Vancomycin has been used extensively since the late 1950s. Despite the introduction of several new valuable anti-Gram-positive antibiotics during recent years and the waning susceptibility of staphylococci to vancomycin, it remains the gold standard for the treatment of bacteraemia caused by methicillin-resistant staphylococci. Vancomycin has clear dose–response and dose–toxicity correlations. It is widely accepted that these correlations are best predicted by the AUC/MIC model, with target levels of 400 being the clinical cut-off. The experimental base of this model is less robust than frequently believed, and several important issues in vancomycin resistance, such as biofilm resistance and the inoculum effect, are not included. Based on this model, current dosing guidelines propose intermittent dosing of vancomycin with target trough levels of 15–20 mg/L. Dose adaptations according to renal function have been proposed but are not yet validated. Clinical data also support the use of continuous infusion with target plateau levels of 20–25 mg/L, with similar efficacy at the cost of lower nephrotoxicity. Despite decades of intense clinical use and numerous studies and publications, the optimal dosing strategy for vancomycin reconciling the high needs of the dose–response relationship with the serious drawbacks of the dose–toxicity relationship remains to be established.

Keywords: staphylococci, dosing, continuous infusion

Introduction

Vancomycin was introduced in 1956, initially to ‘vanquish’ Staphylococcus aureus species that had acquired resistance to natural penicillins. The antibiotic was introduced in an era of incredible enthusiasm and belief in the future, hard to believe for contemporary clinicians. The pipeline for new antibiotics seemed inexhaustible, regulatory requirements for developing and marketing were limited, and complex pharmacological and resistance problems were not yet an issue. Appropriate therapy for every infectious disease seemed close at hand. Vancomycin, however, soon faded into the background, mainly due to frequent side effects attributed to product impurities—the drug was also referred to as ‘Mississippi mud’—and the development of penicillinase-resistant penicillins and cephalosporins.

The steady spread of methicillin-resistant S. aureus (MRSA) from the early 1980s, initially in the hospital environment and later in the community, brought vancomycin back into the picture. Nowadays, the position of vancomycin as a first-line agent against methicillin non-susceptible staphylococci is questioned by the emergence of vancomycin intermediate-susceptible S. aureus strains (VISA) and hetero-VISA (hVISA) and toxicity issues. The ongoing creep in the MIC for vancomycin among susceptible staphylococci also represents a significant concern, although a recent paper seems to suggest that the analysis of historical data can give a misleading impression of trends in MIC values because of experimental variation between tests conducted at different times. Previous infection with MRSA, previous vancomycin therapy, the presence of severe underlying diseases and infections characterized by a high bacterial load such as endocarditis, infected prostheses or undrained deep abscesses have been identified as risk factors predisposing to infections with hVISA and VISA. The inappropriate use of vancomycin has also resulted in increasing emergence of vancomycin-resistant enterococci. For this reason the CDC Hospital Infection Control Practices Advisory Committee developed guidelines for its correct use. These guidelines restrict the use of vancomycin to the following circumstances: serious infections caused by MRSA and methicillin-resistant Staphylococcus epidermidis; infections caused by methicillin-susceptible S. aureus (MSSA) in subjects with allergy to penicillins; pseudomembranous colitis (in case of relapse or lack of response to metronidazole treatment); prophylaxis for endocarditis following high-risk procedures in penicillin-hypersensitive subjects; and surgical
pharyngitis for major procedures involving implantation of prostheses in hospitals with a high prevalence of MRSA. In recent years, the development of new agents (linezolid, daptomycin, tigecycline and ceftobiprole) has ameliorated the situation, although a reliable alternative reference standard agent for the treatment of serious infections with methicillin-resistant organisms is still to be proved on the basis of evidence.

**Vancomycin in a nutshell**

Numerous original studies and reviews have gradually improved our insight into the mechanism of action and toxicity of the drug. Vancomycin definitely does not fulfil the profile of an ideal antibiotic. It is a large molecule, only suitable for parenteral administration. After injection, vancomycin has a complex concentration–time profile. Elimination is mainly by the kidneys and correlates almost linearly with creatinine clearance. Vancomycin is distributed throughout the body, although penetration in many tissues is disappointingly low, being only 0%–18% of serum concentrations in uninflamed meninges, 36%–48% in inflamed meninges, a maximum of 41%–51% in the lung, and 10%–30% in diabetic and normal skin and soft tissues.

Vancomycin has a slow mode of action by inhibition of the incorporation of murein monomers into the growing peptidoglycan, eventually leading to osmotic cytolysis with a delay as long as 24 h. Gradual clogging of the antibiotic into a thickened staphylococcal cell wall is the mechanism underlying the low-grade vancomycin resistance observed in VISA species. The bactericidal activity of vancomycin is weak when the inoculum is high, defined as the inoculum effect, and in the case of biofilm-associated infections, defined as biofilm resistance. Multiple lines of evidence suggest that the efficacy of vancomycin is inferior to that of β-lactam antibiotics in the treatment of serious MSSA infections. In vitro models using standard (low inoculum of 10^5 bacteria) concentrations of S. aureus and coagulase-negative staphylococci, the killing effect of vancomycin did not increase with increasing concentrations of 2–64 times the MIC. These findings support a time-dependent killing effect of vancomycin. Under the same experimental conditions, higher concentrations of vancomycin resulted in a longer post-antibiotic effect. However, an experimental mouse model from S. Ebert, presented at the 1987 Interscience Conference on Antimicrobial Agents and Chemotherapy, identified AUC/MIC as the parameter best predicting the clinical efficacy of vancomycin in S. aureus infections, while T>MIC did not correlate with killing. Despite the paramount importance of these data for the current dosing guidelines of vancomycin, they were never published as a full report. The main clinical data supporting the importance of high vancomycin exposure are derived from a study of 108 patients with S. aureus lower respiratory tract infections. The study demonstrated a highly significant association between clinical cure and an AUC/MIC >400 and between bacteriological cure and an AUC/MIC >850. There was, obviously, no correlation with T>MIC, which was 100% in all patients. The AUCs in this study were based on mathematical modelling and vancomycin dose, as well as a limited number of vancomycin steady-state serum levels in a subset of patients.

These data and the lack of correlation between vancomycin effect and T>MIC endorsed the guideline to use intermittent vancomycin dosing with target trough levels of 15–20 mg/L. Further modelling and Monte Carlo simulations applying these guidelines in a database of 37 patients with various degrees of kidney failure demonstrated a rapidly decreasing probability of attaining the target AUC/MIC ≥400 when the MIC was rising above 1 mg/L, especially in patients with well-preserved kidney function.

**Vancomycin in continuous infusion**

In a pilot trial with a cross-over design, conventional dosing (1 g every 12 h) was compared with continuous infusion (2 g every 24 h after a loading dose of 500 mg). Total drug exposure (expressed as AUC/MIC) was almost identical for the two regimens and both had a T>MIC of 100%. Continuous infusion resulted in more stable drug concentrations. However, when 8 times the MIC or 32 times the MIC was used as the target, target achievement was much higher in the continuous infusion group. Based on these results, a randomized controlled trial (RCT) was designed in 160 intensive care patients to compare conventional dosing (15 mg/kg twice daily with target trough levels of 10–15 mg/L) with continuous-infusion dosing (a loading dose of 15 mg/kg followed by a continuous infusion of 30 mg/kg/24 h with target plateau levels of 20–25 mg/L). These target levels were chosen on the basis of a mix of clinical, microbiological and pharmacological considerations. There were no major differences between the two groups in efficacy, safety and total drug exposure given by the 24 h AUC. The number of control samples needed to maintain targets and the costs were lower in the continuous infusion group.

In 2011, the Infectious Diseases Society of America (IDSA) produced guidelines for the treatment of MRSA infections that did not clarify the issue, stating that ‘because of the lack of a clear benefit over intermittent dosing, and because T>MIC is not the primary predictor of efficacy, continuous infusion vancomycin is not recommended’ (page e41). To support this statement, the authors refer to three studies. Of interest, none of the studies investigated the relationship between T>MIC and vancomycin efficacy and the above-mentioned largest randomized clinical trial comparing continuous with intermittent infusion of vancomycin published to date was not included among the retrieved references. A recent meta-analysis comparing continuous versus intermittent infusion found no difference in clinical efficacy or total drug exposure, but a significantly lower risk of nephrotoxicity in the continuous infusion group.

**Vancomycin dose–response expressed by AUC/MIC**

In in vitro models using standard (low inoculum of 10^5 bacteria) concentrations of S. aureus and coagulase-negative staphylococci, the killing effect of vancomycin did not increase with increasing concentrations of 2–64 times the MIC. These findings support a time-dependent killing effect of vancomycin. Under the same experimental conditions, higher concentrations of vancomycin resulted in a longer post-antibiotic effect. However, an experimental mouse model from S. Ebert, presented at the 1987 Interscience Conference on Antimicrobial Agents and Chemotherapy, identified AUC/MIC as the parameter best predicting the clinical efficacy of vancomycin in S. aureus infections, while T>MIC did not correlate with killing. Despite the
Of note, all but one of these studies had a mean plateau drug level between 24 and 26 mg/L, which is much higher than the MIC cut-off level for susceptibility of 2 mg/L.26

Vancomycin toxicity

Besides idiosyncratic side effects and the infusion rate-related ‘red man (or woman) syndrome’, vancomycin demonstrates not only a dose–response relationship, but also a clear dose–toxicity relationship with a narrow therapeutic window.4,5 The adverse effects mainly involve the kidney and inner ear.5,16 Vancomycin-associated ototoxicity presents with high-frequency hearing loss similar to that observed in presbycusis and affects especially older patients.16

Nephrotoxicity is observed in 12%–43% of patients.4 Most studies define nephrotoxicity as a 50% decrease in creatinine clearance or an increase of 0.3–0.5 mg/dL in serum creatinine.5,26 Limited data in severely sick patients developing renal failure while being treated with vancomycin indicate a need for dialysis in up to 5%–30% of these patients.26 Nephrotoxicity is incremental with higher doses and longer exposure and is more frequently observed in critically ill patients, those with already compromised kidney function and patients receiving concomitant nephrotoxic agents.5 High initial vancomycin trough levels are the best predictors of the risk of nephrotoxicity.7 Vancomycin toxicity acts as an oxidative stressor in the renal proximal tubule and causes interstitial nephritis in some cases.5 Data on the degree of renal recovery are scarce. In the meta-analysis comparing 267 patients treated with continuous infusion and 167 patients treated with intermittent administration discussed in the previous section, the risk of nephrotoxicity was significantly lower (relative risk 0.6, 95% CI 0.4–0.9, P=0.02) in the group treated with continuous infusion.26 As the total exposure or 24 h AUC was similar in the two groups, these findings suggest that peak rather than trough levels predict the risk of nephrotoxicity, although both parameters are obviously interrelated.

Concerning the glycopeptide teicoplanin, a meta-analysis of available studies suggests that teicoplanin is as effective as vancomycin, especially in less sick patients, while having a lower incidence of nephrotoxicity and infusion-related side effects.28

Vancomycin dosing in renal failure

Body weight–based loading doses seem superior to fixed loading doses in target level achievement.6 Whereas the loading dose is independent of kidney function, maintenance doses should be adapted to even moderate decreases in kidney function by either decreasing the dose or by increasing the dosing interval.13 Reliable data to guide dose adaptations for continuous vancomycin infusions in renal failure are lacking. For intermittent dosing, several dosing algorithms have been developed, but none has been validated for current dosing targets.6,10 Based on the 2009 dosing guidelines and the linear correlation between vancomycin and creatinine clearance, a dose-adjustment schedule for various degrees of renal failure has been proposed,9 but has been validated only in the setting of intermittent haemodialysis.29 In haemodialysis patients, vancomycin is administered three times weekly at the end of dialysis and the doses needed to obtain trough levels of 15–20 mg/L can be calculated accurately with a vancomycin dose calculator based on three easily obtainable variables (patient’s body weight, time to the next dialysis session and pre-dialysis trough level).29

Vancomycin versus ‘the others’ in clinical practice: where is the evidence?

Many trials have been carried out to determine and compare the effectiveness of antimicrobial agents in treating infections due to MRSA. In particular, from 2005 to 2012, eight meta-analyses were performed to compare the clinical impact of linezolid versus vancomycin.30–37 Three of these meta-analyses on soft skin infections (SSIs) due to Gram-positive/MRSA showed a clinical superiority of linezolid versus vancomycin.30–32 Other trials were performed to compare the clinical impact of linezolid versus vancomycin for patients with febrile neutropenia, bacteraemia and SSIs. None of the treatments showed differences compared with vancomycin for patients with febrile neutropenia, bacteraemia and SSIs. Comparators were more effective in open-label than double-blind trials, suggesting that the study design makes a major contribution to infection outcome.

Conclusions: the end of the battle?

Despite more than 55 years of extensive clinical use, the story of vancomycin still does not sound like the tale of a vanisher. Vancomycin is far from an ideal antibiotic, but in many clinical settings it remains the best option available.9 The drug has clear dose–response and dose–toxicity relationships, which are at least partially overlapping (see Figure 1). Theoretically,
Vancomycin activity is best predicted by the AUC/MIC, endorsing the guidelines that recommend intermittent administration of vancomycin. However, in clinical practice and trials, continuous infusions targeting plateau levels of 20–25 mg/L appear at least as effective and may be safer than intermittent administration of the drug, with similar AUC/MIC. Limits in the clinical applications of continuous infusions are mainly related to the requirement for infusion pumps and intravenous access. How can this contradiction be explained? The MIC used in the AUC/MIC model is mainly based on the in vitro determination of the inhibition of growth of standardized low inocula ($10^5$–$10^6$) of exponential-phase staphylococci. This parameter does not take into account the disruptive effect on vancomycin activity of higher inocula, as encountered in serious infections or infections with ineffective source control. Under these circumstances, higher vancomycin levels are probably needed to obtain proportionally the same killing effect. In addition, the AUC/MIC parameter does not take into account the noxious effects of stationary-phase growth and biofilm-associated growth mode on vancomycin activity, as observed in, e.g. endocarditis, chronic infections and foreign body-related infections. Higher concentrations of vancomycin may be required for success under these circumstances and the time above a multiple of the MIC, the time above the stationary-phase MBC or the time above an inoculum-corrected MIC as a new PK/PD parameter will probably more accurately predict vancomycin efficacy in clinical practice than does the extensively used AUC/MIC model. In Table 1 dosing recommendations for intermittent and continuous infusion are provided. In our opinion, future clinical trials need to focus on the following open questions: (i) what loading dose of vancomycin should be used? (ii) how can the maintenance dose of vancomycin be calculated to obtain with high accuracy predictable trough levels in patients with varying body weight and kidney function? (iii) is it better to administer vancomycin via continuous infusion or intermittent dosing? and (iv) is the renal toxicity with varying degrees of kidney function reversible?

One possible way to answer these questions is the development and validation of a ‘universal’ vancomycin dose calculator through a multicentre RCT. This achievement would be a major breakthrough in the treatment of serious Gram-positive infections with vancomycin. Such a dose calculator should be based on an extensive database and preferentially not include more input variables that the patients’ kidney function and patients’ body weight to provide the output variables loading dose, maintenance dose and administration mode. Future research should develop and test new clinical indicators for outcomes for patients, such as long-term adverse effects in high-risk populations (e.g. elderly people), and for society, such as the ecological costs of new drug use (Table 2).

### Table 1. Proposed vancomycin dose as a function of kidney function, administered as a continuous infusion or in an intermittent dosing regimen; the maximal infusion rate is 15 mg/min under all circumstances

<table>
<thead>
<tr>
<th>CLCR (mL/min)</th>
<th>Loading dose (mg/kg)</th>
<th>Maintenance dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>30–50</td>
<td>25–30</td>
<td>30–40</td>
</tr>
<tr>
<td>50–80</td>
<td>20–30</td>
<td>25–35</td>
</tr>
<tr>
<td>&gt;80</td>
<td>15–20</td>
<td>20–25</td>
</tr>
</tbody>
</table>

### Table 2. Evidence and unmet needs for vancomycin usage

Key points from the literature

1. Vancomycin has a clear dose–effect correlation.
2. Vancomycin has a clear dose–toxicity correlation, with nephrotoxicity being the major concern.
3. The optimal balance between dose, effect and toxicity is obtained with:
   - (a) trough levels of 15–20 mg/L for intermittent dosing.
   - (b) plateau levels of 20–25 mg/L for continuous infusion.
4. Administration of vancomycin via continuous infusion is as effective as intermittent administration and is associated with reduced nephrotoxicity.
5. The dose–effect correlation seems to be best predicted by the AUC/MIC model.

Where further research is needed

1. Open-label, multicentre, well-powered RCT designed to develop and validate a universal vancomycin dose calculator that includes only kidney function and body weight as input data, providing the following output data:
   - loading dose.
   - maintenance dose.
   - mode of dose administration (continuous versus intermittent infusion, timing of infusion).
2. Optimization of PK/PD models, with integration of data on inoculum size, stationary-phase growth and biofilm growth.
3. High-risk populations (elderly/diabetic patients) with severe bacteraemia infections.
4. Elaboration of composite endpoint for the outcome’s analysis that includes mortality rate, evaluation of short- and long-term adverse effects, risk of development of resistance in the colonizing staphylococcal flora, and achievement of the blood concentration target.

Downloaded from https://academic.oup.com/jac/article-abstract/68/4/743/705696 by guest on 04 February 2019
References


