suggest that vancomycin continues to be used in a suboptimal manner. In this commentary we have outlined strategies to improve the use of vancomycin, which may be considered in future international guidelines. The field of therapeutic drug monitoring would benefit from more high-quality observational and randomised controlled trials. With current evidence, target attainment can be improved using the methods outlined above, while remaining cognisant of the limitations of the evidence used to derive these targets. It is likely that future research will identify varying exposure targets relevant to specific clinical situations, allowing greater individualisation of therapy to enhance efficacy and minimise toxicity. The relevance of these results is dependent on widespread availability of the knowledge and tools required for accurate target attainment.

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430

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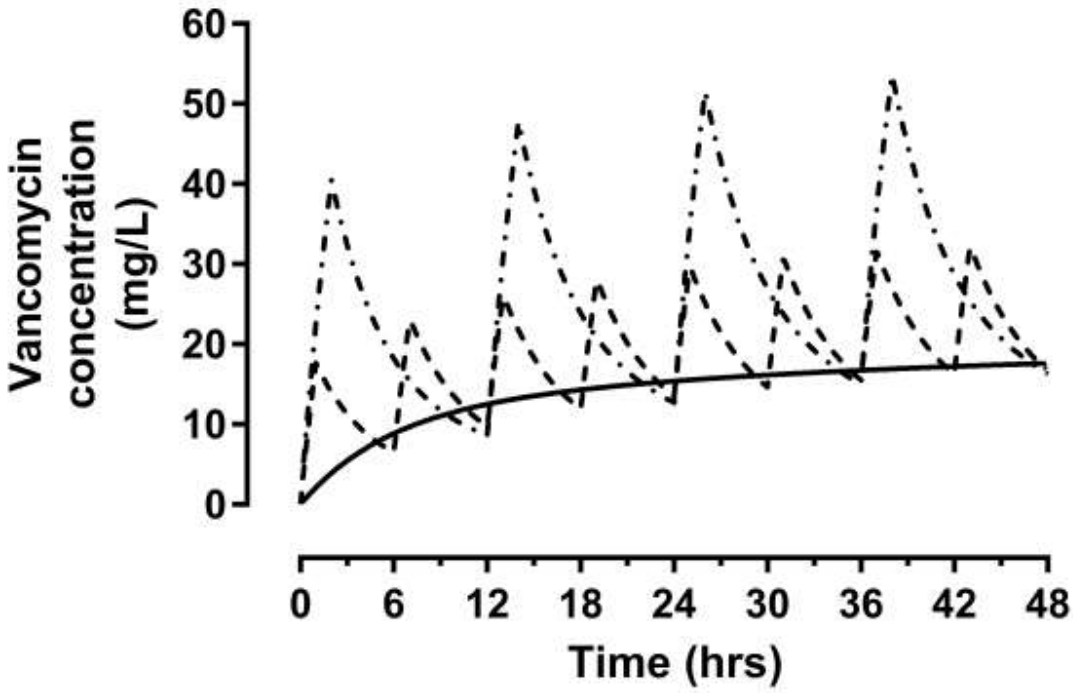
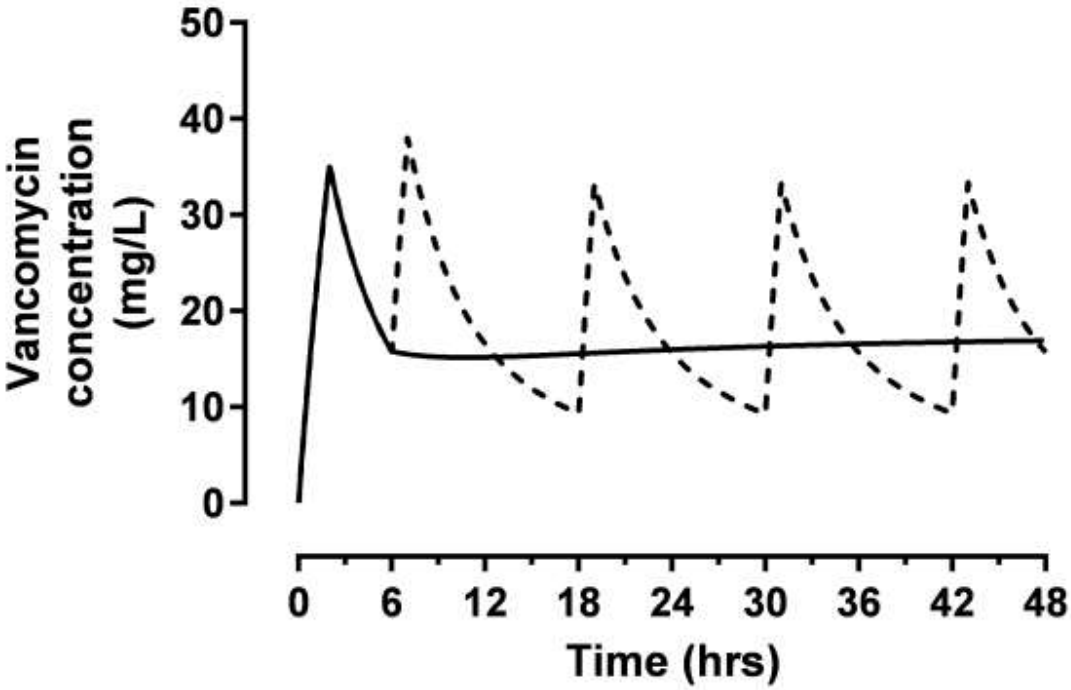


612

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.

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